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Aducanumab: The controversial drug for Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a gradual and irreversible decline in cognitive function. The underlying pathology involves the accumulation of amyloid beta, a protein implicated in the development and progression of the illness. Aducanumab is a type of human monoclonal antibody that exhibits preferential immunoreactivity towards both soluble and insoluble aggregates of Amyloid Beta (Aβ). Two phase 3 studies, namely EMERGE and ENGAGE, were conducted to evaluate the efficacy of aducanumab in individuals with early Alzheimer's disease. These studies were designed identically, randomized, and double-blind in nature. Both trials were suspended early with the ineffective results shown in interim analysis for futility. Aducanumab was reassessed and met the primary and secondary clinical endpoints in EMERGE, but remains ineffective in ENGAGE. Reduction of Aβ plaques was observed in the high-dose group (10 mg/kg), showing a dose- and time-dependent pattern. The primary safety concern with Aducanumab is amyloid-related imaging abnormalities (ARIA), particularly in ApoEε4 carriers. Aducanumab is a new therapeutic strategy for AD, providing new treatment with disease-modifying potential. This paper evaluated the pharmacology, mechanism, clinical studies, and safety assessment of aducanumab. This research aims to provide a reference for the understanding of Aducanumab's current research status and results.

Keywords: Aducanumab, Alzheimer's Disease, Amyloid beta, Clinical trials, Monoclonal antibody

1. Introduction

AD is a neurodegenerative disorder characterized by the gradual deterioration of neuronal structure or function, ultimately resulting in neuronal death. Although the underlying mechanisms of this disease remain unclear, its primary pathological characteristics may manifest several decades prior to the appearance of clinical symptoms. This includes the overaccumulation of abnormally folded Amyloid plaques and their downstream hyperphosphorylated tau protein aggregation [1-3]. The former exerts neuronal toxicity, while the latter leads to the death of neurons. Response targeting the amyloid cascade has dominated many clinical research programmes, with efforts extensively criticised [3,4]. However, treatments are purely symptomatic, and none are effective in reversing or halting the pathological changes of AD [4,5]. Traditional medications approved for AD treatment include acetylcholinesterase inhibitors (AChEI) and N-methyl-D-aspartic acid (NMDA) receptor antagonists, providing only marginal benefits [6].

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Aducanumab is a monoclonal antibody of human origin that exhibits specificity in its binding to Aβ aggregates, which include both soluble oligomers and insoluble fibers [7,8]. Its mechanism of action is antibody-antigen-specific binding. Microglia, which exclude foreign bodies and induce inflammatory responses, devour and decompose the aducanumab-labeled amyloid plaques [8]. In October 2019, Biogen Inc. announced its investigational AD drug aducanumab showed therapeutic efficacy in phase 3 clinical trials and decided to submit a new drug marketing application in early 2020. The initial antibody-drug aducanumab was granted approval by the U.S. Food and Drug Administration (FDA) in June 2021 for the treatment of mild Alzheimer's disease (AD). Since 2003, this treatment has become the initial medication to receive approval and the primary therapeutic intervention to target the fundamental pathophysiological mechanisms associated with Alzheimer's disease (AD). The recent introduction of Aducanumab is a novel therapy approach that effectively targets and diminishes amyloid plaques within the brains of individuals diagnosed with Alzheimer's disease (AD). This innovation presents novel opportunities for the treatment of diseases, showcasing the ability to influence the course of the condition.

The efficacy and safety of aducanumab in early Alzheimer's disease (AD) were evaluated in two phase 3 studies, namely EMERGE and ENGAGE [7]. According to the cited source [7], the ENGAGE initiative was implemented one month prior to the EMERGE initiative, with the recruitment process for both initiatives concluding in July 2018. Both studies were terminated prematurely due to the findings of a futility analysis conducted on interim data [7]. Previous phase 3 clinical trials investigating the effectiveness of anti-Aβ monoclonal antibodies did not yield positive results in terms of efficacy or reduction in Amyloid plaque levels [9-11]. These investigations also included the recruitment of patients in advanced stages of the disease, including individuals who did not have pathological evidence of Aβ. On the other hand, recent findings obtained from the use of second-generation anti-Aβ antibodies suggest a notable decrease in the amounts of Amyloid plaques in individuals diagnosed with early Alzheimer's disease [12,13].

Aducizumab was introduced in a relatively short period, requiring more in-depth long-term studies to evaluate its efficacy and safety. If this is supported, the role of Aβ in the pathogenesis of AD can be clarified, supporting the amyloid hypothesis. Therefore, this paper reviews the pharmacology, mechanisms, clinical studies and safety assessment of aducanumab. Aim to provide a reference for the clinical treatment of AD through pathogenesis of AD and Aducanumab pharmacological development.

2. Pharmacology and mechanism of Aducanumab

Aducanumab is a selective monoclonal antibody derived via stimulation of human B cell clones with Aβ aggregates [7]. It was screened, cloned, sequenced, and recombinantly expressed to selectively immunoreact Aβ aggregates [8]. This drug selectively binds to amyloid plaques and activates the immune system after entering the brain through the blood-brain barrier [7,8]. Clearance of Aβ is concomitant with increased microglia recruitment in a time- and dose-dependent manner [7,8]. Activated microglia encapsulate the core of amyloid plaques, isolating them from the surrounding neurofibrillary network, thereby limiting neuronal toxicity [8]. Inhibition of Aβ may reverse calcium overload and calcium homeostasis disequilibrium in microglia, correlating with bindi. The binding of soluble Aβ oligomers to certain metabotropic receptors has been demonstrated in previous studies [14,15]. Aducanumab exerts a preventive impact on the detrimental consequences of membrane depolarization through its binding to soluble Aβ oligomers, hence perhaps impeding their interaction with such receptors [15]. This drug is degraded to short peptides and amino acids via the catabolic pathway [15]. Body mass, age, gender, and race had no significant effect on the pharmacokinetics of aducanumab [9-13].

3. Clinical studies

The approval of Aducanumab for the treatment of early Alzheimer's disease (AD) is primarily grounded on the findings from two phase 3 clinical studies, namely EMERGE (NCT02484547) and ENGAGE (NCT02477800), which were conducted in a double-blind, randomized, and placebo-

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controlled manner [16,17]. The EMERGE and ENGAGE studies collectively enrolled a total of 3285 participants, with 1638 participants in EMERGE and 1647 participants in ENGAGE [7]. The study participants consisted of individuals between the ages of 50 and 85, with a mean age of 71. Their amyloid pathology was validated using visual examination of positron emission computed tomography (PET) scans [7]. The inclusion criteria for participants encompassed specific parameters, namely a Clinical Dementia Rating (CDR) global score of 0.5, a mini-mental state examination (MMSE) score ranging from 24 to 30, and a repeatable battery for assessment of neuropsychological status (RBANS) score equal to or below 85 [7]. There were no apparent disparities in baseline demographics seen across any of the treatment groups.

The primary endpoint evaluates the patients' function and cognition based on the CDR sum-of-boxes (CDR-SB) score [7]. The assessment of patients' cognitive decline and ability to perform daily activities is conducted through the use of secondary endpoints such as the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale-13 items (ADAS-Cog13), as well as tertiary endpoints like the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory-Mild Cognitive Impairment (ADCS-ADL-MCI) [7]. Additional measures encompassed safety assessments and biomarker endpoints (7). The participants were assigned in a random manner to three groups, with a ratio of 1:1:1, in order to receive either a low dose (1, 3 mg/kg) or high dose (6, 10 mg/kg) of aducanumab, or a placebo, in both studies [16,17]. The medication was delivered at a frequency of once every four weeks throughout a duration of 78 weeks, as shown by references 16 and 17. Nevertheless, as outlined in the trial's initial protocol, the dosage for the ENGAGE low-dose group was adjusted to achieve a target dose of 3 mg/kg for those carrying the ApoEε4 allele, and 6 mg/kg for those who do not carry the ApoEε4 allele [7,17]. The dosage for the high-dose group was adjusted to achieve a target dose of 6 mg/kg for individuals carrying the ApoEε4 gene variant, and 10 mg/kg for individuals not carrying the ApoEε4 gene variant, as stated in references 7 and 17. The ENGAGE protocol underwent three adjustments, leading to the modification of the target dose to 10 mg/kg for a larger proportion of patients in the high-dose group [7,17]. In the fourth iteration of the ENGAGE protocol, an adjustment was made to the target dose for ApoEε4 carriers in the high-dose group of aducanumab. Specifically, their dose was increased from 6 mg/kg to 10 mg/kg in order to optimize the dose-dependent impact [7,17].

The findings from the EMERGE study demonstrated a notable disparity in the clinical CDR-SB scores between the high-dose group and the placebo group [-0.39 (-22%), P=0.0120]. This outcome successfully fulfilled the primary effectiveness endpoint [7,16]. When comparing the high dosage arm with the placebo group in all other endpoints, statistically significant results were observed for MMSE [0.6(-18%), P=0.0493], ADASCog13[-1.4(-27%), P=0.0097], ADCS-ADL-MCI [1.7(-40%),

P=0.0006], and NPI-10 [-1.3(-87%), P=0.0215] [7,17]. There was no statistically significant difference observed between the low-dose arm of aducanumab and the placebo group across all conditions. During the 78th week of the study, a total of 302 patients underwent evaluation. The results of the study demonstrated that the utilization of amyloid PET imaging revealed a decrease in the size of amyloid beta lesions in patients who received aducanumab treatment. This reduction was seen to be dependent on both the dosage and duration of the treatment. Notably, significant changes were observed in both the low-dose and high-dose groups when compared to the placebo group ($P<0.001$) [7,16]. In addition, it was shown that Aducanumab had an impact on the levels of p-tau protein and t-tau protein in the cerebral fluid of patients [7,16]. The group administered with a high dose of aducanumab had a notable reduction in p-tau (-22.44, P=0.0005) and t-tau (-112.05, P=0.0088) protein levels when compared to their initial measurements [7,16]. The aforementioned data indicate that the administration of aducanumab has the potential to enhance cognitive function and successfully eliminate amyloid plaques in individuals diagnosed with moderate Alzheimer's disease. Additionally, their contributions have played a role in the FDA's decision to grant fast approval to aducanumab.

The results of the ENGAGE study demonstrated a statistically significant disparity in the high-dose treatment group, exhibiting a 27% decrease in CDR-SB scores as compared to the placebo cohort [7,17]. The low-dose treatment group did not exhibit statistically significant differences as compared

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to the placebo group [-0.35 (-20%)]. The given interval is [7, 17]. The amyloid PET subgroup of this investigation consisted of 585 individuals, out of which 374 patients were evaluated at week 78 [7,17]. The results of the amyloid PET imaging revealed a notable and statistically significant disparity in the decrease of amyloid plaques between the two-dose group and the placebo group [-54.0 (-59%), $p<0.0001$]. The range of values provided is [7,17]. Nevertheless, the levels of p-tau and t-tau proteins did not exhibit a statistically significant deviation from the baseline alteration value as compared to the placebo group. The study did not provide a clear explanation for the lack of statistically significant alteration in the levels of p-tau and t-tau proteins. The findings of the study indicate that aducanumab exhibits potential efficacy in enhancing cognitive performance among individuals diagnosed with moderate Alzheimer's disease.

4. Safety assessment

Albeit promising effects, there are indeed adverse effects reported. Aducanumab may induce amyloid-related imaging abnormalities (ARIA). ApoEε4 carriers had the highest percentage of ARIA in both EMERGE and ENGAGE, 43% and 42%, respectively [16,17]. Of the 1105 patients treated with aducanumab 10 mg/kg in both studies, the common adverse reactions were cerebral oedema or Hemosiderin deposition in 454 (41%) cases [16,17]. 111 (10%) of the 1087 patients in the placebo group experienced such adverse events [16,17]. Of the 454 patients, 35% had cerebral oedema, accounting for most of the first eight doses (72%) [16,17]. The incidence ascribed to cerebral oedema was higher in ApoEε4 carriers than in non-ApoEε4 carriers, at 42% and 20%, respectively [16,17]. This indicates that genetic screening of patients might be essential when using this drug in the general public to prevent potential detrimental effects among ApoEε4 carriers. 98.2% of cerebral oedema events were fully resolved by symptomatic treatment during the study period, with 91% of these patients fully resolved within 20 weeks [16,17]. Symptomatic drugs most frequently used for treatment are glucocorticoids and acetaminophen [16,17]. Among the 103 patients with symptomatic cerebral oedema or Hemosiderin deposition, the prevalent phenomena were headache [48(46.6%)], confusion [15(14.6%)], dizziness [11(10.7%)] and nausea [8(7.8%)] [16,17]. For symptomatic and moderate-to-severe ARIA, suspension of dosing or discontinuation of therapy is recommended [16,17]. One additional patient reported angioedema and urticaria during aducanumab intravenous infusion [16,17].

5. Discussion

The pathogenic type of amyloid responsible for neurotoxicity is known as soluble Aβ. Aducanumab exhibits the ability to specifically target soluble Aβ and non-pathogenic variants of amyloid, while maintaining a broad selectivity. The variability in the drug's capacity to traverse the blood-brain barrier among individuals may result in potential modifications to the effectiveness of aducanumab. The EMERGE trial provided evidence that Aducanumab exhibited a more notable therapeutic effectiveness, as indicated by a statistically significant decrease in Aβ levels and enhanced cognitive function in individuals with Alzheimer's disease (AD). However, the ENGAGE studies did not yield comparable outcomes. Aducanumab exhibits selectivity towards aggregated forms of Aβ and has previously demonstrated a reduction in Amyloid plaques that is dependent on both dosage and duration. The association between aducanumab treatment and the observed effects was evident in both the EMERGE and ENGAGE studies. The premature conclusion of both investigations raises legitimate concerns regarding the credibility of the research findings. Nevertheless, there is a lack of data indicating that the premature conclusion of the study had any impact on the integrity or validity of the findings. Therefore, there is a limited amount of evidence supporting the treatment effectiveness of Aducanumab and its impact on cognitive enhancement in individuals diagnosed with Alzheimer's disease (AD).

Although the designs of EMERGE and ENGAGE were identical, there were variations in the implementation of the research. Several factors, including demographics, illness features, frequency, severity, and management of ARIA, exhibited similarities throughout the trials and did not seem to

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explain the partially inconsistent clinical outcomes observed across the two investigations. Furthermore, the introduction of protocol revisions facilitated an increase in the number of participants in the high-dose arm who were able to attain the desired dosage of 10 mg/kg. Specifically, ENGAGE had roughly 200 more individuals than EMERGE in this regard. Population diversity was lacking across all studies, including racial diversity, individuals with comorbidities, and patients taking concomitant medications. African Americans and Hispanics in both trials were unrepresentative of their population, restricting the generalisability of the evidence. Therefore, the drug's efficacy remains unstable, and further validation in phase IV clinical trials is required. Many studies need to be conducted, including drug safety studies on teratogenicity, carcinogenicity, and mutagenicity, pharmacokinetic studies in special populations, and quantitative evaluation of Aducanumab immunogenicity as an antibody.

Although amyloid is the dominant hypothesis with much genetic evidence and animal models, there is some evidence to the contrary. For example, Amyloid Beta arises in the brains of healthy individuals surround 40% of older individuals who are cognitively normal. There is a weak correlation between cognition and the presence of beta amyloid plaques, but a stronger correlation for tau. It's also worth pointing out that correlation does not mean causation and the relationship between amyloid beta and tau is unclear. The exact triggers and steps that can go from amyloid beta to synaptic neuronal loss and inflammation are also unclear. It hasn't given us any treatments that can be used in individuals without Alzheimer's. Some scientists would even argue that the dominance of this has prevented research in other areas that could have been more helpful in terms of developing treatments for Alzheimer's disease. The Amyloid cascade hypothesis is dominant but not infallible. Moreover, on July 21, 2022, The "Science" released an in-depth investigation report titled "Blots on a field", pointing out that a foundational paper in the field of Alzheimer's disease 17 years ago was suspected of fraud. The first author of the paper, neuroscientist Sylvain Lesné of the University of Minnesota, has been accused of possible academic misconduct in more than 20 papers. Despite the relatively negative impact of this result on the currently dominant hypothesis, Sylvain's hypothesis is based on the amyloid β_56 variant rather than the dominant variant, known as amyloid β variants 1 to 42. Therefore, there are implications but not a complete denial of the existing efficacy of the Amyloid hypothesis.

6. Conclusion

In conclusion, aducanumab remains the only therapeutic medication that eliminates Aβ precisely with a defined mechanism of action. The clinical trials were designed for asymptomatic and mild cognitively impaired patients, demonstrating that earlier intervention with neuronal damage patients achieved disease-modifying treatment. The FDA approved the drug application under the accelerated approval pathway in response to patient demand for the treatment, providing an early and potentially valuable therapeutic option. However, the FDA's approval was not unconditional, requiring a Phase IV clinical trial to validate aducanumab's efficacy and safety. ApoEε4 carriers showed a higher probability of developing ARIA and its derived side effects during treatment, potentially contributing to the poor assessment of the clinical efficacy of aducanumab. Subsequent studies require genetic screening, possibly with more universal and undiagnosed targets, to prevent existing adverse effects. Additional evidence of aducanumab's efficacy in post-marketing studies could further support the important role of Aβ in the pathogenesis of AD and support the amyloid hypothesis.

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