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Editorial

[Translated article] New Alzheimer disease's treatments: Hope or disappointment

Nuevos tratamientos para la enfermedad de Alzheimer: Esperanza o desilusión

Dementia is a progressive, irreversible neurodegenerative disease that affects brain function, resulting in pathological deterioration of cognitive, behavioural and functional abilities. Alzheimer's disease (AD) is the most common form of dementia and accounts for between 60% and 80% of cases. Diagnosis is based on clinical signs—such as impaired memory, attention, executive functions, learning, and language—and is supported by complementary tests, such as imaging and plasma and cerebrospinal fluid biomarkers.[1]

In 2015, 46.8 million people worldwide were diagnosed with dementia, and this figure is estimated to rise to 131.5 million by 2050. Its prevalence ranges from 4.4% to 8.7% in the population over 60 years of age, increasing exponentially with age, with an estimated 7.7 million new cases each year.[2] A large proportion of the population remains undiagnosed and, therefore, often does not receive adequate treatment or care.[3]

Alzheimer's disease has risen exponentially in the ranking of diseases causing death, rising from 24th place in 1990 to 12th place in 2020, making it the disease with the highest exponential increase.[4] Currently, it is the fourth leading cause of death in people over 75 years of age.[2] The average survival rate is between 8 years and 12 years, although cases of progression lasting more than 20 years have been reported. This variation depends on the quality of care received, which is directly related to the healthcare system, family, and primary caregiver.[5] The pathophysiological bases of AD have been extensively studied, with the amyloid cascade hypothesis being the most well-known. Pathological metabolism leads to the accumulation of extracellular amyloid β (Aβ) plaques and intracellular abnormally phosphorylated tau protein (p-tau). The Aβ peptide is produced by the proteolytic cleavage of amyloid precursor protein (APP) through the activity of two secretases (beta and gamma), resulting in insoluble and toxic deposits within amyloid plaques.[6] The function of p-tau in the brain is to stabilise the microtubule structure of neurons. In AD, this protein undergoes hyperphosphorylation, leading to neuronal death. Several mutations in genes affecting the amyloid cascade have been described, such as those in PSEN1, PSEN2, and PPA.[6,7]

Other pathological processes and theories have been proposed to explain the pathophysiology of AD. These include the inflammatory response of the central nervous system, characterised by the overproduction of proinflammatory neurotransmitters and cytokines,[8] and mitochondrial dysfunction, which can cause oxidative damage that increases p-tau hyperphosphorylation.[9]

To date, the mainstay of pharmacological treatment has been procholinergic drugs, specifically acetylcholinesterase inhibitors (AChEIs)—donepezil, rivastigmine, and galantamine—in the mild to moderate stages of the disease, alongside memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, used in moderate to advanced stages. Although these treatments do not halt the neurodegenerative process associated with AD, they have been widely used since 1996, when donepezil was approved by the US Food and Drug Administration (FDA). These treatments have been questioned due to the mild and temporary symptomatic improvements they provide at both the functional and cognitive levels. Some public insurance companies have therefore defunded them (as is the case in France).[10]

More than 20 years have passed since memantine—the last of the available drugs—was approved by the FDA in 2003, yet the therapeutic arsenal for treating AD still fails to meet patients' needs. However, research has continued throughout these years. Among the therapeutic approaches tested, the main ones, and those supported by the strongest evidence, are drugs that aim to eliminate the production and accumulation of Aβ protein in the central nervous system.[11] This approach includes drugs that reduce the production of Aβ protein, such as semagacestat or avagacestat, which are γ-secretase inhibitors, and verubecestat, atabecestat, and lanabecestat, which are β-secretase inhibitors. However, the latter have not yielded satisfactory results and, in some cases, have even led to cognitive deterioration.[12] Another option is to increase the elimination of Aβ protein accumulations by using the following monoclonal antibodies: aducanumab, donanemab, and lecanemab. These treatments have the potential to act as disease-modifying therapies for AD and have already undergone partial or full evaluation by regulatory agencies such as the FDA and the European Medicines Agency (EMA).

Aducanumab (marketed as Aduhelm) obtained accelerated approval from the FDA in July 2021 following the EMERGE and ENGAGE[13] pivotal trials. However, the EMA denied marketing authorisation due to a lack of an established relationship between the drug's effect and clinical improvement in patients, as well as concerns regarding its safety. Donanemab (marketed as Kisunla) was approved by the FDA in October 2024 following the TRAILBLAZER-ALZ[14] pivotal trial. In March 2025, the EMA initially rejected its authorisation, pending clarification on whether a new re-evaluation will be conducted for its use under restricted conditions. Finally, lecanemab (marketed as Leqembi) was approved by the FDA in July 2023

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following the CLARITY-AD[15] pivotal trial. In July 2024, however, the EMA's CHMP committee issued a negative opinion on its use, although in November, it recommended its restricted use in patients with 1 or no copies of the *ApoE ε4* gene.[16]

Although this editorial does not aim to review the efficacy and safety of the new monoclonal antibodies or to provide a therapeutic position, we do consider it important to highlight some aspects related to the pivotal clinical trials. Firstly, the inclusion criteria focused primarily on patients with early-stage AD (early symptomatic phase), which required positron emission tomography to detect elevated levels of Aβ protein. Given these conditions, we can anticipate that not all patients would be candidates for these treatments (some patients are diagnosed at more advanced stages), and that, in addition to requiring a clinical diagnosis, complementary tests—currently not performed routinely—would be necessary. In terms of the results, the primary endpoint was the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score, which ranges from 0 to 18 points, with higher scores indicating greater severity of dementia and poorer cognitive and functional status. The results showed an average decrease of −0.39 points in the EMERGE/ENGAGE trials and −0.45 points in the CLARITY-AD trial. In the TRAILBLAZER ALZ trial, the CDR-SB score was a secondary endpoint, and a 29% decrease in decline was reported. Thus, although the outcomes were statistically favourable, their translation into real clinical improvement is debatable—especially since the follow-up period in the studies was 18 months, after which the benefit has not been clearly established. When considering the safety of these treatments, it is important to note the occurrence of amyloid-related imaging abnormalities (ARIA), which manifest as intracranial oedema and haemorrhages. The incidence of ARIA was 35% for aducanumab, 13–14% for lecanemab, and 20–31% for donanemab.[17,18] These reactions are more common in patients with more than 1 copy of the *ApoE ε4* gene, which has led the EMA to restrict use to patients with 1 or no copies of this gene. Finally, it is worth mentioning that the dropout rate was approximately 20 to 24% in the clinical trials, which is another factor to consider in relation to both the internal and external validity of the trials.

We now find ourselves in a situation in which the new drugs are either partially approved or pending approval from regulatory agencies, raising important questions about the sustainability of healthcare systems if their use is funded by the public sector. Initially, an accurate diagnosis of the cases that could benefit from their use will be essential. Furthermore, clear guidelines must be established for monitoring these patients as well as the criteria for determining when treatment can be withdrawn. In addition, given their potential for serious adverse effects, it will be more important than ever to involve patients and their carers in shared decision-making. While this situation is still unfolding in Spain, evaluation agencies such as NICE have already conducted a public consultation regarding their position, initially concluding that they do not recommend the routine use of either lecanemab or donanemab due to a lack of favourable cost-effectiveness and uncertainties in the long-term evidence and economic models.

Therefore, the new treatments for AD pose a challenge not only for all those involved in this disease—patients, carers, and professionals—but also for the sustainability of the healthcare system itself.

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