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EDITORIAL

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Monoclonal antibodies for Alzheimer disease: statistical significance vs clinical efficacy

Anticorpos monoclonais para doença de Alzheimer: significância estatística *versus* eficácia clínica

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In recent decades, monoclonal antibodies (MAbs) have dramatically shifted the treatment landscape for multiple malignant diseases, especially lymphomas and leukemias, breast cancer, and colorectal cancer.[1] This change has been so momentous that many biotechnology companies involved in MAb discovery and development are currently estimated to account for a major share of the gross domestic product of their host countries.[2]

Research on MAb therapies for Alzheimer's disease (AD), however, all of which has been based on the amyloid cascade hypothesis, does not seem to have achieved similar results. Some clinical trials carried out with crenezumab and solanezumab failed to demonstrate slowing of clinical progression of AD, causing their respective manufacturers to discontinue further development.[3,4]

The lack of efficacy of these drugs notwithstanding, the recent results of clinical trials with another drug, aducanumab – a human IgG1 MAb which selectively targets aggregated amyloid-beta (Aβ) – led to its FDA approval in June 2021 as the first-ever disease-modifying treatment for AD, specifically at the mild cognitive impairment (MCI) and mild dementia stages. Two years later, the FDA granted accelerated approval to another MAb, lecanemab; a third, donanemab, is likely to follow, with the recent publication of the TRAILBLAZER-ALZ 2 trial.[5]

TRAILBLAZER-ALZ 2 was an 18-month, double-blind, phase 3 clinical trial comparing donanemab with placebo in subjects with MCI or mild AD dementia with evidence of amyloid and tau pathology on positron emission tomography (PET). Donanemab was administered every 4 weeks, with a planned switch to placebo at week 24 or week 52 if PET scans showed sufficient amyloid clearance (which occurred in about half of patients after 12 months). The primary outcome was a change in the integrated Alzheimer Disease Rating Scale (iADRS), an integrated cognition and functionality assessment ranging from 0 to 144 points, with lower values denoting worse performance. Treatment with donanemab resulted in a statistically significant benefit on the iADRS and CDR-SB (Clinical Dementia Rating Scale – sum of boxes) scales both for low and medium levels of tau protein accumulation (as assessed by tau-PET) separately and for combined population outcomes. Overall, there was a 38.6% reduction in the risk of disease progression.

However, a more detailed analysis of this study finds methodological limitations (some openly recognized by the authors of the manuscript) that

preclude generalization of its results. For example, the massive predominance of White and non-Hispanic participants (only 2.2 to 4.1% across all groups were Black) limits generalizability of these results to countries such as Brazil. Manly and Deters draw attention to the fact that the low participation of Black patients in this study was due to the higher prevalence of cerebral microbleeds, infarcts, and white-matter disease among this population, a fact which was not reported in the study.[6]

In addition to sampling bias, major treatment-emergent adverse events (AEs) warrant adequate scrutiny from the regulatory agencies responsible for approving this drug. The frequency of AEs was substantially higher in the treatment arm, with amyloid-related imaging abnormalities (ARIA) observed in approximately 37% of patients (versus 15% in the placebo group) and at an even higher frequency among those homozygous for apolipoprotein E allele ε*4* (40.6%). Microbleeds occurred in 26.8% of the donanemab group versus 12.5% of the placebo group. Therefore, one cannot agree with the assertion that these drugs are, in fact, safe. Considering also that clinical studies suggest that allele ε*4* is associated with attenuation of dementia risk in individuals of African descent, trials with more representative samples are critically needed to investigate the risk of ARIA in Black patients.[7]

One crucial aspect of any study involving surrogate endpoints is the "clinically significant vs statistically significant" debate. The authors note that treatment with donanemab resulted in a "clinically significant" benefit, since clinical progression of the disease was slowed by more than 20%, and further argue that the scales used to measure this (iADRS and CDR-SB) are satisfactorily representative of clinical status. According to LeFort,[8] clinical significance should reflect the extent of change, whether the change makes a real difference to subjects' lives (and, in the context of AD, their caregivers' and family members' lives), how long the effect lasts, consumer acceptability, cost-effectiveness, and ease of implementation. Donanemab was associated with an average delay in disease progression of around 4 months, but the duration of follow-up was limited to 19 months. Studies with longer follow-up will surely clarify the actual clinical impact.

Another major limitation of MAb trials is their eligibility criteria, which would exclude the vast majority of patients in real life. A recent Mayo Clinic study noted that, of a sample of 237 patients with MCI or mild dementia, fewer than 10% met the inclusion and exclusion criteria for the aducanumab and lecanemab trials, with exclusions being most commonly related to other chronic conditions and neuroimaging findings.[9] Although the eligibility criteria for donanemab were not applied in this study, the inclusion rate would possibly have been greatly reduced as well.

In practice, physicians, managers, and patients and their families will need to weigh the actual benefit of treatment against limitations such as financial costs, patient quality of life versus the number of infusions, the need for frequent brain scans, and the risk of ARIA and loss of brain volume. For example, lecanemab treatment is costly, with an annual wholesale cost of about $26,500 for the drug alone, not considering infusions and MRI scans to monitor AEs.[10] ARIAs are life-threatening complications of amyloid-clearing treatments, which, in the case of lecanemab (and aducanumab as well), led to the inclusion of a boxed warning in the prescribing information recommending that serial MRI scans be performed at baseline and before the 5th, 7th, and 14th infusions of the drug.[11] One must also consider the enormous difficulty in accessing imaging modalities such as MRI and amyloid PET – the latter being essential to determine the presence of brain amyloid before treatment – in low- and middle income countries (LMICs) such as Brazil. Although amyloid status can be determined by analysis of cerebrospinal fluid, this test is also not available in the Brazilian Unified Health System or even in private clinical laboratories in many LMICs.

Discoveries made since the 2000s substantially boosted funding for research based on the amyloid hypothesis. Aβ subtypes such as Aβ*56, potentially more pathogenic than insoluble amyloid plaque, gained popularity as the likely main culprit of AD. However, many investigators were unable to prove the relevance of this protein subunit in the pathogenesis of AD, and suspicions were even raised that early research which prompted the later studies – and funding – based on this hypothesis had been forged.[12]

Brazilian regulatory agencies, such as the Brazilian Health Regulatory Agency (ANVISA, for Agência Nacional de Vigilância Sanitária) and the National Commission for the Incorporation of Technologies by the Unified Health System (CONITEC, for Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde), play a key role in evaluating MAbs for the treatment of AD, in order to ensure that these medications will provide real-world benefit to the Brazilian population. In February 2022, ANVISA refused to grant aducanumab marketing authorization, considering trial data were still limited. Therefore, trials must be conducted in Brazil to elucidate the efficacy and safety of these medications in the country. Rushing through approval could pose risks to users, the health system (public and private alike), and even the courts.

Conflict of interest statement

The authors declare no conflicts of interest.

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Author contributions

EFC: conceptualization, writing – original draft, writing – review & editing. CKS: writing – original draft, writing – review & editing. PC: writing – original draft, writing – review & editing.

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