Beta-Amyloid Antibodies for Early Alzheimer's Disease

Revised Background and Scope

January 27, 2022

Background

Alzheimer's disease (AD) is a fatal degenerative brain disease characterized by progressive loss of memory, cognitive skills such as language and problem-solving, and physical function. It is the most common cause of dementia in the United States (US), affecting an estimated 6.2 million Americans, and is the 6th leading cause of death.[1] Two-thirds of those diagnosed with AD are women, and there are racial and ethnic differences in the incidence and prevalence of AD, with African Americans at twice the risk and Hispanic Americans at 1.5 times the risk of developing AD as non-Hispanic white populations.[2-5] Direct and indirect costs of health care related to AD are estimated to be around $500 billion annually,[6] though this may be an underestimate, as non-medical costs such as home safety modifications, adult day care services, and caregiver health costs may not be included.[2]

The hallmark of AD is the progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles of phosphorylated tau protein in the brain.[7] Single-gene mutations such as amyloid precursor protein and presenilin that impact beta-amyloid formation are associated with early-onset (age <65) AD. Genetic variants such as the apoprotein E (ApoE) ε4 allele is associated with 2 to 15-fold increase in one's risk of developing late-onset AD, depending on the number of copies of ApoE ε4 one carries.[8]

Though the exact mechanisms by which neuronal death and damage occur are not fully understood, current disease models hypothesize that beta-amyloid plaques trigger misfolding of tau proteins, which, as they spread through the brain cortex, cause neuronal injury.[5] Neurodegeneration is associated with impairment in cognitive domains such as memory, language, executive function (e.g., problem-solving and completing tasks), and visuospatial function. These deficits result in the loss of ability to perform activities of daily living (e.g., paying bills, bathing, dressing, etc.) as well as changes in mood and personality.[9] As the disease progresses, patients become less independent and the caregiving impact increases, and eventually patients require around-the-clock in-home or institutional care. More than 16 million family members and other caregivers provided an estimated 18.6 billion hours of unpaid care to patients with AD or other dementias, putting these caregivers at risk for negative mental, physical, and emotional outcomes.[2] The average life

expectancy for patients with AD depends on multiple factors, including age, functional status at diagnosis, and comorbidities, but estimates range from three to 10 years.[10]

The course of AD can be described in three phases: preclinical disease, mild cognitive impairment (MCI), and Alzheimer's dementia.[2] In the preclinical phase, patients are asymptomatic but begin to accumulate beta-amyloid in the brain. Presence of beta-amyloid in the brain may be detected through testing such as positron emission tomography (PET) or analysis of cerebrospinal fluid (CSF). Over time, subtle cognitive changes begin to occur and once there is a reduction in cognitive function, MCI is diagnosed. Patients are diagnosed with Alzheimer's dementia when there is impairment of two cognitive domains and these deficits significantly interfere with the ability of the patient to function at work or at home. Disease progression varies, but women, patients with memory loss as part of their MCI (also called amnestic MCI), and carriers of ApoE ε4 are more likely to progress to AD.[11-13]

Treatment of AD begins with supportive care, including treatment planning, caregiver education and support, care coordination, advance care planning, and referral to community-based organizations for services.[14] Non-pharmacologic treatments include physical activity and behavioral strategies to ameliorate neuropsychiatric symptoms (e.g., agitation, delusions, disinhibition), and problem behaviors (e.g., resistance to care, hoarding, obsessive-compulsive behaviors).[15,16] Additionally, avoidance of polypharmacy, elimination of non-essential medications that may impair cognition, and treatment of comorbid conditions can help manage symptoms.[14]

There are two categories of pharmacologic treatment for AD, drugs that treat symptoms, and those that are meant to slow progression (i.e., disease-modifying drugs). Drugs for treating symptoms of AD include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), and memantine, a drug that affects glutamine transmission. Cholinesterase inhibitors are indicated in mild, moderate, and severe AD, while memantine is approved for moderate-to-severe AD. These drugs, either alone or in combination, have been shown to have a modest effect on cognitive and functional symptoms of the disease without altering the underlying progression of disease.[17,18]

In June 2021, the US Food and Drug Administration (FDA) approved aducanumab (Aduhelm™, Biogen), a monoclonal antibody targeting removal of beta-amyloid, as the first treatment for AD that might modify the course of disease.[19] Aducanumab received accelerated approval based on its ability to remove beta-amyloid,[4] despite inconclusive clinical trial results on its ability to slow cognitive decline in these populations.[6] Since approval, some more evidence on aducanumab has become available.

After aducanumab's approval, other monoclonal antibodies have received breakthrough designation by the FDA and two drugs, donanemab (Eli Lilly) and lecanemab (Eisai), have initiated rolling biologics license applications (BLA) with the FDA.

Donanemab is a monoclonal antibody that binds to established beta-amyloid plaques. It is administered as a monthly intravenous injection until plaque clearance is achieved or for 18 months. A BLA for accelerated approval for donanemab to treat patients with early AD was filed on October 26, 2021, with a decision expected in 2022.

Lecanemab is a monoclonal antibody that binds to beta-amyloid protofibril aggregates. It is administered intravenously biweekly or monthly. A BLA for accelerated approval for lecanemab to treat patients with early AD was filed on September 21, 2021, with a decision expected in 2022.

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, payers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public, as well as ICER's prior review on aducanumab.[7]

In response to feedback on the draft scope, we clarified inclusion criteria to specify that only patients with evidence of beta-amyloid deposition will be included, added caregiver outcomes to the patient-important outcomes section, added treatment planning to the list of supportive care that should be provided to patients and caregivers upon diagnosis, and clarified the list of biomarker outcomes to be considered during the review. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of beta-amyloid treatments for AD.

Patients and patient groups emphasized the following issues: the underdiagnosis of AD, the lack of cohesive care after diagnosis, outcomes other than cognition and function that are important to patients and their caregivers that may not be reflected in clinical trial outcome measures, and the impact of AD on the caregiver. The disproportionate impact of AD on underrepresented populations, particularly the African American and Hispanic populations, and lack of representation of those populations in clinical trials was also highlighted as a concern. Finally, the uncertainty about clinical benefits as well as insurance coverage of aducanumab were mentioned as potential barriers to widespread uptake of the anti-amyloid therapy.

Many people with dementia lack a diagnosis or are not aware of their diagnosis.[20] For those who are diagnosed with AD, patient groups described that many patients and their families do not receive adequate counseling about how to navigate the disease at the time of diagnosis. Care at diagnosis should include comprehensive care planning (e.g., functional assessment, review of current medications for high-risk medications, evaluation of home safety, caregiver needs, etc.), linkage to social services, management of comorbidities, treatment planning, information on participation in clinical trials, and discussions about end-of-life care.

The main goal of patients and caregivers is to maintain cognition and function or slow decline as long as possible, rather than prolong length of life, and they are eager for treatments that will help AD patients achieve the highest level of independent function possible and delay the need for around-the-clock care. Patients ranked emotional stability and wellbeing, preventing a "loss of self," avoiding becoming a burden on their families and caregivers, and safety as important outcomes to consider. Some patient-important symptoms are not well-captured in the outcome measures commonly used in clinical trials, and development of better measures of patient-important outcomes, particularly longitudinal measures, is an area of great need in AD.

The impact of AD on caregivers is substantial. Nearly half of all caregivers who provide care to older adults do so for someone with dementia, with women more likely to be caregivers and spend more time providing care than men. As the disease progresses and the patient loses function, caregivers take on a greater physical and emotional load. As a result, caregivers often suffer physical and mental health consequences including increased chronic health conditions, depression and isolation, and increased use of the health care system.

The approval of aducanumab as a potential disease-modifying therapy produced a lot of initial excitement in the AD community. However, the uncertainty of the clinical evidence that aducanumab slows cognitive decline despite clearing amyloid and the potential for side effects such as amyloid-related imaging abnormalities (ARIA) has tempered enthusiasm for the drug. Additionally, lack of insurance coverage – Medicare has issued a draft national coverage decision limiting use of aducanumab to clinical trials[21] and some commercial insurers have declined to cover the drug – and the drug's high cost may be affecting uptake of aducanumab. Furthermore, we heard concerns about the potential burdens (e.g., time spent on visits for treatment and monitoring, as well as obtaining insurance approval) that may be placed on patients who wish to receive aducanumab therapy, as well as their families.

Clinicians also believe that the main goal of treatment for AD is to maintain as much cognition and function as possible, and that disease-modifying drugs would be a welcome addition to the treatment arsenal. Although some clinical experts are cautiously optimistic about anti-amyloid therapies, because there have been multiple purported disease-modifying drugs – both anti-amyloid and others - that have previously failed to show benefit on clinical outcomes, others want clearer evidence demonstrating efficacy on outcomes beyond biomarkers. Additionally, they worry about the impact of beta-amyloid therapies on patients who have common comorbidities such as diabetes and hypertension, as such patients may or may not be represented in clinical trials. With respect to clinical trials, we heard from clinicians that many of the outcomes used do not reflect the full spectrum of AD symptoms and have the potential of being biased based on ceiling effects or the perceived expectations of the observer (expectancy bias).

Manufacturers highlighted the tremendous need for disease-modifying drugs to treat patients with AD, and voiced commitment to addressing racial and ethnic disparities in the diagnosis and

treatment of the disease, as well as recruitment into clinical trials. Additionally, manufacturers suggested that although much work remains to be done to develop meaningful patient-important outcome measures, incorporation of societal factors (e.g., alternative measures of patient and caregiver quality of life, non-healthcare factors) into the review would be helpful in assessing the impact of disease-modifying drugs for AD patients and their caregivers.

Report Aim

This project will evaluate the health and economic outcomes of donanemab and lecanemab for early AD and to update the evidence review for aducanumab to incorporate any new information that may have become available. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER's standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults with early AD, i.e., MCI due to AD (also termed "prodromal" Alzheimer's) and mild AD dementia with evidence of AD pathology (e.g., amyloid positivity). This population approximates patients whose condition would be categorized as Stages 3 or 4 using diagnostic criteria outlined by the FDA.[8] Evidence that includes patients in Stage 2 will only be considered if the sample also includes patients in Stage 3.

Data permitting, we will evaluate the evidence for subpopulations defined by:

- Sociodemographic factors (e.g., age, sex, race, and ethnicity)
- APOE ε4 carrier status
- Stage of disease (MCI or mild AD dementia)
- Risk of rapid/slow progression based on clinical or biomarker data
    - Baseline levels of AD pathology (e.g., beta-amyloid or tau levels)
    - Baseline scores of AD-related instruments (e.g., CDR-SB, MMSE)

Interventions

The interventions of interest for this review will be: donanemab and lecanemab, in addition to supportive care. Supportive care includes both non-pharmacologic and non-disease-modifying pharmacologic interventions. We will also include available updated evidence for aducanumab that was not covered in the previous August 2021 review[22] (please see the final report published in August 2021).

Comparators

We intend to compare anti-beta-amyloid therapies in addition to supportive care to supportive care alone.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Change in:
        - Ability to maintain independence and autonomy
        - Ability to perform activities of daily living (e.g., as measured by AD Cooperative Study-Activities of Daily Living Inventory-MCI, etc.)
        - Cognitive function (e.g., as measured by Clinical Dementia Rating, Mini-Mental State Examination, AD Composite Score, Alzheimer's Disease Assessment Scale – Cognitive Subscale, Integrated Alzheimer's Disease Rating Scale, Montreal Cognitive Assessment Test, etc.)
        - Neuropsychiatric symptoms (e.g., as measured by Neuropsychiatric Inventory Questionnaire)
    - Delayed entry into institutional care
    - Disease progression
    - Symptom progression
    - Maintenance of identity and personality
    - Quality of life

    - Emotional wellbeing
    - Caregiver impact
        - Caregiver quality of life
        - Caregiver health
        - Caregiver productivity
    - Behavioral change
    - Ability to communicate
    - Adverse events including but not limited to
        - Serious adverse events
        - Discontinuation due to adverse events
        - Infusion-related reactions
        - Death
        - Symptomatic amyloid-related imaging abnormalities (ARIA-E and ARIA-H)
- Other Outcomes
    - Level of beta-amyloid (e.g., PET, CSF)
        - Percentage of amyloid
            - Percentage reduction
            - Absolute percentage
        - Amyloid clearance
            - Mean reduction in amyloid from baseline
            - Percentage of patients reaching amyloid negativity
            - Rapidity of patients reaching amyloid negativity
        - Durability of biomarker reductions (e.g., tau levels and beta-amyloid)
    - Level of tau proteins (e.g., CSF phosphorylated tau, total tau, PET ligand)
    - Neuroinflammation
    - Brain atrophy
    - Brain volume (e.g., hippocampal volume, ventricular volume, or whole brain volume)
    - Additional biomarkers may be reviewed based on input from manufacturers and clinical experts as the review progresses.

Timing

Evidence on intervention effectiveness and evidence on harms will be derived from studies of any duration.

Settings

All relevant settings will be considered with a particular focus on the outpatient setting.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration
Acuity of need for treatment of individual patients based on the severity of the condition being treated
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

Potential Other Benefit or Disadvantage
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Health inequities
Other (as relevant)

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of interest relative to supportive care. We anticipate that we will only re-evaluate the economic impact of aducanumab if the evidence review results in a change in the evidence rating for the net health benefit of aducanumab. The model structure will be informed by ICER's model for Alzheimer's disease, key clinical trials, and other prior relevant economic models.[9-11,13,22,23] The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts, caregiver impacts, and other indirect costs will be considered in a societal perspective analysis. Given the magnitude of costs outside of the health care system due to AD, we anticipate the societal perspective analysis will be a co-base case. The target population will consist of adults with early AD, defined as MCI due to AD (also termed "prodromal" Alzheimer's) and mild AD. The model will track the severity of disease (MCI due to AD, mild AD, moderate AD, severe AD) using metrics such as the Clinical Dementia Rating–Sum of Boxes, need for long-term care, and survival. A cohort of patients will

transition between states during predetermined cycles of one year over a lifetime time horizon, modeling patients from treatment initiation until death.

A detailed economic model analysis plan with proposed methodology, model structure, parameters, sources, and assumptions is forthcoming. Key model inputs will include the effectiveness of each treatment on health state transitions, clinical probabilities (e.g., AD disease severity, need for long-term care, treatment discontinuation), quality-of-life values, and costs (e.g., health care costs, caregiving). Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using best available evidence. Quality-of-life weights will be applied to each health state representing the spectrum of AD severity and setting of care, including quality-of-life decrements for serious adverse events. The model will include costs related to drug acquisition, drug administration, drug monitoring, condition-related medical expenditures, uncompensated supportive care, long-term care, serious adverse events, and productivity changes, as data permit. Caregiver impacts (e.g., direct medical costs, quality of life, lost productivity) will be included as data suggest.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and costs. Costs and outcomes will be discounted at 3% per year. Health outcomes will be evaluated in terms of years outside of long-term care, life years, QALYs, and equal value of life years (evLYs). Relevant pairwise comparisons will be made between each treatment and supportive care, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life year gained, and cost per additional year outside of long-term care.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER Value Framework). These services are ones that would not be directly affected by anti-beta-amyloid therapies (e.g., MRI for monitoring of ARIA), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of mild cognitive impairment or mild AD beyond the potential offsets that arise from a new intervention that could be reduced, eliminated, or made

more efficient. We received a suggestion that repeated use of expensive neuropsychological testing to assess disease progression could be of low value. We plan to review with experts whether the repeated use of neuropsychological testing is common outside of clinical trials and whether such testing provides value. ICER encourages all stakeholders to continue to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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