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EDITORIAL

Treatment of Alzheimer's disease: a critical appraisal

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In January 2023, the US Food and Drug Administration (FDA) approved lecanemab – an antibody medication that decreases beta amyloid protein accumulation in the brain, as a treatment for Alzheimer's disease (AD). The evidence came from a large, randomised trial of people with early AD.[1] By the end of that 18-month study, patients in the placebo group scored on average 1.66 points worse than their starting scores. The mean score of treated participants worsened by 1.21 points on a standard dementia test. Are these improvements in test scores relevant and meaningful for patients and their families?

In 2024 the National Institute for Health and Care Excellence (NICE), the authority that decides which treatments are available on the National Health Service (NHS) in the UK, rejected the drugs, lecanemab and donanemab for AD, arguing that the small benefit they may provide does not justify the large cost of providing them. However, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) has authorised use of these drugs and they can be provided for private healthcare at an approximate yearly cost of about 20,000 pounds. Their positive effects seen in clinical trials have sparked hope that newer and more effective drugs are on the horizon.

There are two major categories of drugs used to treat AD: symptomatic drugs, which treat the symptoms, and disease modifying drugs, which target the root cause. Rivastigmine, donepezil and memantine are the well-known symptomatic drugs that balance the chemical neurotransmitters, but they do not stop the progression of the disease. Drugs such as lecanemab target the amyloid build up in the brain and are thereby thought to slow or arrest the disease progression.

This article will focus on pharmacological treatment, but there is evidence that lifestyle and risk factor modification can help to prevent the cognitive decline that occurs with ageing. One of the main confirmations of success with preventive treatment of dementia was obtained from a study performed in Finland, known as FINGER, which included individuals aged 60 to 77 years with mild cardiovascular risk factors and with cognition at mean level or slightly lower than expected for age.[2] The multidomain intervention lasting two years consisted of diet, exercise, cognitive training, and vascular risk monitoring. Individuals were randomly selected to participate in the intervention group, or in the control group that received general health advice. There was less cognitive decline in the group undergoing multidomain intervention. The difference was small but statistically significant. Similar studies are being conducted in many countries around the world.[3] It is known that more than 50% of the risk factors for dementia are currently uncontrollable. Genetic factors are most likely more important than environmental ones.

Pharmacological treatment

Donepezil, rivastigmine, and galantamine are the cholinesterase inhibitors (ChEIs) we use today to treat AD symptoms. This is based on the discovery of reduced acetylcholine

activity in the cerebral cortex of patients with AD. These three drugs have a similar clinical effect, causing a slight improvement in memory and attention and have similar side effects due to the stimulation of peripheral muscarinic receptors. The treatment effect is small and does not modify the pathophysiology of the disease and the clinical progression. Hence, they are classified as drugs with a symptomatic effect.

A retrospective study from Italy compared AD patients who received ChEIs with those who did not.[4] It showed that treatment with ChEIs was associated with a slower cognitive decline and reduced mortality, after a mean follow-up of almost 8 years. Another recent retrospective study performed in Sweden included a matched cohort of 11,652 ChEI users and 5,826 nonusers and were compared with nonusers after 5 years.[5] The evolution of cognitive decline assessed by the Mini Mental State Examination (MMSE), the evolution to severe dementia (MMSE score<10), and death as outcome were investigated. ChEI use was associated with higher MMSE score at each visit and lower risk of death compared with non-users. Galantamine in this study demonstrated a significant reduction in the risk of developing severe dementia. The benefit seen in this study was modest but significant. Both studies provided class III evidence.

Another drug, memantine, which is in use, acts as a non-competitive blocker of the N-methyl-D aspartate receptor and prevents the neurotoxicity of high concentrations of glutamate that occur in the moderate and advanced phases of AD.[6] Combined use of memantine with donepezil has had a proven positive effect[7] and can prolong survival, compared with the use of donepezil or memantine alone.[8] ChEIs and memantine have been the only specific pharmacologic treatments approved for AD dementia until recently.

Recently approved treatments

Three monoclonal antibodies against the 42 amino acid β-amyloid peptide were approved by the FDA: aducanumab, lecanemab, and donanemab. The first was aducanumab, which had demonstrated using amyloid Positron Emission Tomography (PET), an effect on reducing β-amyloid protein deposits. There was a strong expectation of success. In two clinical trials EMERGE and ENGAGE, the primary outcome measure was defined as a change on the Clinical Dementia Rating Sum of Boxes (CDR-SB, an integrated scale that assesses function and cognition) from baseline to week 78.[9,10] The primary endpoint was met in only one of the two clinical trials. Aducanumab treatment produced statistically significant dose-dependent reductions in cerebrospinal fluid (CSF) p-tau levels, CSF total-tau levels, and in brain amyloid plaque, as measured by PET, at week 78. The approval of aducanumab by the FDA caused controversy throughout the scientific community because the clinical effect was small and had only been demonstrated in one of the two trials performed. Aducanumab had its production suspended by Biogen at the beginning of 2024, supposedly due to financial reasons such as poor prescribing and lack of insurance coverage. In July 2023, the FDA approved lecanemab,[11] which binds with high affinity to soluble Aβ monomers, oligomers, and protofibrils. As with aducanumab, it was possible to demonstrate a reduction in β-amyloid protein deposits with amyloid PET. However, the size of the clinical effect, also assessed by CDR-SB, was small. Scores on this scale range from 0 (absolutely normal) to 18 points (severely compromised). At the beginning of the treatment, the average score in both groups was 3.18. After 18 months, the lecanemab-treated group had an average increase in CDR-SB of 1.21 while the placebo group had an increase of 1.66. A very small but statistically significant difference.[1] Furthermore, side effects were not infrequent, the most common adverse events being infusion-related reactions, amyloid-related imaging abnormalities (ARIAs), which may present as oedema (ARIA-E) or as haemorrhage (ARIA-H) and can be serious,[12] and which also had occurred with aducanumab. Amyloid-related imaging abnormalities are more frequent when the patient is a carrier of the allele e4 of the APOE gene, mainly when it is homozygous.

Though the effect of lecanemab is small, it may be considered as proof of the theory that reducing amyloid in the brain parenchyma has an effect on cognition. This suggests that if treatment is started very early, it could prevent the progression of AD.[13] However, this is still a hypothesis, without any scientific evidence. The lecanemab data stand in contrast to the controversy surrounding the FDA approval of aducanumab (Aduhelm), the previous amyloid removing drug reported, a year earlier. The reported failure of gantenerumab, a third amyloid removing drug, also was a disappointment. Why has lecanemab worked, why was the aducanumab outcome controversial at best, and why did gantenerumab fail? In fact, the answer to these important questions is largely clear and predictable based on the disease and treatment modelling proposed by Karran and De Strooper.[14] They suggested that the rate and degree of amyloid removal matters, and that clinical benefit accrues once enough amyloid has been removed for a sufficiently long period. Lecanemab effectively removes amyloid and clearly succeeded; of the two aducanumab trials, the one showing greater amyloid removal produced some clinical benefit, whereas the one that showed less removal did not; finally, gantenerumab had disappointing amyloid removal despite its long treatment time and consistent with its non-significant clinical benefits.

Some argue that because of the small effect, this is not the way to go,[15] or that this treatment may be combined with other more effective drugs (with less side effects) in the near future. The treatment requires an intravenous infusion every 15 days, there are potentially ominous side effects, it is expensive and must have periodic monitoring with brain MRI. Also, it should not be misunderstood as a treatment for all with AD dementia,

as evidence is available only for treatment of the early stages of AD. The European Medicines Agency (EMA) recommended approval of lecanemab (Leqembi) for treating early AD in November 2024. The recommendation is for a limited population of patients who do not carry two copies of the APOE4 gene. NICE United Kingdom have not approved or are still evaluating lecanemab for clinical use in the NHS though the MHRA has licensed it for use in the UK. Countries that have approved lecanemab are the United States, China, Hong Kong, Israel, Japan, and South Korea.

In July 2024, a new monoclonal antibody against the 42 amino acid β-amyloid peptide, donanemab, was approved by the FDA. The TRAILBLAZER-ALZ 2 randomized clinical trial showed that after 76 weeks of treatment, there was an impressive reduction of amyloid deposits, evaluated by amyloid PET.[16] The primary outcome of the study was a change on a scale integrating cognitive and functional evolution (integrated AD Rating Scale-[iADRS]). There was a statistically significant effect between donanemab and placebo on this scale, but it did not reach the minimal clinically important difference. In the study, it is informed that the meaningful within-patient change should be from 5 (for patients with mild cognitive impairment (MCI) to 9 points (for patients with mild AD) on the iADRS. The mean observed differences in the study did not reach 4 points in either very mild MCI or mild AD. There was no difference between donanemab and placebo in tau PET change, which was included as a secondary outcome. This is now a relevant issue, because tau PET is the biomarker for staging AD according to the new proposed criteria.[17]

Future

There are many drugs that are being researched for the treatment of AD.[18] In the last available publication (2024), there were 164 trials assessing 127 drugs, 32 of which are in phase 3 (i.e., in the pre-submission phase for approval, if successful). It is interesting to focus on this group of 32 drugs, because they are the closest to being approved for the treatment of AD. Of these, 11 drugs target neurotransmitters/synaptic receptors, 7 the β-amyloid protein, 4 synaptic plasticity and neuroprotection; two drugs targeted neuroinflammation, 2 metabolism and bioenergy, and another two proteostasis and proteinopathies. Only one phase-3 study targeted tau protein, neurogenesis, growth factors, and circadian rhythm. Most clinical trials are focused on the initial phase of AD, in which it is believed that it is possible to act to prevent progression and to evaluate cognitive enhancing agents that could have an effect on the symptoms of cognitive decline in the MCI or dementia phases of AD.[18]

CONCLUSION

AD is a complex disorder with several risk factors of which the greatest is advancing age. A minority of subjects have genetic abnormalities in the processing of amyloid precursor protein and generation of Aβ, that occur 20 years before appearance of symptoms. The more prevalent sporadic AD is associated with the presence of the APOE4 gene and with other pathologies including metabolic syndrome, insulin resistance and cardiovascular disease. The recognition that mitochondrial dysfunction and oxidative stress accompanied by excess glial activation correlate better with neuronal damage and memory loss than the presence of Aβ in subjects with sporadic AD has led to the development and evaluation of other medications to address these factors. However, so far, either they were unable to reduce deterioration in cognitive function or their development was discontinued because of serious adverse effects. To be more effective in preventing loss of memory the drugs should be given at the stage of MCI and appropriate tests applied rather than those used in previous studies developed for subjects with AD. Their cost should not prevent them from being readily available to all who need them, and they should be administered orally, reach the brain, and be devoid of serious adverse effects.

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