The progress of Aduhelm in the treatment for Alzheimer's disease (AD)

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Abstract: Alzheimer's disease is a devastating neurodegenerative disease, and the most common form of dementia. Alzheimer's disease (AD) is the leading cause of mortality in the United States, affecting 50 million people worldwide. Alzheimer's disease (AD) is characterized by the deposition of intracerebral amyloid beta (Aβ) plaques and neurofibrillary tangles accompanied by synaptic dysfunction and neurodegeneration. However, traditional treatments are limited and cannot treat the disease or relieve symptoms. In recent years, significant advances have been made in understanding its pathogenesis, diagnostic methods, and treatment of this disease. Aduhelm is an amyloid beta-directed antibody used in the treatment of Alzheimer's disease, and the first drug to be approved as a potential disease regulator. The reduction of amyloid beta plaques was utilized as an alternative endpoint in its accelerated approval. Aduhelm reduced the development of amyloid beta plaques in the brain. Clinical trials data show that Aduhelm drug is associated with significant reductions in A-PET signal in the brains of Alzheimer's disease patients. However, Aduhelm seems to reduce MMSE and CDR-SB deterioration in a dose-dependent way. Some research showed that Aduhelm decreased amyloid accumulation in six cortical regions in a dose and time dependent manner. This paper introduces the current situation of AD, briefly introduces its pathogenesis, summarizes its clinical research, and the controversy over the efficacy and/or safety of Aduhelm in Alzheimer's disease. Aduhelm may be promising drugs for a wide range of treatments in the future. This is an important step forward and this focus, attention and discussion of Alzheimer's is expected to bring about many changes.

1. Introduction

Alzheimer's disease (AD) is the biggest cause of mortality in the United States, with a global incidence of 50 million people [1]. It is defined by two neuropathological hallmarks, extracellular amyloid plaque deposition and intracellular neurofibrillary tangles, according to current knowledge. It is defined by two neuropathological hallmarks, extracellular amyloid plaque deposition and intracellular neurofibrillary tangles, according to current knowledge [2]. FDA approval of Aduhelm to lower amyloid-beta levels paves the way for more effective clinical studies and, ideally, faster approval of alternative, safe and more cost-effective anti-amyloid drugs that can be used in secondary prevention to lower beta amyloid-beta levels [3].

Aduhelm was the first drug that has been approved as a potential disease regulator. Aduhelm is an amyloid beta-directed antibody used in the treatment of Alzheimer's disease, and the alternative endpoint used in its accelerated approval is the reduction of amyloid beta plaques. This is expected to improve cognition and overall function. Moreover, Aduhelm is a human immunoglobulin γ 1(IgG 1) monoclonal antibody against aggregated soluble and insoluble amyloid β proteins. Aduhelm decreased amyloid beta plaques, according to recent studies.

However, Aduhelm may cause some serious side effects, including Amyloid Related Imaging Abnormalities or “ARIA”. ARIA is a common side effect, which usually does not cause any
symptoms, but it can be serious. Some people may also have small spots of bleeding in or on the surface of the brain with the swelling. Although most people with swelling in areas of the brain do not have symptoms, some people may have headache, confusion, dizziness, vision changes, nausea as symptoms.

In this review, we briefly introduced several aspects of AD. Firstly, Alzheimer's disease pathology shows that the disease is characterized by two neuropathological features: extracellular Aβ plaque deposition (Amyloid-β) and intracellular neurofibrillary tangles. Secondly, the clinical trials of Aduhelm show that Aduhelm drug is related to the decrease of A-PET signal in the brains of patients with Alzheimer's disease. Finally, controversy over the efficacy and/or safety of Aduhelm in Alzheimer's disease contains that after the FDA approved Aduhelm drug, this drug has been beset by a lot of controversy. Thus, it's important to mention that anti-amyloid monoclonal antibodies' effectiveness and/or safety in the treatment of Alzheimer's disease has been a point of controversy.

2. Overview Summary of AD

In 1901, Auguste Deter, a fifty-five-year-old female patient of German psychiatrist Alois Alzheimer, was identified as the first described case of a special form of dementia, which was later reported as the Alzheimer's Disease in 1907 [4]. This disease that encompassed most cases of dementia, has long occurred and thrived among geriatric patients, of which has been referred to as “chronically insane and the impoverished sick” since much earlier times. Yet, not until 1798 did people properly view the disorder as a form of sickness and for French housing center Bicêtre to remove the inhumane chains that had confined the three to four thousand “insane elderly.”

Described in Auguste Deter’s case, the woman’s symptoms began with unreasonable jealousy and evolved into memory declines, delusions, auditory hallucinations, and eventual apraxia, andagnosia. The recorded observance of “one quarter to one third” disappearance of cerebral cortical neuron and cell death-marking tangles along with the remaining neurons that contains “thick, coiled masses of fibers within their cytoplasm” spoke to Alois Alzheimer that it is perhaps a dementia disorder with unique entity [5].

Alzheimer’s Disease (AD) is a chronic and progressive neurological disorder characterized by brain cell death and brain atrophy. With high fatal rates, it ranks at the sixth in the United States and seventh in the world’s leading causes of death [6]. Yet, few effective pharmaceutical treatments are currently available for the vast number of patients worldwide. Studies in 2009 have already shown that AD affects around 6% of the population over the age of sixty-five with increasing rates parallel to age (Burns & Iliffe, 2009). Specifically, in 2021 United States, an estimated 6.2 million Americans above sixty-five are living with Alzheimers which encompass 11.3% of that population. As age increases, 13.8 and 34.6% of people between seventy-five and eighty-four and 85 and older, respectively, have Alzheimer’s [7].

Severe AD dementia in its late stages often leads to complications such as dysphagia, immobility, severe delusion, auditory hallucination, malnutrition, etc. According to United States Center of Disease Control (CDC)’s data from 2019, within the 271,872 deaths from all types of dementia, 121,499 had AD listed as the underlying cause of death, defining Alzheimer’s as “the disease or injury which initiated the train of events leading directly to death” [8]. As health awareness increased throughout the years in modern society, public reports have also shown significant growth in the number of deaths resulting from Alzheimer’s Disease between 2000 and 2009. The number of deaths with AD listed on the death certificate has increased by 145% shockingly, while other significant death causes have decreased. Specifically, -65.2%, -10.5%, and -7.3% for HIV, Stroke, and heart disease respectively [9,10]. Therefore, significant innovations must occur to overturn the tides.

Alzheimer’s Disease causes brain atrophy, and specifically, the loss of neurons of the cerebral cortex decreases intellectual functioning. Investigating the disease’s symptomatic appearances, the early-stage symptoms are most significantly characterized by the lapse of memory. Some outstanding demonstrations are forgetting conversations and events, misplacing items and repetitive questionings. Studies have shown that since the ability to think logically still prevails, the symptoms could be
purposely concealed, and forgetfulness alone results in being misinterpreted as careless and unmotivated [11].

While the previous stage lasts for about two to four years, Alzheimer’s mid-stage could extend over long periods of time. Along with progressive loss of memory, repetitive physical actions known as perseveration is also apparent. For instance, lip-licking, tapping, and chewing. Concurrently, memory loss and other intellectual-related functions aggravate without remission. Specifically, aphasia, agnosia, and apraxia progress and invade daily life at a higher rate. Patients in this stage are likely to forget their names, home address, and even time of the day. They are also reported to desire constant movements, which are often meaningless and directionless. For instance, aiming to touch everything in sight, walk both feet on a single line, move rapidly towards a destination-less direction, etc. Linguistic barriers are also increasingly demonstrated. It is likely that the patient progressively loses the ability to articulate clearly, and combined with decreased intellectual ability, struggle to finish a complete sentence [11].

Patients in the late-stage of Alzheimer’s Disease are often in primary care and have lost significant ability. External stimuli could cause catastrophic emotional swings and fears, agitation, and anxiousness for being alone is common. The patient’s daily life is completely dependent and often fails to respond to commands nor other communications. Besides inappetence, Dysphagia, a struggle to swallow, also causes the patient to experience severe malnutrition and weight loss. At this point, it is often unclear to caregivers how much the patient can comprehend and whether the patient could recognize those around them, therefore the critical comfort source from tones and facial expressions [12].

3. The pathology of AD

Current scientific knowledge claims the disease to be characterized by two neuropathological hallmarks, specifically extracellular deposition of amyloid plaques (Amyloid-β) and intracellular neurofibrillary tangles (figure 1). Different to other typical diseases, AD could develop silently without symptoms for up to 20 years, therefore causing this disease and effective medications to be even tougher to tackle and research. Previously approved medication for AD, namely Donepezil, Rivastigmine & Memantine, and Donepezil, acts only provisionally for clinical semiology of AD to bring relief to patients, but lacks the ability to challenge the progression of AD itself. Biogen Inc.’s product Aducanumab-avwa, marked as Aduhelm, was pushed through the accelerated approval pathway of FDA in June 2021. Developed to reduce the commonly observed Amyloid-β build-ups, Aduhelm has become the first and only approved medication for the progression delay of AD, serving as a milestone and the first step of a potential AD cure [13].

![Figure 1: The 3 main features of AD in the nervous system](image)

Figure 1: The 3 main features of AD in the nervous system [14]. a. Cleavage of APP, formation and accumulation of extracellular A-beta. b. Formation and deposition of intracellular NFT. c. AICD = APP intracellular structural domain.

Many molecular alterations occur in an AD patient’s brain. Firstly, often observed in AD patient’s neocortex is the Amyloid-β (Aβ) build-ups that could assemble into amyloid plaques. The Aβ structure
includes peptides ranging from 37-49 amino acids in size, whose sequence was extracted in 1984 from extracellular deposits. Initiated as monomers, as displayed in Figure 2, Aβ forms aggregation of different types, for instance oligomers, and further into protofibrils, and mature fibrils. Compared to amyloid fibrils that occur in larger forms and are insoluble, highly toxic and soluble oligomers that spread through the brain structure more easily. The mis-folded oligomers are argued, according to the Amyloid Hypothesis, to have induced more Aβ molecules to misfold, causing a chain of inflammation and intracellular deposition of tau protein. This is the crucial key to which causes AD patients to experience gradually increasing memory loss and confusion [15].

The tau protein’s abnormal accumulation is what causes so called neurofibrillary tangles. While the tau protein binds to the microtubules for support on neuron stability, AD comes with malfunctioning tau proteins to detach from microtubules and aggregates with others instead, composing threads that joins to form tangles inside neurons. Memory-involved brain sections are pictured with the complex co-occurrence of neurofibrillary tangles and Aβ, for which clumps of Aβ appear between the abnormal neurons [16].

![Figure 2. Structures of Aβ monomer, fibril, and oligomers]([17](#)).

4. The clinical trials of Aduhelm in AD

First, Aduhelm is a novel treatment for Alzheimer's disease, an antibody molecule that targets amyloid beta protein buildup in the brain, a hallmark of the disease. Significant progress has been made in finding similar alternative end targets for Alzheimer's disease. These diseases are investigated in vivo with the same accuracy as neuropathologists such as Alois Alzheimer and Eva and Heiko Braque. According to data from two randomized, placebo-controlled phase 3 trials, adman drug treatment was associated with reduced A-PET signaling in the brains of Alzheimer's disease patients. Aduhelm is also the first drug to directly target these plaques, aiming to slow disease progression in the early stages of the disease. The approval of this monoclonal antibody is the first new Alzheimer's disease treatment in two decades, and research in this area has accelerated in recent years. The drug works by preventing the formation of amyloid beta plaques in the brain, a known pathophysiological driver of neurodegeneration.

PRIME is a multicenter study that includes 166 patients with prodromal or mild Alzheimer's disease [18]. Prospective participants must score 19 or lower on the Mini-Mental State Assessment, a clinical dementia rating of 0.5 to 1, and a score of 27 or lower on the Free and Cued Selective Memory Test. Results shown that the continued development of aducanumab as a type A beta-blocking, disease-modifying therapy for Alzheimer's disease. Based on the data, 19 imaging sites sent data to a central reading cathode-ray oscilloscope using 12 different scanner types that used binary classification techniques and quantified standardized uptake value ratios in the aducanumab precursor test [19]. In addition, the first 80 individuals were scanned and 44 were found to be prodromal, 36 of whom had moderate Alzheimer's disease [20]. The visual data did not contain false positives. The scientists provided preliminary results from a phase 1b randomized, double-blind and placebo-controlled trial can Aβ is mainly caused by abnormal secretion of α, β and γ secretase enzymes, resulting in abnormal
APP hydrolysis. αβ is neurotoxic, and when its level is elevated, cells do not metabolize it, but will accumulate in large quantities in cells, forming Aβ senile plaques, prompting neuronal cell damage or death.

As a monoclonal antibody with high affinity for targeting the Aβ conformation, it binds to amyloid in the brain of Alzheimer's disease (AD) patients for ultimate clearance. The purpose of this study was to investigate the safety, tolerability, and pharmacodynamics of monthly infusions of adducanumab in people with prodromal or mild Alzheimer's disease and brain injury. Beta pathology was verified by molecular positron emission tomography PET imaging [21].

Adducanumab reduces amyloid deposition in six cortical regions in a dose- and time-dependent manner according to three studies.

ENGAGE is a large, randomized, double-blind preference study that will assess the effectiveness and long-term effects of cognitive training and cognitively stimulating leisure activity treatment. Training will be provided in 24 two-hour sessions over a four-month period. The third part of the eMERGE project is the EMERGE study, which stands for Electronic Medical Records and Genomics. The study sponsor and investigators are responsible for the safety and scientific validity of the study. The existence of a study does not mean that it has been evaluated by the U.S. government. The companies stopped the clinical trials after an analysis of the interim data from the ENGAGE and EMERGE trials for futility, which, as Biogen and Eisai put it, were "unlikely to achieve their clinical goals upon completion." When one result was that ARIA-E became more prevalent as doses and Apo 4 genotypes rose. In hindsight, almost a third of the patients were symptomatic, with mild headaches and dizziness. There were two additional exploratory indications after one year. Only doses of 1, 3 and 10 mg/kg have been reported in AD, however adducanumab appears to reduce the worsening of MMSE and CDR-SB in a dose-dependent manner.

In May 2015, a phase 1 trial began in Japan with 25 patients with mild to severe Alzheimer's disease at increasing doses of 6 mg/kg. In August 2015, two efficacy studies entered phase 3. 221 The purpose of the AD301 ENGAGE study was to enroll 1,350 individuals with MCI due to Alzheimer's disease or mild Alzheimer's disease, as determined by amyloid PET positive scan decision [22].

Biogen stated that the intermediate futility analysis was incorrect and that a broader examination of the data set showed that EMERGE had achieved its primary goal [23]. Biogen began a Phase 3b open-label study of 2,400 participants in a prior trial of adducanumab. Participants will receive monthly injections of 10 mg/kg for two years. 4 carriers and non-carriers of ApoE A statistically significant dose-dependent decrease in all brain locations was demonstrated for pre-specified areas of SUVR alteration, except for pelvic and subcortical white matter, where Aβ plaques are not expected to occur.

5. The controversy of Aduhelm's efficacy and/or safety for Alzheimer disease

It is worth noting that the efficacy and/or safety of anti-amyloid monoclonal antibodies for the treatment of Alzheimer's disease has been a source of controversy. FDA approval of Aduhelm to lower amyloid-β levels paves the way for more effective clinical trials and, ideally, more rapid approval of alternative, safe and less expensive anti-amyloid drugs that may be used in secondary prevention to lower beta amyloid-β levels.

In patients with early Alzheimer's disease, the phase 3 EMERGE study with adducanumab provided the first large-scale clinical confirmation of the scientific basis and utility of targeting amyloid [24]. Because of the growing body of data linking soluble Aβ oligomers to the development of Alzheimer's disease, it makes sense and practical to hunt for Aβ oligomer inhibitors as a future treatment for AD. The success of clinical trials can be further improved by employing therapeutic doses that block Aβ oligomers, invalidate CSF testing, and focus on APOE4 carriers at the onset of disease. More proof of efficacy is needed before these drugs may be reviewed for FDA approval [25].

For millions of people with Alzheimer's disease and their caregivers, a drug that slows the difficult progression of dementia would be groundbreaking. Guidelines for appropriate use were developed during the Alzheimer's Association Global Conference in July. Individuals with reticulocyte features should be selected, and patients with cerebral amyloid angiopathy and other cerebrovascular risk
factors should be excluded, as well as routine MRI monitoring, the researchers said. There was no control group in the form of a placebo or any other form. The study could take up to 10 years to complete.

Therapies that lower Aβ may eventually become a treatment for AD. Trials of lecanemab7 and donanemab6 have produced encouraging results, including preliminary data suggesting that the treatments have an effect on biomarkers of tau tangles, which may prove to be alternative markers for AD. However, further evidence of efficacy is needed before these drugs can be considered for FDA approval. The authors of the donanibizumab study noted that the effectiveness and safety of doniizumab in the treatment of Alzheimer's disease need further research [26].

6. Conclusions

Alzheimer's disease is fatal, and there is no available treatment. Moreover, there hasn't been a drug approved for Alzheimer's in almost 20 years. As transitional drugs and previous treatments of Alzheimer's disease did not solve any problem. Moreover, In the absence of available options, the approval of Aduhelm became a new source of optimism. Hence, the Aduhelm drug is a welcome option after decades without any actual treatment. Aduhelm drug can relieve the symptoms of AD well. As the Aduhelm drug would work best to people at an early stage of the AD disease, when it can target and destroy amyloid before it forms large sticky plaques that stiffle and damage nerves. Alzheimer's disease (AD) is a chronic and progressive neurological disorder characterized by brain cell death and atrophy, which leads in brain atrophy and, more specifically, the loss of neurons in the cerebral cortex, which reduces intellectual functioning. It is the sixth greatest cause of death in the United States and the seventh in the world, with high fatality rates. Second, Alzheimer's disease pathology identifies two neuropathological features: extracellular A plaque deposition (Amyloid-) and intracellular neurofibrillary tangles. Third, Aduhelm drug is associated with reductions in A-PET signal in the brains of individuals with Alzheimer's disease, according to data from two randomized, placebo-controlled phase III studies, such as ENGAGE and EMERGE. Although this Aduhelm drug is good, it still has some disadvantages, it has side effects, for example Although most people with swelling in areas of the brain do not have symptoms, some people may have headache, confusion, dizziness, vision changes, nausea as symptoms. Thus, the mechanism is not very clear, and has some harmful effects. Therefore, Aduhelm still needs further treatment. This report can enable clinicians to better comprehend Alzheimer's disease and medications, as well as perform clinical testing.

References


