STAFF PERSPECTIVE

Aducanumab: The Controversial New Drug Licensed to Treat Alzheimer's Disease

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Key Points

- Alzheimer's Disease is a neurodegenerative condition that results in both cognitive and functional decline. It has a high prevalence in the developed world, accompanied by a large burden of disease.
- There are few treatment options for Alzheimer's Disease which has led to a high interest in Aducanumab, a monoclonal antibody designed by Biogen Incorporated and Eisai Corporation Limited. It selectively targets the aggregated forms of β-amyloid and decreases plaques, which is a pathological feature of Alzheimer's Disease.
- Trials of Aducanumab showed significant reductions in amyloid plaque (61%; p<0.0001] in PRIME, 59%; p<0.0001 in ENGAGE, 71%; p<0.0001 in EMERGE), but proved inconclusive when determining if there was any clinical benefit associated with this mechanism.
- These results, accompanied by various events in the history of this drug, namely its approval by the United States Food and Drug Administration through an accelerated pathway and the subsequent resignation of three panel members, has aroused controversy.

Keywords: **Aducanumab, Alzheimer's Disease**

Introduction

Alzheimer's Disease is a neurodegenerative condition associated with cognitive and functional decline, largely involving memory, visuospatial aptitude, language, and executive functioning. With an insidious onset, the condition often presents after the age of 65 years, and accounts for around two-thirds of all dementias[1]. Its already high prevalence in the developed world, with an estimated 5.5 million currently living with diagnosis of Alzheimer's Disease in the US, is believed to rise significantly by 2050. Furthermore, being the sixth-leading cause of death in the US, with an average life expectancy of four to eight years and estimated economic cost of $259 billion[2], the burden of the condition is great. Despite this, Alzheimer's Disease has no cure. Therefore, the proposition of any new treatment is the subject of much interest.

In 2020, aducanumab set the medical community ablaze for its potential to be the first medication for Alzheimer's Disease approved by the United States Food and Drug Administration (FDA) in 18 years. On June 7th 2021, that potential became a reality. Met with both delight and disapproval, the drug was passed through an unconventional, accelerated pathway as compared to the more traditional pathway used for most other drugs, a decision taken by the FDA owing to the potential benefits that the drug could contribute to those diagnosed with a disease that has no current cure. However, questions relating to the efficacy and safety of aducanumab, supported by the subsequent resignation of three FDA advisory panel members in response to its approval[3], resulted in this drug that once stirred much interest becoming the subject of great controversy.

This review aims to clarify the events involved in development of aducanumab, the difficulties in getting approval for the drug, and what this means for its future as a treatment for Alzheimer's Disease.

What is Aducanumab?

Aducanumab, sold under the brand name Aduhelm, was developed by Biogen Incorporated (Biogen) in collaboration with Eisai Corporation Limited (Eisai Co.), as the "first and only" treatment to address a "defining pathology" of Alzheimer's Disease[4]. Aducanumab is a recombinant, fully-human IgG1 monoclonal antibody originally developed by Neurimmune and later licensed by Biogen in 2007. Neurimmune, in collaboration with the University of Zurich, had previously identified the presence of anti-amyloid antibodies in otherwise healthy individuals with slowly progressing dementia[5]. The protective function of these antibodies inspired the development of Aducanumab.

The monoclonal antibody is designed to, like these other anti-amyloid protective antibodies, enter the brain and target parenchymal β-amyloid (Aβ), reducing both soluble and insoluble Aβ in a dose-dependent manner[6]. Aβ is a fragment of amyloid precursor protein (APP) implicated by the amyloid cascade hypothesis as a prime culprit in the pathogenesis of Alzheimer's Disease[7]. This hypothesis claims that cleavage of APP by the endosomal-lysosomal pathway results in the production of an intact Aβ protein which is deposited in the brain to form plaques, leading to the formation of neurofibrillary tangles and cell death[7]. This disrupts cell-to-cell

communication and causes inflammation, resulting in damage to neuronal tissue and the subsequent presentation of cognitive decline.

Aducanumab initially proved favourable as trials removed any doubt as to its role in selectively targeting aggregated forms of Aβ to decrease plaques[6]. It was a question of whether there was any clinical benefit linked to this clearance of Aβ that led to skepticism surrounding its approval by the FDA, especially considering its original price at US$56,000 per year per patient[3], a number that far exceeds cost-efficacy despite the potential benefits aducanumab could offer[8]. Furthermore, the results of the trials appeared to align with previous studies that investigated the effects of other anti-amyloid antibodies on Alzheimer's Disease[9].

A Promising Start

While not unanimously considered to be the primary cause of Alzheimer's Disease, it is widely supported that Aβ plaques are a key pathological feature of the condition[10]. It was based on this principle that the PRIME study, phase Ib clinical trials of aducanumab, was initiated in 2012.

The study examined the effects of monthly IV infusions of 1, 3, 6, and 10 mg/kg doses of Aducanumab[6] on the levels of Aβ in patients with a clinical diagnosis of prodromal or mild Alzheimer's Disease and a positive Aβ PET scan[11]. Results showed that, following 54 weeks of therapy, the drug had an effect on reducing the levels of Aβ plaques by 61% ($p<0.0001$) in a time- and dose-dependent manner[4], particularly in the 3, 6 and 10 mg/kg dose groups, as measured by florbetapir PET imaging[11]. The results also suggested that Aβ clearance by aducanumab could potentially slow the clinical decline of an individual with Alzheimer's Disease in accordance with the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score and Mini-Mental State exam (MMSE). However, these findings were only exploratory as the PRIME trial was not designed to assess clinical outcome and further studies were required to investigate this clinical potential[6].

The primary drawback of aducanumab therapy indicated by the PRIME trial was the development of amyloid-related imaging abnormality-edema (ARIA-E). This was found to be a dose-dependent adverse effect more frequently occurring in ApoE ε4 carriers, in line with previous studies of anti-amyloid antibodies such as Bapineuzumab[12]. It presents as hyperintensity in T2-weighted sequences, observed in the parenchyma and/or leptomeninges in various regions of the brain, including the frontal, parietal, and occipital lobes[13]. Limited data on the physical manifestation of ARIA-E has led to uncertainty surrounding the potential severity of its clinical course. What data is available describes symptoms such as headaches, altered mentation, nausea, and gait disturbances.

A phase II clinical study, EVOLVE, was designed to determine the clinical significance of aducanumab-induced ARIA-E. It was commenced in December 2018, but terminated prematurely in 2019 in line with the discontinuation of phase III clinical trials (which had been going on simultaneously) following a prediction of futility[14]. EVOLVE was set to be evaluated by an independent Adjudication Committee. However, this committee had not been assembled by the time that the study, along with all other ongoing aducanumab trials, was terminated by Biogen and Eisai Co. As such, no assessment of the EVOLVE study occurred[14].

While the PRIME trial indicated a reduction in Aβ levels, and the EVOLVE study was looking set to investigate the safety of the aducanumab, the unanswered question remained as to whether a decrease in Aβ plaque slows down cognitive and functional decline in Alzheimer's Disease. This was to be determined by two large phase III clinical trials, EMERGE and ENGAGE.

EMERGE and ENGAGE

EMERGE and ENGAGE, initiated in 2015, were two identically designed trials that aimed to determine the ability of aducanumab to slow cognitive and functional decline in participants with early Alzheimer's Disease. Before aducanumab, all other trials of anti-Aβ treatments had failed to prove clinical efficacy in their larger phase III stages, despite promising results from earlier phases[15]. Therefore, the question lay in whether the EMERGE and ENGAGE studies would prove any different. To great surprise, Biogen announced in October 2019 that their EMERGE study had done just this, several months after terminating all ongoing aducanumab trials due to a prediction of futility made on the grounds that one trial was not demonstrating clinical benefit in an interim analysis, even though the other was trending positive[16].

The results of both trials were assessed based on changes from patient baseline by the CDR-SB score. A secondary outcome was to assess the effects of aducanumab on the clinical progression of the disease, as measured by MMSE, AD Assessment Scale-Cognitive Subscale (ADAS-Cog 13), and AD Cooperative Study-Activities of Daily Living Inventory for MCI (ADCS-ADL-MCI). While both studies showed a significant decrease in Aβ (59%; $p<0.0001$ in ENGAGE, 71%; $p<0.0001$ in EMERGE)[4], it was only the EMERGE trial that met its primary endpoint, that is, a slowing of cognitive and functional decline. ENGAGE, on the other hand, showed no benefit of aducanumab therapy on cognition and functioning, a result that raises doubt about the causal link between lowering Aβ levels and clinical improvement.

This difference in result was not anticipated as both were randomized, double-blind, and involved the use of a placebo. However, post-hoc analysis of the trials found that while their designs were identical, the implementation of them was not. At baseline, ENGAGE was initiated one month earlier than EMERGE[17]. Additionally, ENGAGE enrolled more participants overall, and with the introduction of protocol amendments at different stages along the timelines of each trial, discrepancies arose between them concerning the duration that patients were exposed to high-dose Aducanumab[16]. In line with this, post-hoc analysis of the ENGAGE study found that results from a subset of patients exposed to high-dose aducanumab supported the positive findings from the EMERGE trial. This difference in dose-dependent

aducanumab exposure was the variable proposed by Biogen as the critical cause of the initial failure of the ENGAGE study[16]. Furthermore, it was revealed that the placebo groups in each trial responded differently to each other, where less progression of disease was seen in the ENGAGE placebo group as compared to those in the EMERGE trial, a result most likely due to the heterogeneity of the Alzheimer's Disease phenotype[16]. Finally, the futility analysis was based only on data from 1,748 participants, rather than the full 3,285 participants[18].

Given the FDA's requirement for two positive studies to pass a treatment, aducanumab appeared to follow in the footsteps of other anti-amyloid antibodies that showed to reduce levels of amyloid deposits in phase I and II trials, but did not have a significant impact on cognitive and functional decline in phase III trials[19]. However, following Biogen's announcement to pursue approval for the drug, the results of the phase III trials were presented publicly in December 2019, during which Biogen concluded that the EMERGE trial met both its primary and secondary endpoints when using high-dose aducanumab while the ENGAGE study did not, except in a subset of patients exposed to high-dose aducanumab as revealed by the post-hoc analysis. It was here that the medical community split into those hopeful for an innovative new treatment for a high-burden disease, and those more skeptical given the initial prediction of futility.

This division became more apparent following the rejection of aducanumab by the FDA Peripheral and Central Nervous System Drugs Advisory Committee, where ten out of eleven members voted against the approval of the drug, and the last voted uncertain. Concerning this, the Advisory Committee said, "Does Study 302 (EMERGE), viewed independently and without regard for Study 301 (ENGAGE), provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's Disease?"[20]. In answer to this, they determined that the positive EMERGE study, paired with the negative ENGAGE study, resulted in "a statement of inconclusiveness"[21].

Additionally, the side effects observed in the PRIME study were evident in the phase III trials, most notably ARIA-E, along with the development of microhaemorrhages accompanied by haemosiderosis, an effect known as amyloid-related imaging abnormality-haemorrhage (ARIA-H). This was seen in 41% of participants who were treated with the highest aducanumab dose (10 mg/kg), in comparison to 10% on placebo[22]. While the majority of these cases were asymptomatic, the effects of these reactions have yet to be fully established, which further complicates the calculation of a benefit to risk ratio[23].

Resignation of FDA Panel Members

Despite the FDA requiring two positive studies to pass a treatment, in June 2021 aducanumab was approved under an accelerated pathway, granted based on evidence from clinical trials that show the effect that aducanumab has on lowering levels of Aβ, a result that is "reasonably likely" to predict slow clinical decline[4]. This unconventional approval of aducanumab by the FDA was described by George Vradenburg, Chairman and Co-Founder of UsAgainstAlzheimer's, as a "transformational breakthrough" that offers "new hope" for all those affected by the disease[4]. Others were left feeling less than enthusiastic.

Three FDA panel members resigned following this approval, all of whom were members of the FDA Peripheral and Central Nervous System Drugs Advisory Committee[3]. One member, Mayo Clinic neurologist David Knopman, explained how he felt the Advisory Committee's opinions were disregarded by the FDA's ruling on aducanumab given the strong objection delivered by the committee which was composed of experts in the fields of neurology and medicine[3]. These feelings were further amplified by the inconclusive results of both the aducanumab-related trials and those of other anti-amyloid antibodies.

Lon Schneider, Professor of Psychiatry, Neurology, and Gerontology at the Keck School of Medicine of the University of Southern California, also vocalized disapproval for the decision made by the FDA. He remarked that the existing controversy should not exist in the first place as the phase III clinical trials were never completed, instead terminated for futility before all data could be collected. As such, all subsequent discussions about Aducanumab concerned data from "incomplete" studies[21].

Schneider and Knopman have both advocated in favour of another phase III trial being carried out. The results of such a study would help to clarify whether aducanumab should be supported or rejected for the treatment of Alzheimer's Disease. They, like others who objected to the FDA's approval of aducanumab, are not opposed to the drug's potential use in the treatment of Alzheimer's Disease. Instead they are uncertain as to whether it should have been approved now, given the inconclusive results concerning its clinical benefit. As such, there is concern that its approval may cause more emotional, medical, and economic harm than good.

An Ethical Dilemma

In contrast to healthcare professionals who appear divided in opinion concerning the approval of aducanumab, patient advocacy groups have largely been supportive of the decision made by the FDA. COO of UsAgainstAlzheimer's, Russ Paulsen, has advocated in favour of patient autonomy, that being the right of a patient to make a "free and voluntary act" where correctly informed and considered to have full capacity[24]. He has stated that some patients have expressed the wish to "have that choice" and to "have a chance"[25], given that Alzheimer's Disease is a fatal condition that can have a massive impact on patients and families.

On the other hand, the ethical principle of nonmaleficence, which is described as the obligation to avoid "harm or injury to the patient" that may occur through acts of "commission or omission"[24], is seen by some to be threatened by the approval of aducanumab Joel Perlmutter, a neurologist at Washington University who was among the three Advisory Committee members

to resign, expressed concern that offering patients false hope may cause emotional harm that could have otherwise be prevented, especially given that autonomy itself is not absolute as medical professionals are not obliged to administer a certain treatment that is seen to have a negative benefit to risk ratio. He described the responsibility of the FDA and Advisory Committee to "protect these patients and families" even if at times this requires "facing difficult decisions"[25].

This ethical discussion is yet another topic of debate alongside the scientific basis of aducanumab, and one which has no simple answer.

Further Obstacles

The FDA's approval of aducanumab did not come without stipulations. The agency granted this approval on the condition that phase IV confirmatory studies be conducted with the aim of collecting "real-world" data to evaluate the long-term effectiveness and safety" of aducanumab in clinical practice[26]. Of these, the ICARE AD-US trial was terminated the following year, while the ENVISION trial was initiated in May 2022. The aim of this latter 18 month trial is to enroll around 1500 patients with early Alzheimer's Disease and confirmed Aβ pathology, with at least 18% of the participants being from Black/African American and Latino communities[27]. Biogen's decision to increase participation among previously underrepresented communities was made with the aim of better assessing the efficacy and safety of the drug when considering health disparities. This is significant given that individuals of such ethnicities are at a higher risk of developing Alzheimer's Disease than Non-Hispanic Whites[28].

A phase IIIb trial known as EMBARK, another trial required by the FDA, is a re-dosing study that aims to investigate the data from previous trials of aducanumab, particularly the phase III trials EMERGE and ENGAGE. It involves monthly administration of the highest dose assessed in these trials (10 mg/kg) for 100 weeks to patients involved in the previous trials[29]. This will allow for the assessment of the long-term tolerability and safety of aducanumab after a wash-out period, as well as its efficacy in those with more advanced Alzheimer's Disease.

Progress concerning the authorization of the marketing of aducanumab has been slower outside of the US. In a meeting of the Committee for Medicinal Products for Human Use (CHMP) in December 2021, an official announcement was made against the approval of licensing aducanumab by the European Medicines Agency (EMA). The EMA's particular concerns regarding the drug involved the dominant side effect, ARIA-E, and the lack of clarity on whether such an abnormality can be effectively monitored and managed[30]. As such, it was rejected on the grounds that any potential benefits of the drug were not shown to outweigh the risks to health. In response, Biogen Inc. asked for this decision, along with their marketing authorisation application (MAA) for aducanumab, to be re-examined[31]. They also declared their intention to obtain initial results from their confirmatory phase IV trials in 2026, five years ahead of the deadline granted to them by the FDA[32]. Just under half a year later, Biogen announced the withdrawal of their MAA[33].

In addition to this rejection by the CHMP, aducanumab's launch fell short of predictions, making third quarter sales of only $0.3 million[34]. Biogen's aducanumab also faces competition from other drugs designed to treat Alzheimer's Disease, such as donanemab, a monoclonal antibody created by Eli Lilly and Co. that also targets deposited Aβ and was granted the status of "Breakthrough Therapy" by the FDA in June 2021[35].

Where Does Its Future lie?

With the recent approval of Biogen and Eisai's lecanemab (brand name Leqembi) by the FDA in January 2023 through a similar accelerated approval pathway, any future progress that aducanumab could make may well be overshadowed[36]. As is the case with aducanumab, lecanemab is a humanized IgG1 monoclonal antibody found to decrease Aβ plaques in the brain. However, unlike its predecessor, Lecanemab proved itself to be the first drug of its kind to demonstrate a slowing of cognitive decline in the early stages of Alzheimer's Disease when compared to placebo[37]. This may potentially be explained by a difference in binding profiles to different forms of Aβ between the two drugs. Furthermore, Lecanemab is expected to cost around half of the original price of aducanumab at an estimated US$26,500[37]. However, safety risks that require further investigation may present a future obstacle for this new drug and potentially allow attention to return to aducanumab once again[37].

Despite these recent events, the development of aducanumab has evidently sparked hope that future studies might focus on the development of drugs that can treat the pre-clinical stages of dementia before the manifestation of debilitating symptoms. At the very least, the controversy has brought to light the challenges of studies concerning Alzheimer's Disease, caused by the heterogeneity of phenotypes and the influence that sex and ethnicity has on the impact of disease[21]. Lastly, it may set a precedent for the future of such research[21].

Conclusion

Alzheimer's Disease continues to be a pressing issue in the Western World due to its heavy burden, yet still there remains no cure. Despite the initial promise that aducanumab presented in this avenue, evidenced by the results of its phase I trial, the process of its development and approval since has been fraught with disagreements both between healthcare professionals as well as those outside of this sector. This has only been heightened by the question mark surrounding the validity of its phase III trials, EMERGE and ENGAGE, furthered by the subsequent resignation of three FDA panel members. More recently its reputation received a blow when its third quarter revenue fell far short of its predicted sales.

With further trials in progress, the future of aducanumab remains unclear. However, the significance that its development holds should not be underestimated. As expressed by Marwan Sabbagh, director of Cleveland

Clinic Lou Ruvo Centre for Brain Health in Las Vegas, and Jeffrey Cummings, research professor at the University of Nevada in Las Vegas, aducanumab's approval is not indicative of a cure, but is instead "the first incremental step in transforming the disease from an untreatable terminal illness to a manageable chronic disease"[38]. Having prompted further research by Biogen Inc. and other pharmaceutical companies, it represents a stepping stone to an uncertain but hopeful future for Alzheimer's Disease. ◄

Declarations

Ava Janes is a staff writer on the editorial board of the TSMJ, and was asked to contribute an invited Staff Feature to the TSMJ Volume 22. The author declares that the article was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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