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Aducanumab

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Abstract

Introduction and Definition: Aducanumab is "a human monoclonal antibody that selectively targets aggregated Aβ [amyloid-beta protein]". This has been used as a novel therapy for treating Alzheimer's disease (AD), as AD is characterized by an accumulation of amyloid plaques in the brain, which are proposed to lead to the cognitive decline attributed to this disease. Millions of people are impacted by this disease worldwide, highlighting its importance for research. Aducanumab was the first drug designed to bind to Aβ plaques in the brain and was approved by the U.S. Federal Drug Administration (FDA) in 2021 for treatment of AD.

Body: By binding to Aβ, aducanumab triggers microglia to phagocytose the fibrils and plaques created by the aggregation of Aβ, reducing the neuroinflammatory effects often seen in AD. Aducanumab has the highest affinity for amyloid oligomers and fibrils, which are the most detrimental structures when accumulated. Not only does aducanumab function by removing Aβ plaques, but it may also reduce neuroinflammatory cytokine production and decrease the rate of astrogliosis, both of which fluctuate depending on levels of Aβ. Patients in early or middle stages of AD, and who have been screened for Aβ levels via amyloid positron emission tomography (PET) scans, can be prescribed aducanumab by their healthcare providers. Aducanumab is administered once every month intravenously, at a dose of 10 mg/kg of body weight. Despite its ability to target and breakdown Aβ oligopeptide aggregates, significant positive effects on cognitive decline have not yet been proven. High doses of aducanumab were found to have moderate effects only in patients with early onset AD and did not show improvements for prior memory loss. Further, aducanumab treatment has been linked with amyloid-related imaging abnormalities (ARIA), a group of neurological harmful effects comprised of two main subdivisions of edema and microhemorrhages. Other pharmacological drugs are being formulated to target Aβ in a more specific manner than aducanumab, such as lecanemab. Additionally, research is further investigating the effects of holistic treatment interventions, like maintaining good physical health, on the progression of AD.

Keywords: aducanumab; Alzheimer's disease; novel treatment; amyloid-beta plaques; clinical use; amyloid-related imaging abnormalities; lecanemab

Introduction

Alzheimer's disease (AD) is a debilitating neurodegenerative disease that affects millions of lives. Over 55 million people are living with some form of dementia globally; 60-70% of these cases are classified as AD [2]. A current hypothesis surrounding the source of the neurodegeneration seen in AD is the amyloid cascade hypothesis, which proposes that the accumulation of amyloid-beta peptides (Aβ) into soluble oligomers, and later insoluble plaques and neurofibrillary tangles (NFT), causes the neurotoxic effects [3]. Further, cortical atrophy due to significant neuron loss and reduced synapse formation are additional negative features of AD [4]. It is also thought that there is a relationship between Aβ accumulation and tau protein, a microtubule stabilizing protein, leading to destabilization of microtubules in the brain [5]. Microfilaments of this hyperphosphorylated protein become twisted due to a reduced ability to stabilize microtubules, resulting in the formation of paired helical filaments; these structures are key components of NFT. As AD continues to progress, more oligomers accumulate and destabilizing events occur, resulting in the cognitive decline characteristic of AD.

Aducanumab, "a human monoclonal antibody that selectively targets aggregated Aβ", was created based on the amyloid cascade hypothesis [1]. The drug aims to alleviate AD symptoms by degrading the Aβ oligomers, therefore reducing the neurotoxic effects in the brain. Aducanumab was the first drug produced to target Aβ oligomers to combat AD progression and was granted accelerated approval by the U.S. Federal Drug Administration (FDA) for clinical use in 2021 after two phase III trials, EMERGE and ENGAGE [6].

There is currently widespread debate around the use and efficacy of aducanumab, with concern over some of the side effects [7]. Some common side effects include amyloid-related imaging abnormalities (ARIA), headaches, dizziness, and nausea [3]. Though debated over, aducanumab provides an important basis for other drugs to be designed upon by introducing the possibility of targeting Aβ as a means of slowing the rapid progression of AD symptomology.

Here, we aim to synthesize recent information regarding aducanumab with the help of an artificial intelligence platform, ChatGPT3.5, to provide a concise and current explanation of the subject.

Body

Biological Mechanism

The accumulation of Aβ plaques within the brain is initiated by the proteolytic cleavage of the amyloid precursor protein (APP) [8]. Two fragments predominate, $Aβ_{1-40}$ and $Aβ_{1-42}$, with the latter being most neurologically damaging in patients with AD. APP proteolysis also generates high quantities of N-truncated peptides; these variants promote the transition into an aggregated state while also strengthening Aβ plaque structure [9]. Aducanumab binds to soluble Aβ oligomers and insoluble Aβ fibrils with high affinity, and less so to the non-pathological Aβ monomeric form [10]. This varying selectivity is significantly influenced by the intrinsic multivalent binding that is unique to Aβ aggregates, and the specific structure of epitopes present in Aβ peptides [8]. When subjected to increased concentrations of monomeric Aβ, aducanumab exhibits increased binding affinity; the binding of multiple Aβ receptors simultaneously increases multivalent effects, hence favoring oligomeric and fibril forms of Aβ. Further, aducanumab binds a specific linear sequence of N-terminal amino acid residues on the Aβ epitope. Residues 3-7 of the Aβ peptide are the specific targets of aducanumab binding; N-terminal and C-terminal truncation experiments defined these residues and proved the significance of specific residue selectivity on antibody-binding affinity. Aducanumab has a fragment antigen-binding (Fab) region for Aβ, as well as a fragment crystallizable (Fc) region which can bind to the Fc regions on microglia. When aducanumab binds to Aβ, it recruits and binds microglia, which mediates phagocytosis of the bound Aβ plaque [11]. Furthermore, when the microglia are activated, they can release pro-inflammatory cytokines to additionally modulate and clear Aβ plaques. These biological mechanisms allow for the overall reduction of Aβ plaques in those with AD who are undergoing aducanumab treatment.

While Aβ plaques are the primary target of aducanumab, NFTs of tau proteins are indirectly affected with aducanumab treatment. Total tau (t-tau) in cerebrospinal fluid (CSF) and phosphorylated tau (p-tau) are two important biomarkers of AD; p-tau may be more indicative, as Aβ-induced NFTs exist primarily in the hyperphosphorylated form [12]. Aducanumab treatment proves significant, as the clearance of Aβ plaques induces a reduction in t-tau and p-tau levels [13]. This is due to a reduction in glycogen synthase kinase-3β (GSK3-β); its activation contributes to Aβ plaque formation and tau phosphorylation, resulting in severe cognitive decline [14]. Further research will seek to establish a clearer relationship between NFT formation induced by tau protein hyperphosphorylation and aducanumab treatment.

Administration and Dose Dependence

Prior to aducanumab administration, the patient's health must be the primary consideration. It has been established that the presence or absence of Apolipoprotein e4 (APOE4) is the most significant contributing genetic factor to AD, primarily in the later phases [15]. APOE4 contributes mainly to neuronal dysfunction, specifically astrogliosis and the formation of amyloid plaques and NFTs. Patients homozygous or heterozygous for this form of the APOE gene are not only at higher risk of developing late-onset AD, but are also more susceptible to ARIA; an individual's response to aducanumab treatment will vary based on genetic composition [16]. The presence of Aβ plaques can be confirmed via an amyloid positron emission tomography (PET) scan; varying levels of plaque formation will require varying forms of treatment. Only patients in early or middle stages of AD, characterized by mild cognitive impairment (MCI) confirmed via a PET scan, are eligible to be treated with aducanumab. Further, limited testing of aducanumab has disallowed treatment in patients with varying neurological or genetic conditions. Such conditions may contribute negatively to Aβ degradation and may exacerbate AD development, however no correlation between specific conditions and aducanumab treatments have been established.

Clinicians administer aducanumab as an intravenous infusion once every four weeks [16]. While still under examination, the recommended final dosage is 10 mg/kg. A dose of 10 mg/kg has been found to have the largest effect for slowing clinical progression of AD compared to smaller doses (1, 3, or 6 mg/kg) [1]. To ensure maximum effect, doses are increased incrementally over the 76-week testing period. Prior to the first intravenous infusion, a brain magnetic resonance imaging (MRI) scan is conducted to establish a patient baseline. The recommended first and second doses are 1 mg/kg. The third and fourth doses are 3 mg/kg, the fifth and sixth doses are 6 mg/kg, and the seventh and remaining doses are 10 mg/kg. All increases in dose are followed by an MRI scan, along with measuring vitals signs to detect any side effects, primarily ARIA.

Side Effects

As with many disease-altering drugs, aducanumab does have some safety concerns that patients and practitioners must be cognizant of before enrolling in treatment. Some of

the most common adverse effects experienced by patients on aducanumab are headaches, diarrhea, and upper respiratory tract infections [17]. Some patients may experience ARIA while undergoing treatment, but this symptom is more common with higher doses of aducanumab (≥10 mg/kg) and is often resolved within a few months of treatment [18]. Those who are APOE4 carriers have also been reported to have an increased risk of ARIA with aducanumab treatment. There are two main types of ARIA that patients undergoing aducanumab treatment can experience: ARIA edema (ARIA-E), which is characterized by proteinaceous fluid leaking through the brain, and ARIA hemosiderin (ARIA-H), which is characterized by microhemorrhages [19]. Both have been reported as side effects, but there have been more reported cases of ARIA-E with aducanumab treatment. ARIA-E can induce headaches, fatigue, confusion, differences in vision, and nausea, but can also be asymptomatic and only detectable via MRI scans. Patients undergoing treatment with aducanumab must be consistently monitored to detect these side effects, and in some cases, treatment may be reduced or stopped altogether if the side effects are having a negative impact on the patient's life. It is often recommended that patients receive MRI scans at the 5th, 7th, 9th, and 12th infusions, as ARIA commonly occurs during the titration process upon starting the aducanumab treatment [20]. There has been one suspected treatment-related death since the approval of aducanumab, but no treatment-related deaths were reported in any trial studies [21]. Overall, aducanumab has proven to be a relatively safe drug with some side effects that can be mitigated with time or withdrawal of treatment.

Recent Findings

The safety and efficacy of aducanumab was formally accessed in 2015. Two phase III trials, EMERGE and ENGAGE, were conducted amongst patients with MCI or mild AD dementia; phase III trials are designed to compare new treatments with current treatments [6]. Patients aged 50-85 were categorized into three separate groups based on their APOE4 genetic composition, and received either a high dose of aducanumab (6 mg/kg for patients APOE4+ and 10 mg/kg for patients APOE4-), a low dose of aducanumab (3 mg/kg for patients APOE4+ and 6 mg/kg for patients APOE4-), or a placebo. Patients with pre-existing mental or cognitive conditions were excluded from both trials; this was verified via MRI. All patients received their respective dose via an intravenous infusion once every four weeks over a 76-week period, in accordance with previously established administration regulations. The Clinical Dementia Rating Sum of Boxes (CDR-SB) was the primary method used to analyze the results of EMERGE and ENGAGE, while the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale-13 items (ADAS-Cog13) were used as secondary methods.

The EMERGE and ENGAGE trials were halted prematurely in 2019 for reasons of futility [22]. Biogen, the sponsor of these trials, specified that both trials were required to demonstrate positive results with aducanumab. However, interim results collected prior to trial termination had shown positive trends in the EMERGE trial, while the ENGAGE trial had shown no beneficial trends with treatment; it is unknown why the EMERGE trial was terminated. As a result, final data analysis excluded data following the futility announcement [6]. The EMERGE trial proved significant results with aducanumab treatment; patients subjected to a high dose demonstrated differences in CDR-SB and ADAS-Cog13. Contrarily, the ENGAGE trial proved no significant results; both the primary and secondary methods of testing displayed no significant differences with aducanumab treatment, regardless of dosage. EMERGE was the first phase III trial to show significantly improved cognitive ability in patients due to reduced Aβ formation from aducanumab treatment. Post hoc analysis was subsequently conducted to rationalize the significant differences in trial results [22]. While several factors were considered, the duration of exposure to the high dose of aducanumab was determined to be the most significant contributing factor; fewer participants received the high dose in the ENGAGE trial compared to the EMERGE trial. Additionally, the ENGAGE trial displayed more outliers; more participants in this trial experienced cognitive decline [23]. Due to conflicting results, conclusions regarding the efficacy of aducanumab are still under investigation. Further studies, particularly phase III trials, are needed to support or refute the results demonstrated in EMERGE and ENGAGE.

Previous studies have suggested a correlation between aducanumab treatment and Aβ plaque formation. PRIME, a phase Ib clinical trial conducted in 2012, assessed the safety and maximum tolerability of aducanumab [24]. Phase Ib trials are classified as multiple ascending dose (MAD) studies, in which multiple varying doses can be tested simultaneously to establish a maximum tolerated dose (MTD); dose escalation is closely monitored to ensure patient safety [25]. The experimental methods used in PRIME were similar to those used in EMERGE and ENGAGE: patients with MCI or mild AD participated in this randomized double-blind clinical trial. However, following the initial placebo-controlled (PC) period, in which patients were administered either a placebo or an aducanumab dose, patients could continue their participation in the study via long-term extension (LTE) [24]; patients would be guaranteed aducanumab treatment. The PRIME trial proved significant results with aducanumab treatment. The accumulation of Aβ plaques was significantly reduced over the 12-month treatment period. Reduced accumulation was also noted during the LTE period, and cognitive decline was observed at a reduced rate. However, ARIA-E was the most observable

side effect; side effects were the primary endpoint of this study, while effects on reducing Aβ plaques and clinical decline were considered exploratory. Patients APOE4+ displayed increased ARIA-E during LTE in comparison with patients APOE4-, however dose titration was found to decrease ARIA-E incidence regardless of APOE4 genetic composition. Overall, the PRIME trial proclaimed aducanumab's safety, and demonstrated 48-month efficacy; further research is needed to establish long term effects of aducanumab treatment.

A study completed in 2022 sought to further understand the effects of aducanumab on AD neuropathology. Brain tissue samples from an 84-year-old patient previously diagnosed with mild AD underwent neuropathological examination [26]. Prior to this study, the patient participated in the PC and LTE of the PRIME Ib study, and had displayed signs of cognitive and physical decline, primarily memory loss and weakened motor skills, prior to receiving aducanumab treatment. Aducanumab dose titration during LTE had proved significant; decreased amyloid plaque formation was reported via amyloid PET, and cognitive ability improved as reported by the patient's CDR-SB and MMSE scores. These results are in comparison with patients with AD who remain untreated. The brain tissue analysis performed in this study supported these results. While still observed in the neocortex and hippocampus, amyloid PET revealed a lack of Aβ plaque accumulation in the striatum. Researchers also noted a reduced accumulation of tau protein, reducing neurotoxicity and the spread of neuronal damage; hyperphosphorylation of NFT is further reduced as a result. However, Aβ immunohistochemistry assays revealed persistent neurofibrillary deterioration, although marginally reduced. While aducanumab treatment has proved positive effects, continued neuropathological research amongst varying patient conditions will contribute to current findings.

Associated and Alternative Treatments

Aducanumab has introduced the medical world to the novel idea and mechanism of targeting the Aβ plaques that are a pathological marker in AD. Before the approval of aducanumab, cholinesterase inhibitors and N-methyl-d-aspartate (NMDA) receptor antagonists, such as memantine, were the most common treatments for AD, both of which focus on relieving specific symptoms rather than altering the progression of the disease [27]. Since the development of aducanumab, other drugs have focused on targeting Aβ with different binding affinities and mechanisms with the hopes of creating a drug that leads to a more efficacious reduction of AD progression. One such drug is lecanemab, a monoclonal antibody that also targets Aβ, though its mechanism of action differs slightly from that of aducanumab.

Lecanemab aims to have a more specific biological mechanism than aducanumab by binding with the highest affinity to protofibrils, which are the most toxic aggregates of Aβ [28]. There is a lower frequency of ARIA-E cases for patients engaging in lecanemab treatment compared to those taking aducanumab. A limitation of this treatment is that patients must be administered the drug twice as often in comparison with aducanumab treatment (two intravenous injections per month instead of one) [29]. This can act as a practical and financial barrier for providers and patients, as the cost of travel to treatment, the time and staff required are double that of what is needed with aducanumab treatment. The U.S. FDA has approved lecanemab treatment for those with early Alzheimer's as of 2023, and Health Canada is currently reviewing the drug, in hopes of granting its approval if it can meet criteria [30].

Currently, aducanumab has been discontinued by Biogen due to financial constraints [31]. However, concepts of using monoclonal antibodies to attack Aβ are still being developed based on the mechanisms that aducanumab introduced, but with more directed approaches. As many of these drugs, such as lecanemab and gantenerumab, have showed statistically significant changes in disease progression, further research will investigate the clinical significance of the drugs as well [32].

Though our focus has been on medical treatments, holistic-based treatments have gained support over the years as well. Central to these alternative treatments is the concept of the "brain-healthy lifestyle", characterized by staying physically, socially, and mentally active, as well as consuming a healthy diet [33]. This approach has proven to have effects on slowing the progression of AD, specifically in earlier stages of the disease [33, 34]. Individuals are often encouraged to adopt a "brain-healthy lifestyle" as a preventative measure, since it has been found to mitigate risk more than alter disease progression [35, 36]. It is crucial to consider that there are barriers in place for many individuals that make it difficult to adopt this lifestyle, such as socioeconomic and cultural differences [37]. Therefore, the development of aducanumab and other pharmacological drugs have laid the foundations for intervention care for those with AD, allowing those diagnosed with AD to lead a longer functional life.

List of Abbreviations

Ab: amyloid-beta peptides
AD: Alzheimer's disease
ADAS-Cog13: Alzheimer's disease assessment scale-cognitive subscale-13 items
APOE4: apolipoprotein e4
APP: amyloid precursor protein
ARIA: amyloid-related imaging abnormalities
ARIA-E: amyloid-related imaging abnormalities edema
ARIA-H: amyloid-related imaging abnormalities hemosiderin
CDR-SB: clinical dementia rating sum of boxes
CSF: cerebrospinal fluid
Fab: fragment antigen-binding
Fc: fragment crystallizable
FDA: federal drug administration

GSK3-β: glycogen synthase kinase-3 beta
LTE: long-term extension
MAD: multiple ascending dose
MCI: mild cognitive impairment
MMSE: Mini-Mental State Examination
MRI: magnetic resonance imaging
MTD: maximum tolerated dose
NFT: neurofibrillary tangles
NMDA: N-methyl-d-aspartate
PC: placebo-controlled
PET: positron emission tomography
P-tau: phosphorylated tau
T-tau: total tau

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors' Contributions
KM: Contributed to the literature search, generated prompts to use with ChatGPT 3.5, drafted the manuscript, edited the manuscript, and gave final approval for the version to be published.
CC: Contributed to the literature search, generated prompts to use with ChatGPT 3.5, drafted the manuscript, edited the manuscript, and gave final approval for the version to be published.

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