COMMENTARY

ICER report on Alzheimer's disease: implications from a patient perspective

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Alzheimer's disease (AD) affects nearly 6 million people in the United States and is expected to affect more than 14 million people by 2060.^{1,2} The cost of caring for patients with AD was estimated to be \$305 billion in 2020 and is expected to increase to more than \$1 trillion as the population ages.¹ On June 7, 2021, the US Food and Drug Administration (FDA) approved Aduhelm (aducanumab) for the treatment of AD with mild cognitive impairment or mild dementia stage of disease through the accelerated approval pathway based on the reduction of amyloid beta plaques observed in patients treated with the drug.^{3,4} Aducanumab is administered as an intravenous infusion every 4 weeks, at a cost of \$56,000 per year.⁴ The Institute for Clinical and Economic Review (ICER) recently conducted an assessment of aducanumab for AD.⁵ This commentary focuses on the findings of the assessment and policy recommendations and their implications from a patient perspective.

ICER Report and Recommendations

The ICER assessment was conducted from a payer and a societal perspective and used the 2 identical phase 3 randomized clinical trials conducted by Biogen—ENGAGE and EMERGE. The ICER review committee unanimously found the evidence to be insufficient

to determine the net health benefit of aducanumab, given the uncertainty of benefits, and certainty that harms can occur in patients treated with aducanumab.⁵ The annual health-benefit price benchmark as determined by ICER ranged from \$3,000 to \$8,400, depending on the threshold and perspective, which subsequently means that an 85%–95% discount from the listed \$56,000 annual price would be required to reach the threshold price as set by the assessment.⁵

Several mitigating factors precluded a straightforward assessment of aducanumab. Both clinical trials randomized patients with early AD to low- or high-dose aducanumab or placebo, and the primary clinical outcome was change in the mean score on the Clinical Dementia Rating Scale–Sum of Boxes (CDR–SB). Aducanumab effectively removed beta amyloid at all doses, but both trials were terminated following a prespecified interim analysis for futility. A potential positive treatment effect was noted in the EMERGE trial, although the definition of improvement on the CDR–SB has not been solidified. Results from the ENGAGE trial failed to yield any improvement on the CDR–SB in the high-dose group when compared with placebo.⁵

Further confounding matters was the FDA's role in the regulatory process. As stated by ICER in its policy recommendations, the FDA should

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“set a clearer regulatory framework in place by specifying a threshold range for amyloid clearance that will be accepted going forward as ‘reasonably likely’ to provide patient benefit.”⁶ The FDA advisory panel that was convened voted against approval, but further deliberation by the FDA resulted in approval, not on the basis of the interpretation of the clinical outcomes data from the trials, but by pivoting and considering amyloid clearance to be a surrogate endpoint now considered “reasonably likely” to lead to a benefit. This shift was controversial since no data were ever disclosed to show the correlation of amyloid clearance with cognitive outcomes from the clinical trials, and the accelerated approval pathway was leveraged to approve

a drug in a therapeutic area where clinical outcomes measures do exist and can be measured in relatively short clinical trials.⁶

In its assessment, ICER pooled the results of the 2 trials, which under ordinary circumstances may have raised concern from a methodological perspective, but given the existing complexities underlying the trials and the interpretation of the results, this likely did not affect the final conclusions drawn by the committee. Furthermore, ICER performed sensitivity analyses and did a thorough examination of all of the evidence presented from the trials.

The cost-effectiveness of aducanumab in addition to supportive care was evaluated against supportive care alone. From a health care system perspective, the percentage of patients that could be treated before crossing the ICER potential budget impact threshold of \$819 million per year is 2.5% (approximately 35,000 of the 1.4 million AD patients eligible for treatment with aducanumab). These results prompted ICER to issue an access and affordability alert for aducanumab.⁵

Implications for Patients with AD

HEALTH DISPARITIES

Health disparities exist in the US health care system, and patients with AD are no exception. Black and Hispanic patients are 1.5 to 2 times more likely to develop AD, yet in the ENGAGE and EMERGE trials, the patient population was remarkably homogenous, since 0.6% of patients were Black and 1.5% were Hispanic.⁵ ICER faced some criticism from the public comments for using this against aducanumab, but the population of the trials only serves to highlight the disparities in treatments. The American Academy of Neurology (AAN) also echoed ICER's concerns regarding the lack of racial and ethnic diversity in the clinical trial population, given the disproportionate impact of AD on Black and Hispanic patients.

It can be surmised that the lack of diversity in the trial populations is indeed problematic, since there are potential biomarker implications in AD that may vary by ethnicity. Evidence of the magnitude of the variance is still not well defined but appears to be a consideration that could carry ramifications for different populations.⁷ Understanding amyloid clearance with aducanumab and the relationship to ethnicity could also be important from a clinical and safety perspective. ENGAGE and EMERGE combined had approximately 35% of patients who experienced amyloid-related imaging abnormalities (ARIA) that ranged in severity from asymptomatic to having to discontinue treatment.⁵ Because the trial populations were predominately White,

any differences in safety attributable to ethnicity were unlikely detected.

APPROPRIATE USE AND EXPECTATIONS FROM ADUCANUMAB TREATMENT

The population studied in the trials was one of mild cognitive impairment or mild dementia. Initially, the FDA issued blanket approval for the drug but later narrowed the scope of the approved label. The Alzheimer's Association has shown support for the FDA's narrowing of the label.⁸ ICER stated in its policy recommendations that, in order to keep patients and their families from being misled, a collaborative effort should be employed to characterize potential benefits of aducanumab for slowing the natural progression of the disease, and not as a cure or a treatment resulting in "improvement" or "return to quality of life."⁶ Given the lack of treatment options for patients with AD, patients and caregivers are desperate for a viable option, and setting realistic expectations and ensuring that patients and caregivers are grounded in the limitations and expectations from treatment with aducanumab is paramount. Some providers have expressed concern regarding the approval and use of aducanumab, and several prominent medical centers have announced that they will not currently recommend aducanumab.⁹⁻¹¹

ACCESS

Perhaps the largest hurdle facing patients with AD who may benefit from aducanumab is the annual price tag. As the AAN has pointed out in its public comments to ICER, patients with AD are likely to incur a significant amount of financial hardship given the recent trend in rising out-of-pocket costs for many neurologic medications.⁵ Traditionally, coverage determinations for Medicare are made without taking cost into consideration. For drugs covered under Part B, Medicare reimburses 106% of the average sales price (ASP). For drugs such as aducanumab, where an ASP is not available, Medicare pays 103% of the wholesale acquisition cost (WAC), which is currently \$56,000 per year for aducanumab. Based on an analysis by the Kaiser Foundation, nearly 2 million Medicare beneficiaries used 1 or more AD treatments covered under Part D in 2017. If even just a quarter of these patients are prescribed aducanumab (~500,000) at the reimbursement assumption of 103% of WAC costs, then the total spending of aducanumab in 1 year alone would be \$29 billion, which far exceeds spending on any other drug covered under Part B or Part D (for context, total Medicare spending for all Part B drugs was \$37 billion in 2019). Based on the current assumption for most Part B covered drugs and services for which Medicare pays 80% and beneficiaries are responsible for the remaining 20%, beneficiaries would

incur \$11,500 in coinsurance for 1 year of treatment with aducanumab—nearly 40% of the \$29,650 median annual income of Medicare beneficiaries in 2019.¹²

Centers for Medicare & Medicaid Services announced in July that it will conduct a National Coverage Determination (NCD) analysis for monoclonal antibodies directed against amyloids for the treatment of AD.¹³ The results of the NCD will ultimately determine how or if aducanumab is covered. The Alzheimer's Association has stated its support for the NCD, as well as a coverage with evidence development (CED).¹⁴

Summary

The lack of efficacy demonstrated in the clinical trial data coupled with the regulatory irregularities from the FDA have created a slippery slope for future approvals. The steep discount needed to reach the threshold price presents a conundrum for payers and patients with AD. The current approval of aducanumab may offer a glimmer of hope for a portion of patients with AD, but it comes with a steep price tag that patients may not be able to afford. However, it must be noted that this is the first drug targeted for AD to be approved in almost 20 years and may provide some learnings to be carried forward in the quest for future viable treatments for patients with AD.

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