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Health system change for new therapies in Alzheimer's Disease: putting the cart before the horse?

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Alzheimer's disease is a terrible condition where new memories cannot be formed anymore, old memories disappear, and affected persons become unable to care for themselves or interact with their loved ones. Despite intensive research efforts, the therapeutic landscape for Alzheimer's Disease has remained essentially unchanged for more than 2 decades, with the only positive news stemming from prevention strategies including risk factor management (1). Symptomatic treatment with cholinesterase inhibitors remains the most common pharmacologic option, with modest efficacy, frequent side effects, and ongoing controversy regarding the magnitude of treatment effects (2). The lack of disease-modifying therapies despite more than 20 years of immunological interventions on the amyloid cascade has not prevented many investigators, and many actors of the pharmaceutical industry, to persevere on this path (3).

This led to the controversial approval of aducanumab in 2021 by the FDA, then the approval of lecanemab in 2023 in the USA (4). The former has been withdrawn from review and the latter has been under review by Health Canada since May 2023. These two monoclonal antibodies (mAb) have demonstrated small reductions in the rate of clinical decline, but did not bring to a stop the unrelenting degenerative process that leads to clinical dementia. Several other anti-amyloid mAbs like gantenerumab have shown efficacy only in reducing the amyloid burden without effect on clinical outcomes (5). Lecanemab was associated with a 0.45-point difference on a cognitive and functional scale totalling 18 points (less decline than placebo but still decline) after 18 months. This difference is statistically significant but is of debatable clinical significance. Clinicians and families would likely not detect such a difference. This modest clinical effect should be balanced with the risk of side effects. Amyloid-related imaging abnormalities (cerebral edema or microhemorrhages) were more common in the treatment group (21.5% vs. 9.5% in controls), albeit only 2.8 % of these complications were symptomatic for that trial (4). Also, reduced brain volume was found in patients who received mAb in a recent meta-analysis of 40 anti-amyloid trials, that included the lecanemab study (6). The meaning of this finding is unclear, but atrophy is generally not believed to be a marker of brain health (7). Furthermore, there is a credible body of science that support a positive, physiological role for amyloid(8).

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These considerations suggest that that mAbs targeting amyloid are better considered an interesting addition to the therapeutic landscape, rather than the breakthrough they have been claimed to represent.

In this issue, Frank et al (9) advocate for a major overhaul of the health care system to accommodate the new medications. Such an agenda may be premature. A series of changes to health systems in Canada are proposed to prepare for the large-scale application of monoclonal antibody (mAB) therapy for mild Alzheimer's disease. The selection of appropriate candidates for treatment according to the inclusion criteria of the pivotal clinical trials will be complex and expensive. They include clinical case-finding with cognitive testing in primary care, proof of abnormal levels of Alzheimer's disease biomarkers either with cerebrospinal fluid analyses or brain positron emission tomography scanning, brain MRI, and possible apolipoprotein E genotyping. Lecanemab is given as an IV infusion every 2 weeks. Close follow-up with three MRIs in the first year to monitor for possible side effects would be needed. This complex care pathway is indeed different from current clinical care. It would entail major financial costs and increased access to imaging technology that would be difficult to achieve. Current specialized memory clinics across the country would not be able to meet the expected increase in the number of patients seeking mAB therapy. The cost of the drug lecanemab is expected to be high ($26,500 USD annual cost in the USA) but this would only represent a fraction of the total cost of the care pathway. The required investment would not align with the expected clinical benefit of the drug (10).

This leads to the question of how much to change our health care system to fit the needs of mAB and how much of our limited financial resources should be channeled towards a treatment with such modest clinical effects? What will be the opportunity cost of such wide-range changes and massive spending for our publicly funded health care systems? I believe we should refrain from implementing major changes for a molecule that is minimally effective and has an unfavourable side effect profile.

Alzheimer's disease is complex syndrome involving many processes in addition to the role attributed to amyloid. Associations between the clinical phenotype of dementia and the main pathological hallmarks of Alzheimer's disease (amyloid plaques and tau neurofibrillary tangles) become less significant as patients get older and multiple pathologies become the most frequent

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correlate of clinical dementia, with synaptic and neuronal loss the presumed proximal cause of dementia (11). This raises further issues. The pharmaceutical industry has not presented detailed responder analyses of the new anti-amyloid drugs. It is highly likely that age, sex, and comorbidity profiles influence the response to these drugs, but we do not know which subgroups benefitted the most or the least. Such information is vital in computing the number needed to treat and should be required before making major decisions about the use of mAB.

In practice, assessing the contribution of different pathological processes to the cognitive impairment of an individual is challenging. How will the clinician judge the contribution of amyloid in the presence of other pathologies (12)? A recent study on the real-life application of the lecanemab trial revealed that only 8% of participants in a cognitive aging study would meet study eligibility criteria (13). This low percentage would result in a more manageable number of patients appropriate for this type of treatment in our country. It is estimated that there will likely be more than 1 million patients with Alzheimer's in Canada within the next decade(14). If approximately 8% are suitable for lecanemab and other mAB, that would represent "only" 80,000 individuals appropriate for treatment. This would still be a challenge for our health care systems but more manageable. Challenges in obtaining brain MRI and amyloid biomarkers would persist. Serum biomarkers are promising but not robust enough to be used in clinical practice at this time (15). Once available, though, there will likely be an upsurge in requests for testing by those with cognitive complaints in primary care, outside of academic or research settings. We know there will be false positives, as less than 100% of people with positive biomarkers will develop dementia during their lifetime. How much excessive anxiety or depressive symptoms will be induced by the knowledge of abnormal biomarker levels? The psychological impact of this knowledge has been studied in research settings but not in primary care (16). We can anticipate a situation where the majority (maybe more than 90%) of patients with positive biomarker results will not be eligible for these new therapies.

In conclusion, a new era has begun in Alzheimer therapeutics, but these are modest beginnings. Many patients, families and clinicians are discouraged from the lack of progress in this field, which has an impact on the reception of positive news, however modest. If eventually there is a day when we have new treatments that have more than a minimal impact on the degenerative

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processes that leads to dementia, stakeholders of our health systems will likely accept major costs in terms of financial and human resources. Unfortunately, this day has not arrived.

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