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Aducanumab in Alzheimer's disease: efficacy and controversies

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Abstract

Alzheimer's disease (AD) is a leading cause of dementia, characterized by memory loss and cognitive decline. Aducanumab, a monoclonal antibody approved by the FDA in 2021, targets amyloid-beta plaques linked to AD pathogenesis. Despite its ability to reduce these plaques, aducanumab's clinical efficacy remains controversial, with mixed results from phase 3 trials. While the EMERGE trial reduced cognitive decline, the ENGAGE trial demonstrated no significant benefit. Furthermore, 41% of patients experienced amyloid-related imaging abnormalities (ARIA), raising safety concerns. Given the multifactorial nature of AD, involving tau pathology, oxidative stress, and environmental factors, a single therapeutic approach may be inadequate. Although aducanumab represents progress in AD treatment, its high cost and uncertain benefits emphasize the need for further research and development of comprehensive therapies. *(Farm Współ 2025; 18: 10-14) doi: 10.53139/FW.20251810*

Keywords: Alzheimer's disease, dementia, amyloid-beta, aducanumab

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative illnesses, responsible for 60% up to 80% of dementia cases. Its symptoms are progressive loss of memory and cognitive decline. Brain changes leading to them are thought to begin 20 years or more before these symptoms start – which makes it problematic to diagnose and treat the disease in the early stage of development when it's crucial [1]. It is estimated that in 2018 around 50 million people were suffering from AD worldwide, and this number is projected to triple by 2050 [2]. The extracellular accumulation of beta-amyloid plaques and intracellular accumulation of tau proteins, along with neurodegeneration, are essential features of AD pathogenesis [3]. Identification of abnormal levels of beta-protein and tau is possible in cerebrospinal fluid.

Aducanumab was the first monoclonal antibody and disease-modifying therapeutic agent for AD treatment, approved by the U.S. Food and Drug Administration in 2021 [4]. This decision was made based on the drug's ability to reduce beta-amyloid plaques, which is believed to correlate with clinical benefits [4]. This decision, however, didn't include evidence of clinical efficacy [4]. Additionally, there are new proofs that increasing brain amyloidosis with high levels of soluble beta-amyloid is associated with better neuropsychological and cognitive functions [5]. The above reports made us investigate aducanumab's impact on the disease.

This work aims to summarize current knowledge on the mechanism of action and safety concerns of aducanumab's use in treating AD and to explain controversies that arose after the drug's approval by the FDA. Even though the development of aducanumab was discontinued and the company abandoned it, its story shifted attention to monoclonal antibodies targeting amyloids and offered hope to patients suffering from AD [6].

This review systematically analyzed and summarized current literature on the mechanism of action, safety concerns, and clinical perspectives of aducanumab in AD. A comprehensive search was performed in PubMed, Scopus, and Web of Science databases to identify relevant peer-reviewed articles, clinical trial reports, and regulatory documents.

Molecular mechanisms

The central hypothesis explaining the mechanism of AD is amyloid-beta plaque-associated neurodegen-

eration. According to this hypothesis, the formation and deposition of plaques in various brain regions trigger an immune response, leading to inflammation. This, in turn, ultimately results in cell death and neurodegeneration [7]. Immunotherapy arose as a potential therapeutic option as amyloid beta is an attractive target for monoclonal antibodies [8]. However, effects of clinical trials varied significantly. The most probable reason is the multifactorial mechanism of AD, including many more causes than amyloid beta deposits. Another essential reason is protein tau pathology. Tau proteins are microtubular neuronal proteins, and in the described mechanism, they get hyperphosphorylated, which leads to the creation of deposits in the cytosol and an inflammatory state, causing neuronal death. The reason is mutation in the tau genes and dysregulation of kinases and phosphatases [9]. One of the main factors contributing to brain disorders is oxidative stress, which is particularly toxic to the nervous system due to its high content of metal ions and unsaturated fatty acids. Zinc, iron, copper, and manganese support neurotransmission in healthy brains and function as antioxidant agents. Their imbalance can cause oxidative stress and contribute to neurodegeneration [10]. Except for previously described factors, neurological pathologies can be caused by air pollution, smoking, and lack of physical and mental activity, which makes finding a sufficient drug for AD a challenging task.

Aducanumab is a high-affinity, recombinant, fully-human immunoglobulin G1 monoclonal antibody targeting soluble amyloid-beta deposits and insoluble fibrils [11]. It is administered in monthly infusions with a starting dose of 1mg/kg, and over 24 weeks, the dose can be increased to 10 mg/kg. The drug is labeled for treatment in patients with mild cognitive impairment [11]. Aducanumab can differentiate monomers and oligomeric or fibrillar aggregates based on weak monovalent affinity, fast binding kinetics, and strong avidity for epitope-rich aggregates. It explains the drug's low affinity to non-pathogenic monomers and higher selectivity for aggregated forms of amyloid beta [12]. Since the described drug targets only one pathological mechanism while several others of unspecified significance exist, further research is needed to assess its efficacy and safety.

Efficacy and safety of aducanumab

Alzheimer's disease is possible to detect by brain imaging and its biomarkers, and currently, there are

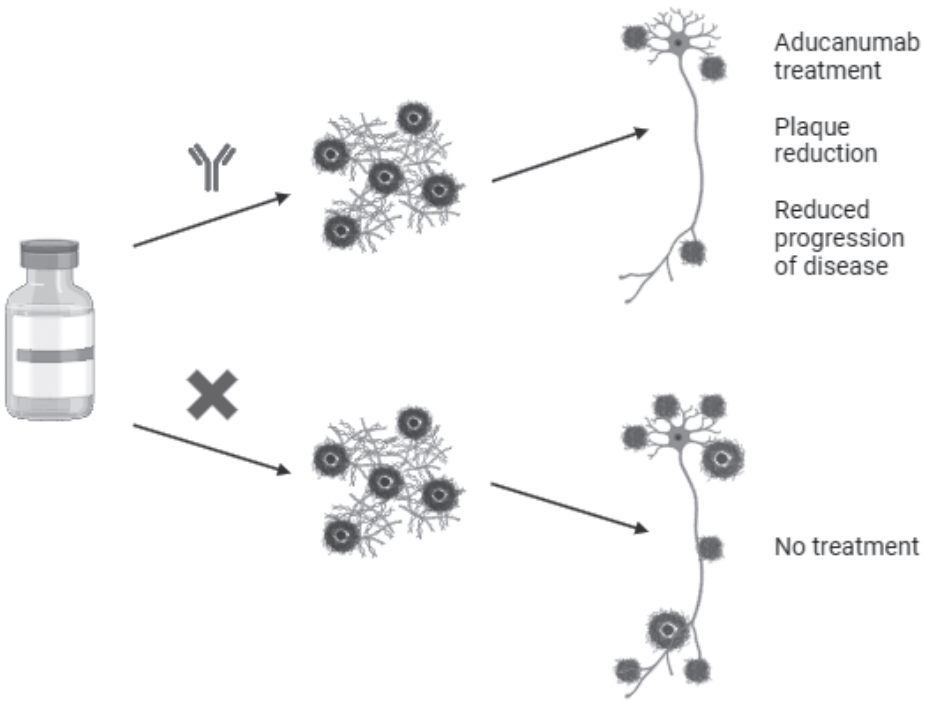

Figure 1. Potential mechanism of action of aducanumab

many more new strategies for early detection. The most crucial biomarker up to this day remains amyloid-beta, measured in blood plasma and cerebrospinal fluid (CSF). Its increased levels were associated with a higher risk of AD. However, a study conducted on mice showed that amyloid beta levels increase with age but then decrease along with the onset of amyloid beta accumulation in the brain and cognitive impairment. As the authors suggest, these differences can occur due to peptide compartmentalization in the brain, making interpretation of its level a disputable method of detecting disease early [13]. Another diagnostics method is brain imaging, including both Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), which allows tracing cerebral and amyloid metabolism [14]. PET can significantly improve diagnostic confidence and lead to diagnostic revision in almost a third of patients suffering from dementia [15]. Future biomarkers of Alzheimer's disease (AD) may include sphingolipids found in neurons and glial cells. Their blood levels are decreased in AD[16]. Summarizing, biomarkers can be grouped into those of beta-amyloid deposition – measured by the level of amyloid-beta in CSF, pathologic tau protein – defined as an elevated level of phosphorylated tau in CSF, and neurodegeneration – visible as atrophy in MRI or elevated level of total tau in CSF. Amyloid plaques and neurofibrillary tau deposits define AD as a unique neurodegenerative disease, among other causes leading to dementia [17]. Identifying new disease biomarkers is crucial and can play a significant role in earlier detection.

The first clinical trial of aducanumab started in 2011 and aimed to assess the safety profile and pharmacokinetics of the drug. A year later, in 2012, the first randomized clinical trial, PRIME, began for patients with mild cognitive impairment and amyloid-beta plaques detected through positron emission tomography. In this study, participants got 1,3,6,10 mg/kg of aducanumab once a month, and the results showed a significant reduction of amyloid-beta plaques, which was accompanied by the slowdown of cognitive impairment, classified as a possible correlation [18]. The promising results of the initial studies led to the initiation of

Table 1. Studies characteristics of aducanumab efficacy

Study ID	Phase of the study	Number enrolled	Duration of the study	Study characteristics	Clinical criteria	Result
NCT01397539	Phase 1A	53	24 weeks	Placebo-controlled; single ascending dose study	Clinically confirmed AD	Single dose up to 30 mg/kg was safe and tolerable
PRIME	Phase 1B	197	56 weeks	Placebo-controlled; multiple dose study	Prodromal or mild AD	Aducanumab decreased amyloid vale measured with PET
ENGAGE	Phase 3	1647	78 weeks	Placebo-controlled; parallel group study	Mild cognitive impairment due to AD or mild AD	Aducanumab did not significantly affect mean change in CDR-SB
EMERGE	Phase 3	1638	78 weeks	Placebo-controlled, parallel group study	Mild cognitive impairment due to AD or mild AD	Aducanumab at dose 10 mg/kg resulted in less worsening of CDR-SB
EVOLVE	Phase 2	52	52 weeks	Safety study in early AD	Mild cognitive impairment due to AD or mild AD	NA
PROPEL	Phase 1	21	42 weeks	Placebo-controlled, single and multiple ascending dose study	Mild-moderate AD	NA
EMBARK	Phase 3B	2400	104 weeks	Open label, re-dosing study	Prodromal or mild AD, Mild cognitive impairment due to AD	NA

two identical phase 3, large, multicenter, double-blind, randomized, placebo-controlled trials: the EMERGE study, which included 1,638 participants, and the ENGAGE study, which included 1,647 participants. The effects showed a 22% decrease in Clinical Dementia Rating Sum of Boxes (CDR-SB) in the EMERGE study – meaning it met the primary endpoint; however, in the ENGAGE study, there was a 2% increase in CDR-SB (2). Both studies demonstrated, however, the ability to reduce brain amyloid-beta plaques, which stood as a reason for the FDA's drug approval despite questionable results [11]. Due to controversies caused by the FDA, BioGen – the company that developed the drug, launched two independent studies in phases 3 and 3b/4 (ENVISION) that were supposed to be completed by 2026 [19,20,21]; however, due to sponsor's decision and futility analysis all clinical studies were abandoned in November 2024 as the company decided to allocate its resources into the development of different monoclonal antibodies. Taking advantage of the fact that AD is a multifactorial disease with pathophysiology based not only on brain accumulation of beta-amyloid but also on the drug's lack of spectacular activity and possible adverse effects, aducanumab stands as a controversial therapeutic option. Studies revealed that the most common adverse effects were amyloid-related imaging abnormalities (ARIA), which applied to up to 41% of patients receiving aducanumab and no patients receiving a placebo. The incidence of ARIAs increased with the drug's dose, and 7,5% of described ARIAs were symptomatic. Less common adverse effects included headache, urinary tract infection, and upper respiratory tract infection [18]. The main problem with ARIAs is the fact that they can lead to intracerebral hemorrhages. Such patients should be excluded from therapy, and all ARIAs should be monitored [22]. Additionally, up to 9% of patients receiving aducanumab experienced superficial siderosis of the central nervous system. In comparison, such a finding applies to no patient from the placebo group [18]. Contrary to the FDA decision, the European Medicines Agency recommended against granting marketing authorization due to insufficient evidence of the drug's clinical efficacy in December 2021.

Conclusions

Despite the hopes placed in aducanumab for Alzheimer's disease treatment, many factors significantly influence the onset and progression of the disease. Therefore, monotherapy based on a monoclonal antibody is insufficient, and the drug discovery strategy must be adjusted. Furthermore, there is no guidance on which patients can be treated with this drug; however, studies' participants suffered from prodromal to mild dementia. Another negative aspect is related to the costs of therapy – it was reduced in 2021 to 28 200 dollars yearly, but it's still a very high cost for the majority of people [23]. The drug is no longer available because of the company's withdrawal of the product. However, the decision was not made due to safety or efficacy but because of the reprioritization of resources. Regardless of the disadvantages described, it is clear that aducanumab reduced amyloid beta plaques, and immunotherapy in AD may be a possible treatment solution. Still, more trials are needed to assess the effectiveness of this therapy.

Conflict of interest
None

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