In the US, 5.8 million people are currently living with Alzheimer disease (AD), and by 2050, that number may reach 16 million. Up to 15 million additional adults may have some form of mild cognitive impairment (MCI), a substantial proportion of whom will progress to AD. If costly, disease-modifying therapies come to market, Medicare could face unprecedented challenges in financing care for people with the disease. Is coverage with evidence development (CED) the financing mechanism that could help Medicare remain solvent?

Most investigational therapies are biological agents or vaccines intended to modify the course of AD by targeting formation or removal of β amyloid plaques or tau proteins. Aducanumab, a monoclonal antibody, is furthest along in the clinical pipeline. With Biogen’s recent announcement of its submission of a Biologics License Application to the US Food and Drug Administration (FDA) for approval of this therapy, aducanumab could come to market as early as 2021.

Aducanumab was evaluated in 2 identical trials—the ENGAGE and EMERGE trials—both of which were terminated when a futility analysis indicated that the primary end point would not be achieved. However, subsequent analyses demonstrated that a subset of patients in the EMERGE trial who received a higher dose of aducanumab met the primary end point and experienced a 23% reduction in cognitive decline compared with the placebo group. With limited treatment options, the FDA faces a difficult decision as it considers results from the failed ENGAGE trial, questionable efficacy in a limited population from the EMERGE trial, and concerns over adverse effects.

The cost of aducanumab is difficult to predict and will depend on the eligible treatment population. The 2 largest populations of potential aducanumab candidates are the roughly 6 million individuals with AD—approximately 3 million with mild disease, of whom 2 million have mild AD with likely amyloid burden—and the 15 million adults with MCI, 3 million of whom are estimated to have amyloid burden. However, if the FDA approves aducanumab, only those with mild disease and definitive amyloid burden are likely to benefit.

The pricing will take into account development costs and the route of administration as well. Therapies for multiple sclerosis, a disease affecting around 1 million people in the US, cost approximately $60,000 per year, and some are facility-administered, intravenous drugs similar to aducanumab. At $60,000 per year, the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab for treatment of highly prevalent hypercholesterolemia is at the low end of the price range for biological agents. It is reasonable to assume that aducanumab will be more expensive due to the complexities of administering the drug and the smaller, eligible treatment population if it is limited to people with definitive amyloid burden. Taking these factors into consideration, we estimate a $40,000 annual price tag for aducanumab. A simple, informal calculation, which assumes a minimum aducanumab market of 5 million (2 million people with mild AD and 3 million people with MCI, both with amyloid plaque burden), modest uptake of 50%, and a pricing estimate of $40,000 annually, yields direct costs of around $100 billion per year. Assuming evidence of amyloid burden is required, we can expect use of diagnostic modalities, such as amyloid positron emission tomography or cerebrospinal fluid amyloid testing, that add significant up-front expense on a per-patient basis. Once initiated, these medications would be hard to discontinue and likely will be used indefinitely; clinicians will not be able to definitively determine if the drug is effective for a given patient because the trajectory of symptoms without the drug will be unknown.
In a scenario in which an FDA-approved indication does not require evidence of amyloid plaques, 18 million adults, including 3 million patients diagnosed with mild AD and 15 million with MCI, could be eligible for aducanumab treatment. We could experience a financial impact on the health care system in excess of $360 billion annually, or nearly one-third of the $1.2 trillion spent on Medicare in 2019.

Given the high potential costs associated with either scenario, it is imperative that Medicare uses available financing tools to tie reimbursement to effectiveness. Specifically, the use of the National Coverage Determination (NCD) "significant cost threshold" paired with CED criteria would allow the medical system to learn and address the societal tension between clinical benefit and affordability.

The government recently explored these financing mechanisms during the coverage decisions for costly chimeric antigen receptor T-cell (CAR-T) therapies. It may appear there is little to be learned regarding AD financing from a cancer therapy, but CAR-T therapies could serve as a model for AD therapy coverage. CAR-T therapy spending projections represented a "significant cost" determination of at least 0.1% of the national average per-capita cost and would be reimbursed through the fee-for-service program, even for Medicare Advantage patients. While aducanumab will certainly be priced far lower than CAR-T therapies, some of which have a $500 000 price tag, it is possible that the drug's annual cost could exceed the significant cost threshold.

Furthermore, the initial draft NCD for CAR-T therapies proposed inclusion of a CED requiring all patients be enrolled in Centers for Medicare and Medicaid Services (CMS) registries with patient outcomes tracked for 2 years. The CED, coupled with the significant cost determination, allows CMS to gain greater insights into spending patterns and additional data to support decisions regarding payment models. Ultimately, CED was not required as part of CAR-T therapy's final NCD owing to a robust Risk Evaluation and Mitigation Strategy (REMS) program. However, CED for high-cost medications remains a useful but rarely used tool that should be employed more often.

As Medicare continues to transition from volume to value, it is crucial to explore and implement transformative payment initiatives, such as CED, which allow us to learn about new therapies during their early time on the market. This is particularly true for treatments for conditions with a high unmet need and/or treatments that demonstrate questionable clinical efficacy. Despite the tension between clinical effectiveness and payment, one thing is clear: Should aducanumab gain approval, our health care system will face both an opportunity and a challenge to ensure that the therapy is evaluated and used in a manner that safeguards value for patients, families, and the Medicare program.

ARTICLE INFORMATION

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REFERENCES

1. Michaud TL, Su D, Siahpush M, Murman DL. The risk of incident mild cognitive impairment and progression to dementia considering mild cognitive impairment subtypes. Dement Geriatr Cogn Dis Extra. 2017;7(1):15-29. doi:10.1159/000452486

2. Huang L-K, Chao S-P, Hu C-J. Clinical trials of new drugs for Alzheimer disease. J Biomed Sci. 2020;27(1):18. doi:10.1186/s12929-019-0609-7
3. Salloway S, Honigberg LA, Cho W, et al. Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer’s disease (BLAZE). Alzheimers Res Ther. 2018;10(1):96. doi:10.1186/s13195-018-0424-5

4. Petersen RC, Aisen P, Boeve BF, et al. Mild cognitive impairment due to Alzheimer disease in the community. Ann Neurol. 2013;74(2):199-208. doi:10.1002/ana.23931

5. Hartung DM, Bourdette DN, Ahmed SM, Whitham RH. The cost of multiple sclerosis drugs in the US and the pharmaceutical industry: too big to fail? Neurology. 2015;84(21):2185-2192. doi:10.1212/WNL.0000000000001608

6. Jackevicius CA, Choi K, Krumholz HM. Access to evidence-based statins in low-cost generic drug programs. Circ Cardiovasc Qual Outcomes. 2016;9(6):785-787. doi:10.1161/CIRCOUTCOMES.116.002985

7. Leech AA, Dusetzina SB. Cost-effective but unaffordable: the CAR-T conundrum. J Natl Cancer Inst. 2019;111(7):644-645. doi:10.1093/jnci/djy195