Aducanumab for Alzheimer's Disease

Revised Background and Scope
November 18, 2020

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), accounting for up to 80% of all dementia diagnoses. AD affects an estimated 5.8 million Americans ages 65 years and older and, with the aging population in the US, by 2050, the number of people living with AD is projected to more than double.[1] Two-thirds of those diagnosed with AD are women, and there is evidence that symptoms of the disease may manifest differently in women and men, particularly with respect to neuropsychiatric symptoms.[2,3] There are racial and ethnic differences in the incidence and prevalence of AD, with higher rates noted in the African American and Hispanic populations compared with non-Hispanic white and Asian populations.[1,4] Deaths from AD have increased by almost 150% in the first two decades of the twenty-first century, making it the sixth leading cause of death in the US. Direct and indirect costs of health care related to AD are estimated to be around $500 billion annually.[5] However, the economic burden of the disease may be underestimated, as many non-medical costs such as home safety modifications, adult day care services, and adverse effects on caregiver health and productivity may not be included in cost estimates.[1]

The hallmark of AD is the progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles of phosphorylated tau protein in the brain;[6] these are believed to lead to damage and eventual death of neurons over decades. Single-gene mutations that impact beta-amyloid formation (e.g., amyloid precursor protein and presenilin) are associated with early-onset AD. Genetic variants such as the apoprotein E (ApoE) e4 allele increase one's risk of developing late-onset AD; having one copy of the gene is associated with a two to threefold increase in developing AD, while two copies of the gene may increase risk of AD by as much as 15 times.[7] Changes in the brain from accumulation of beta-amyloid plaques and neurofibrillary tangles are thought to lead to impairment in cognitive domains such as memory, language, executive function (e.g., problem-solving and completing tasks), and visuospatial function, which result in the loss of ability to perform activities of daily living (e.g., paying bills, bathing, dressing, etc.).[8] Changes in mood and personality, along with decreased or poor judgment and sleep disturbances, also occur.

As the disease progresses, patients become less and 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.[1] 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.[9]

The course of AD can be described in three phases: preclinical disease, mild cognitive impairment (MCI), and Alzheimer's dementia.[1] In the preclinical phase, patients begin to accumulate beta amyloid in the brain, but are asymptomatic. Additionally, certain biomarkers in the cerebrospinal fluid (CSF) such as increased CSF tau protein levels become apparent and imaging biomarkers such as the presence of amyloid on positron emission tomography (PET) scans may also be detected; such CSF and imaging biomarkers can be used to differentiate AD from other dementias. Over time, subtle cognitive changes begin to occur and once there is a reduction in cognitive function, MCI is diagnosed; however, at this point, the patient can still live and function independently. 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. Patients with memory loss as part of their MCI (also called amnestic MCI) are more likely to progress to AD, as are women, particularly those who are carriers of ApoE e4.[10-12]

Treatment of AD remains largely supportive, including creation and implementation of individualized dementia care plans (e.g., treatment of dementia symptoms, medication and home safety assessments, advance care planning), caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (e.g., adult day care, caregiver training, etc.).[13] 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).[14,15] Additionally, avoidance of polypharmacy and elimination of non-essential medications that may impair cognition as well as treatment of comorbid conditions can help manage symptoms.[13]

Pharmacological therapy of AD focuses on symptom management. The most commonly prescribed drugs are the cholinesterase inhibitors, including 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 be effective in stabilizing cognitive and functional symptoms of the disease.[16,17] Memantine was approved by the US Food and Drug Administration (FDA) in 2002; no new drugs targeted for treatment of AD, other than a combination pill of extended-release memantine and donepezil, have been approved since then.

To date, there have not been any disease-modifying drugs for AD that have been approved by the FDA, and many drugs targeting purported molecular pathways of AD (e.g., beta amyloid or tau proteins) have either failed in clinical trials or are still in development. Aducanumab (Biogen, Inc.), a monoclonal antibody that binds to beta amyloid, is the first disease-modifying drug to apply for approval from the FDA. A Biologics License Application was accepted for priority review on August 7, 2020, with a decision expected by March 2021.[3]

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, including patients and patient groups, clinicians, researchers, and the manufacturers of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders, open input submissions from the public, and public comments received on a prior version of the scope. 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 preventive treatments.

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, 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 mentioned as a concern.

Patient groups describe the lack of information that patients and caregivers receive about the disease after diagnosis. Many patients and their families do not receive adequate counseling about how to navigate the disease, including 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, information on participation in clinical trials, and end-of-life care. The main goal of patients and caregivers is to prolong the time the patient remains independent, rather than prolonging length of life, and they are eager for treatments that will help the patient remain independent and delay the need for around-the-clock care. Furthermore, in addition to cognition and function, patients ranked emotional stability and wellbeing, preventing a "loss of self," becoming a burden on their families and caregivers, and safety as important outcomes to consider.

The impact of AD on caregivers is substantial. Nearly half of all caregivers who provide care to older adults do so for someone with AD or dementia, with women not only more likely to be caregivers but also to spend more time providing care than men. As the disease progresses to moderate-to-severe dementia 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.

Clinicians also believe that the main goal of treatment for AD is to maintain independence, and that disease-modifying drugs would be a welcome addition to the treatment arsenal. However, because there have been multiple purported disease-modifying drugs that have previously failed during the clinical trial phase, they are cautious and feel they need clear evidence demonstrating such an effect from a new therapy.

Report Aim

This project will evaluate the health and economic outcomes of aducanumab for AD. 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 standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Data permitting, we will consider combined use of evidence in pairwise meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/; expected publication on November 25, 2020).

Populations

The population of interest for this review is adults with early AD, i.e., MCI due to AD and mild AD dementia. This population approximates patients whose condition would be categorized as Stages 2 or 3 using diagnostic criteria outlined by the FDA.[18]

Data permitting, we will evaluate the evidence for subpopulations defined by race/ethnicity, ApoE carrier status, and amnestic (vs. non-amnestic) MCI.

Interventions

The intervention of interest for this review will be aducanumab in addition to supportive care. Supportive care includes both non-pharmacologic and non-disease-modifying pharmacologic interventions.

Comparators

We intend to compare aducanumab in addition to supportive care to supportive care alone.

Outcomes

The outcomes of interest are described in the list below.

- Patient-important outcomes
    - Ability to maintain independence and autonomy
    - Delayed entry into institutional care
    - Ability to perform activities of daily living (e.g., as measured by AD Cooperative Study-Activities of Daily Living Inventory-MCI)
    - Cognitive function (e.g., as measured by Clinical Dementia Rating, Mini-Mental State Examination)
    - Symptom progression
    - Maintenance of identity and personality
    - Quality of life
    - Emotional wellbeing
    - Behavioral change
    - Ability to communicate
    - Adverse events including:
        - Discontinuation due to adverse events
        - Death
- Other outcomes
    - Caregiver impact

        - Caregiver quality of life
        - Caregiver health
        - Caregiver productivity
    - Level of amyloid beta (e.g., PET)
    - Neuroinflammation
    - Amyloid-related imaging abnormalities (ARIA-E and ARIA-H)
    - Brain atrophy
    - Level of tau proteins (e.g., CSF phosphorylated tau, PET ligand)

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. Potential Other Benefits or Disadvantages and Contextual Considerations

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute quality-adjusted life year (QALY) shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

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 aducanumab as compared to supportive care. The model structure will be based in part on a literature review of prior published models[19-22] of adults with early AD, including MCI. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs). Productivity impacts, caregiver impacts, and other indirect costs will be considered in a separate modified societal perspective scenario analysis. This modified societal perspective will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per quality-adjusted life year (QALY), and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. Given the magnitude of costs outside of the health care system due to AD, we anticipate the modified societal perspective will be a co-base case. The target population will consist of adults with early AD, defined as MCI due to AD 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 be tracked using 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. Model inputs will include clinical probabilities (e.g., AD disease severity, need for long-term care), quality-of-life values, and costs (e.g., health care costs, caregiving). 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 condition, clinical events, adverse events, and costs. Costs and outcomes will be discounted at 3% per year. Health outcomes will be evaluated in terms of years not in long-term care, life years, QALYs, and equal value of life years gained (evLYG). Relevant pairwise comparisons will be made between aducanumab and supportive care, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life year gained, and cost per additional independent (e.g., non-long-term care) year.

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

As described in its Value Assessment Framework for 2020-2023, ICER will include 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's Value Assessment Framework). These services are ones that would not be directly affected by aducanumab (e.g., reduced need for institutional care), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of early AD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient. During the public comment phase for the draft scope, we received a suggestion that more timely and accurate diagnosis could minimize the wasted care that results from missed or delayed diagnosis of AD.

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