Challenges with new treatments for Alzheimer disease

Accelerated approval of aducanumab in the United States raises questions

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Alzheimer disease (AD) affects hundreds of thousands of Canadians and is a major cause of morbidity and mortality in our country.[1] As family physicians are keenly aware, there are no disease-modifying pharmacotherapies for AD available in Canada. Extracellular accumulation of amyloid-β plaques is felt by many to be key in the pathogenesis of AD. Aducanumab is a human amyloid-β–directed monoclonal antibody that uses a microglia-mediated phagocytic process to target and clear amyloid-β plaques found in the brains of people with AD.[2] The development of this and similar drugs has raised hopes for disease-modifying AD therapies, but its accelerated approval by the US Food and Drug Administration (FDA) in 2021 has led to substantial controversy.[3,4] The many challenges in evaluating, approving, and then safely using pharmaceuticals for AD are highlighted by the history of this agent.

Family physicians are usually the first clinicians to evaluate people with cognitive symptoms of AD and the first to be asked questions about new medications and possible advances in treatment. Many physicians have already had patients ask about aducanumab. Here we provide an overview of this agent and its current status.

Background

The manufacturer of aducanumab conducted 2 phase 3 placebo-controlled randomized trials (EMERGE and ENGAGE) that included participants aged 50 to 85 years with mild cognitive impairment (MCI) or mild dementia owing to AD who had positron emission tomography evidence of amyloid pathology in the brain.[5] It was later estimated that 91.0% of Medicare beneficiaries in the United States with dementia and 85.5% with MCI would have met 1 or more of the studies' exclusion criteria (eg, age, comorbidities, use of antiplatelet agents other than low-dose acetylsalicylic acid, use of anticoagulants).[5] Both trials were terminated early in 2019 after interim results indicated the studies were unlikely to achieve statistically or clinically significant results, but additional submitted study data and further analyses led the manufacturer to reconsider this conclusion.[6]

The results of the 2 trials were published in 2022.[6] The EMERGE trial showed statistically significant but clinically doubtful benefit at week 78 on the primary outcome measure (Clinical Dementia Rating Sum of Boxes score) in the subgroup receiving the higher-dose treatment. The ENGAGE trial failed to show this benefit. While drug approval has traditionally depended on 2 rigorous trials showing positive results, the FDA—against the advice of its own advisory committee[7]—gave accelerated approval to aducanumab for MCI and mild AD dementia primarily based on the drug's ability to remove amyloid-β plaques in the brain.[3]

The accelerated approval pathway does allow for use of a surrogate end point if it is deemed reasonably likely to predict clinical benefit. Unfortunately, the relationship between amyloid removal and improvement in clinical outcomes for those with AD is unclear. Subgroup analyses and use of surrogate outcomes have been called 2 of the "great deceivers" in clinical trial design and reporting.[8] With accelerated approval there is a requirement to conduct a postmarketing study to confirm the predicted benefits, but reliance on future confirmatory evidence is problematic for many reasons.[9] In this case, the manufacturer was given 9 years to submit its final report of the required confirmatory trial.[10]

Aside from the questionable efficacy of aducanumab, there are concerns about adverse effects. The principal adverse effect found with aducanumab has been amyloid-related imaging abnormalities (ARIA), such as edema and microhemorrhages. Among those trial participants who received higher-dose aducanumab therapy, 41.3% developed ARIA.[11] Associated symptoms (eg, headaches, confusion, dizziness, nausea) occurred in about one-quarter of those with ARIA.[11] While most cases were not deemed serious, a few fatalities potentially related to aducanumab have occurred.[12]

The studies that led to the approval of aducanumab were limited to participants with MCI or mild AD dementia who had evidence of amyloid-β deposition in the brain. Logically, use of the agent should be constrained to this target group. A magnetic resonance imaging scan should be done to look for microhemorrhages before therapy is initiated, and scans should be repeated periodically afterward to monitor for development of ARIAs.

Aducanumab is given as a monthly infusion.[3] The initial wholesale price of the drug in the United States was $56,000 (US) per year for a patient of average weight before the manufacturer announced in 2021 it was being reduced to $28,200 (US) per year.[13]

Situation in Canada

The manufacturer filed an application to Health Canada in May 2021 for approval of aducanumab. In June 2022 the

manufacturer withdrew its submission from regulatory review after Health Canada indicated the submitted data were insufficient to support marketing approval.[14]

Even if aducanumab had been approved for marketing in Canada, it is unlikely that it would have been covered by any provincial or territorial drug formulary without severe restrictions on its use. It is also clear that our health care system is not prepared for aducanumab or a similar AD medication.[15] Widespread use of aducanumab in Canada would have led to disruptive changes in the medical care of people living with AD. Its delivery would have required making substantial investments in radiology, training physicians to prescribe the drug safely, funding the increased physician services required, and augmenting infusion capacity.[16] Importantly, the setting in which this care would have been provided might also have changed. All Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia proceedings have recommended that most dementia care be provided in primary care settings.[17] It is unclear whether family physicians would feel comfortable with, or be fairly reimbursed for, prescribing and monitoring the use of drugs such as aducanumab. The potential implications of shifting a substantial portion of dementia care to memory clinics and other specialists requires careful consideration. Additional concerns include dealing with challenging ethical considerations (eg, cost of the medication and use of incomplete data to guide prescribing)[18] and weighing the relative value of investing in aducanumab or similar drugs against directing our limited financial resources toward enhancing prevention or improving continuing care. The pharmaceutical industry appears to assume that the health care system should accommodate itself to the characteristics of an AD drug rather than have the industry develop agents whose delivery is possible within the system's existing approaches and capacity. Accommodating the system to a drug based on its particular characteristics would be justifiable only if there were more impressive evidence of benefit than has been seen with aducanumab.

While the Alzheimer Society of Canada was initially "cautiously hopeful" about the possible approval of aducanumab in Canada,[19] many other reactions were negative. A group of experts on clinical dementia (including an author of this article, D.H.) representing several organizations and convened by the Canadian Consortium on Neurodegeneration in Aging discussed the available evidence to determine what advice could be offered to Health Canada. In July 2021 they agreed it would be premature to approve aducanumab for the treatment of AD.[20] A similar conclusion was reached in a commentary published in the *Canadian Medical Association Journal*.[21]

Conclusion

Clinical trials exploring the potential of various agents, including other monoclonal antibodies, to treat AD are ongoing. An efficacy study of the monoclonal antibody lecanemab was published in November 2022,[22] and the FDA granted accelerated approval of the drug for the treatment of AD in January 2023.[23] Aside from assessing the merits of these new agents, the health system considerations outlined above will also need to be reckoned with if these agents are approved and become available in Canada.

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Competing interests
None declared

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