COMMENTARY

Anti-Amyloid Therapies for Alzheimer's Disease: Not the Way Forward

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INTRODUCTION

Monoclonal antibodies targeting amyloid, including lecanemab and donanemab, have generated both considerable hope and controversy in the context of Alzheimer's disease (AD) treatment.[1] Most of the recent publications published on the topic, while raising the issues of controversial clinical effectiveness and costs, focus on the planning at the health system level needed to support widespread implementation of these potential new treatments.[2] The debate is all the more important at this time as lecanemab and donanemab are currently under review by Health Canada to assess their safety and efficacy.[3] The possible approval of these drugs would be followed by assessments and recommendations regarding public drug plan coverage by INESSS for Quebec and Canada's Drug Agency (CDA-AMC) for the other Canadian Provinces and Territories.

DISCUSSION

For over two decades, the amyloid hypothesis has guided the Alzheimer's therapeutic pipeline, despite the lack of compelling evidence that amyloid plaques are sufficient to induce late-onset, sporadic AD.[4] Several previous clinical trials with successful amyloid-reduction strategies did not stop ongoing clinical deterioration, and the same can be said for lecanemab and donanemab.[5] This discrepancy between amyloid removal and ongoing neurodegeneration provides a strong argument that amyloid accumulation plays a more peripheral role than what is generally believed by proponents of the amyloid cascade hypothesis, and casts a serious doubt on the value of amyloid-based therapies in AD.[6] Indeed, the clinical syndrome of Alzheimer's disease is a complex and multifaceted entity, most often explained by multiple disease processes in elderly patients.[7]

Lecanemab and donanemab received regulatory approval—as well as approval for reimbursement—only in the United States and Japan. These drugs have yet to be approved for reimbursement in the vast majority of European countries in spite of the fact that, after an initial rejection of both molecules, the European Medicines Agency (EMA) has recently reversed its position, recommending regulatory approval under a "controlled access program" for lecanemab.[8] Australia has withheld approval, while the United Kingdom and China have given regulatory approval, but not reimbursement due to high risk of side effects and insufficient clinical benefit.[9]

The clinical benefit of these drugs remains indeed marginal, failing to meet the minimal clinically important difference (MCID), a value that has been previously estimated to be around 1.6 points on the Clinical Dementia Rating (CDR).[10] The main outcome of the lecanemab trial showed a difference of only 0.45 points in 18 months—less decline but still decline—on the CDR (range 0 to 18 points), and it was 0.7 points for donanemab on the same scale, similarly below the MCID. This effect is of similar magnitude when compared to the cholinesterase inhibitors, which are considered symptomatic treatments.[11] For most patients and families, the clinical benefits of these monoclonal antibodies would arguably be undetectable. The frequent designation of these two treatments as "disease-modifying" appears unfounded, based on the magnitude of their effect, and the fact that the trials have not been designed to demonstrate disease modification.[12]

Recent analyses have highlighted the substantial human and material resources necessary for administering these treatments, in addition to the cost of the drugs, including patient selection that will have to go beyond standard clinical assessment (ApoE4 genotype, a screening MRI, amyloid PET scans, or *p*-tau/Aβ42 CSF from lumbar punctures), a difficult to implement drug delivery (a visit every two weeks for lecanemab infusion with up to two-hour observation periods), and ongoing monitoring of side effects (four MRIs over the course of one year), in addition to the added burden of managing complications.[13] Such a complex care pathway would require significant resource allocations and specialized

training for health-care professionals directly and indirectly involved in Alzheimer's care. Moreover, there could be increased pressure on primary and specialty care providers, as many patients would likely seek access to these treatments, even though eligible patients are a small fraction of the total cases of AD.[14] This problem might be exacerbated by the availability of blood-based biomarker tests that could generate many false-positives in primary care.[15] In addition to the direct costs to the health-care system, important time investment and financial losses are expected to be incurred by caregivers, with the high frequency of visits to health-care facilities.[16] These large costs must be weighed against the marginal magnitude of possible clinical benefits.

Potential approval of these drugs raises important issues of equity, not only because of the high costs. Alzheimer's disease disproportionately affects individuals with lower socioeconomic status and limited educational attainment. These populations were underrepresented in clinical trials, and will face structural barriers to the specialized services required for access to monoclonal antibody therapies. A recent study of lecanemab in the US Medicare system found that early uptake of the drug was "marked by racial, ethnic, and socioeconomic disparities," with the drug being more accessible to advantaged populations.[17] As well, Canadians living in rural communities have limited access to MRI and PET scans. This highlights a critical issue: while these treatments may modestly benefit some patients, their availability may in fact exacerbate disparities in health-care access.

Additionally, the risks associated with these monoclonal antibodies are non-negligible. Approximately one-fifth of lecanemab patients and over one-third of donanemab patients have brain hemorrhages or swelling on MRI, although most are asymptomatic.[18] Furthermore, the unexplained loss of brain volume observed in patients using anti-amyloid drugs remains a significant concern.[19]

If Canadian Provinces and Territories approve reimbursement for these drugs, substantial resources would be redirected toward their use, potentially leading to significant opportunity costs. In a publicly funded system with fixed resources, rational allocation is fundamental. Without additional funding into the system, resources will be diverted away from emerging brain health promotion and prevention initiatives, which appear to have reduced the incidence of dementia. A recent study of observational cohorts showed an incidence reduction of 13% per decade in the past 25 years, in high-income countries like Canada.[20] In addition, this could limit funding for medical and social care, home care and caregiver support, as well as for research into other promising biological pathways for Alzheimer's treatment.

CONCLUSION

The search for a disease-modifying drug for Alzheimer's disease remains an ongoing challenge. In addition to optimizing preventive measures, the first priority must be to discover a treatment, or more likely a combination of treatments, that is both clinically effective and meaningful for patients. Acknowledging the complexity of this disorder beyond amyloid is essential for this to succeed.[21] The second priority is to ensure equitable access to diagnosis, management, and treatment for all Canadians, particularly those from underrepresented and underserved communities. The path forward must balance hope with rigor, addressing both the scientific and societal challenges inherent in Alzheimer's care. This discussion will take on crucial importance as drug costs are exploding in many fields of medicine, and publicly funded health-care systems around the world are struggling to meet the demands of an aging population.

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CONFLICT OF INTEREST DISCLOSURES

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