Alzheimer's disease conundrum

Two approvals, but many questions remain

It is a measure of the enormous difficulties in understanding, let alone treating, Alzheimer's disease, that it took 18 years for a new therapy to receive an approval from the US Food and Drug Administration. On 7 June 2021, the FDA granted an accelerated approval to Aduhelm (aducanumab), a monoclonal antibody developed by Biogen Inc and Eisai Co Ltd, that reduced amyloid beta plaque in the brains of patients in clinical trials. Prior to this, the only approved drugs for Alzheimer's treated symptoms of the disease. The Aduhelm approval was controversial, yet the drug remains a marker for the industry.

A second monoclonal antibody treatment for Alzheimer's, Leqembi (lecanemab), also developed by Eisai, was given an accelerated approval by the FDA on 6 January 2023. Two weeks later, an application for a third, donanemab, was sent back by the FDA to the developer, Eli Lilly and Co pending answers to a number of questions. Despite these mixed results, patient groups have applauded the two approvals. The Alzheimer's Association said that while neither Aduhelm nor Leqembi are cures, they slow the progression of the disease when taken at an early stage, making it possible for individuals to live longer independently[1]. In this article, we examine these regulatory decisions in the context of what is known and not known about Alzheimer's disease, and outline some of the newer scientific approaches going forward.

Alzheimer's disease is described by the US National Institute on Aging as a brain disorder that slowly destroys memory and thinking skills. Early-onset disease can occur in a person as young as 30 years, while late-onset can show symptoms as early as the mid-60s. Alzheimer's is the most common form of dementia, which in turn affects more than 55 million people worldwide[2].

First case of pre-senile dementia

The disease is named after the German psychiatrist and neuropathologist Alois Alzheimer who is credited with reporting the first case of pre-senile dementia. In 1901, when he was working at a mental asylum in Frankfurt, he became interested in a 51-year old patient who showed an unusual loss of short-term memory. A *post mortem* examination of the brain showed that the patient's cerebral cortex was thinner than usual and included neurofibrillary tangles and amyloid plaques, previously only found in the brains of much older people. In a lecture in 1906, he described the disease that would later bear his name.

The amyloid plaques identified by Dr Alzheimer more than a century ago still constitute the main hypothesis driving research into the disease. Beta-amyloid is part of a larger amyloid precursor protein that extends from the inside of brain cells to the outside.

According to the hypothesis, the clustering of beta-amyloid disrupts communication between cells and activates immune cells which in turn triggers inflammation. This leads to the death of brain cells.

It was this theory that informed the discovery and early development of Aduhelm. Data from an early clinical trial of the monoclonal antibody, published in *Nature* in September 2016, showed that the drug reduced beta-amyloid in the brain and that this reduction was dose dependent. The results were obtained using positron emission tomography (PET)[3]. At the time, there was considerable excitement about the results. But they were not fully replicated in two later Phase 3 studies. As a consequence, Biogen and Eisai announced in March 2019 that they were stopping the trials on the recommendation of the trial's independent data monitoring committee[4]. However, according to Biogen, while data used in the interim analysis showed that one of the trials met the criteria for futility, the other showed a positive trend. Then in October 2019, the companies announced that a new analysis of a larger dataset showed that patients who received the drug demonstrated significant benefits on measures of cognition and function.

Based on discussions with the FDA, the companies said they would proceed with an application for approval. This was submitted on 8 July 2020. A subsequent meeting of an advisory committee to the FDA in November 2020 resulted in a vote not to recommend approval. However, after reviewing all the material, the agency took a different view, and on 7 June 2021 granted an accelerated approval. This was based on data showing that patients who received the treatment had a significant dose-and-time-dependent reduction in beta-amyloid plaque. By comparison, patients in the trial's control arm had no reduction in plaque. Accelerated approvals can be based on evidence from a surrogate endpoint likely to predict clinical benefit. But it requires a developer to show this clinical benefit in a follow-up clinical trial.

The Aduhelm approval was controversial. Not only did the developers come forward with a new interpretation of existing data, but the FDA's own advisory committee opposed the authorisation. Separately, the European Medicines Agency turned down the Aduhelm application on 17 December 2021. It said that, although the drug reduced beta-amyloid in the brain, the link between this effect and clinical improvement had not been established.

The second Alzheimer's drug approval came a year and a half later. This was the accelerated approval for Leqembi, a monoclonal antibody that binds to beta-amyloid protofibrils. This authorisation was based on Phase 2 data showing a reduction in plaque in Alzheimer's patients that also was confirmed by PET imaging. In a step ahead of other developers, Eisai promptly submitted a follow-up application for full US approval based on data from a Phase 3 study called Clarity AD. This study showed a significantly reduced decline on a cognitive and functional scale of 27% at 18 months compared with a placebo. A more thorough analysis of the data, however, showed an absolute difference of 0.45 points when measured by an 18-point scale called the Clinical Dementia Rating Sum of Bones (CDR-SB). Eisai has

submitted a marketing authorisation application for Leqembi in Europe and in Japan, where it has been given a priority review. A submission in China is underway.

Donanemab, the third new antibody treatment for Alzheimer's disease, is still in the regulatory queue. Lilly announced on 20 January that it had received a complete response letter from the FDA saying that there was insufficient data on patients who received the drug continuously for a minimum of 12 months. There should have been data from at least 100 patients. No other deficiencies in the application were identified. The company is currently conducting a confirmatory which will form the basis of a traditional, rather than an accelerated application. Data from this trial is expected in the second quarter of this year.

Unresolved questions

The recent drug approvals show that the FDA is prepared to accept beta-amyloid reduction as a marker for clinical benefit in Alzheimer's disease even in the most testing of circumstances. The catch is that these accelerated approvals must be backed up by solid clinical data in a follow-up study, or the drugs face withdrawal from the market. This has created momentum for developers, but it hasn't answered many basic questions about Alzheimer's disease. Is beta-amyloid the main cause of the disease, or is it a consequence? Is there a possibility that Alzheimer's is induced through a virus infection? Is there a genetic component for the disease for most patients? How early should one start medical intervention?

An illustration of the complexity of the disease is the contrasting clinical data presented in late 2022 for Leqembi and a second anti-beta-amyloid antibody drug, gantenerumab at the Clinical Trials on Alzheimer's Disease (CTAD) conference in San Francisco, US.

Eisai presented data on Leqembi, which were largely positive. Roche, on the other hand, had to explain the failure of a Phase 3 programme for the monoclonal antibody gantenerumab, which was being studied in people with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's dementia. The drug was designed to bind to aggregated forms of beta-amyloid, including oligomers, fibrils and plaques, and to activate microglia. Microglia are the immune cells of the central nervous system and they play an important role in brain infections and inflammation. At the time of analysis, the participants showed some slowing of their disease, but this was not statistically significant.

The Alzheimer's Drug Discovery Foundation issued a statement on 30 November 2022 saying that the lecanemab (Leqembi) and gantenerumab results "demonstrate why optimal treatment of Alzheimer's will require drugs that do more than clear amyloid plaques."

What are some of these non-beta-amyloid approaches? One is GV-971 (sodium oligomannate), a mixture of acidic linear oligosaccharides derived from algae which acts on the brain-microbiome connection through an inhibitory inflammation process. The goal is to prevent peripheral immune cells from invading the brain and targeting protein folding errors in brain tissue. The drug was approved in China in 2019 on the basis of a significant improvement in a word recall test called ADAS-Cog12 after four weeks of treatment. At the time, the developer, Green Valley (Shanghai) Pharmaceuticals Co Ltd, announced plans to invest $3 billion in new research on the drug, including clinical studies involving more than 2,000 participants at 200 clinical research centres in North America, Europe and the Asia-Pacific.

A second, ALZ-801 (valiltramiprosate) developed by Alzheon Inc, is an orally available prodrug that blocks the formation of soluble beta-amyloid oligomers. In mechanism of action studies, the drug blocked the formation of amyloid oligomers, suggesting effectiveness in people at the highest risk of Alzheimer's disease who are those with two copies of the APOE4 gene. The reason APOE4 increases the risk of Alzheimer's is not well understood. But the hypothesis is that it may affect lipid metabolism in brain cells[5]. According to the company, the drug has a favourable safety profile with no events of vasogenic oedema seen in trials of antibody drugs targeting amyloid plaque. The drug has received a 'fast track' designation from the FDA.

A third, ANAVEX 2-73 (blarcamesine), developed by Anavex Life Sciences Corp, is a small molecule activator of the sigma-1 receptor which is located on the endoplasmic reticulum of neurons and oligodendrocytes. The goal of the treatment is to restore neural homeostasis and promote neuroplasticity. In a presentation at the recent CTAD conference, the company said that patients treated with the drug were 84% more likely to have improved cognition, as measured by the ADAS-Cog12 word recall test, than those on a placebo.

While it will take some time before the less traditional therapies reach registration, they are being supported by an abundance of new research. These include one study on why women are more susceptible to the disease than men, and another on how hormone replacement therapy might represent an effective treatment strategy in women who are APOE4 positive.

There are many research projects underway. In our view, the approaches most likely to succeed in the future will be the ones in which the nervous system, the immune system and the vascular system are part of the therapeutic solution.

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