Effects of Aducanumab on treating Alzheimer's disease: targets and clinical trials

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1. Introduction

Alzheimer is a disease characterized by continuous cognitive impairment and brain function decline. It is affecting about 50 million people globally and is noted as one of the major death factors in the United States. Presently, the cause of AD can be ascribed to two major factors: Tau and Amyloid-β accumulation in the brain. In both the hypothesis, the accumulation of excessive protein in the brain blocks neural signal transduction pathway and thus leads to symptoms of AD [1].

Before aducanumab, there are several existing drugs designed to reduce symptoms of AD: cholinesterase inhibitors (ChEIs), donepezil, galantamine and rivastigmine as well as memantine. These drugs are unable to cure AD, but simply act as a buffer of its progression [1]. They worked by inhibiting the breakdown of a neurotransmitter or activating the chemical messenger of neural transmission in the brain [1]. In June 2021, aducanumab, the first drug stating to be the cure of this disease based on the Amyloid β hypothesis, was approved by the FDA.

This review summarizes some controversies about the efficacy of the drug during phase 1 and phase 3 clinical trial as well as FDA approval. However, the drug's efficacy remains undetermined, and existing evidence is still insufficient in proving its efficacy in generating actual clinical benefits.

2. Theoretical basis

2.1. Tau and Amyloid Theory

In the Amyloid hypothesis, Amyloid β proteins are formed by editing the Amyloid precursor protein, a protein related to neuron growth and signal transport [2]. Long term accumulation of oligomers will form Amyloid β plaques and that will build up neurotoxic substance and induce Tau pathology [3]. Ultimately cause the brain to shrink, damaging the person's ability to think, remember, and act independently [3]. This hypothesis is the most popular ideology for 20 years since its discovery [3]. In Tau pathology, Tau become the main causation of the disease [3]. Tau is originally

a protein responsible for maintaining the structure of nerve cells [4]. Modification of this protein after translation, mainly in the form of phosphorylation, can change the structure of the protein and let it accumulate [4]. These substances will form neurofibrillary tangles that interference with neural signals and cause neuron death [5]. The tangles will spread from transentorhinal regions to limbic region and to neuro-cortical regions, eliciting symptoms of cognitive impairment [3]. Likewise, in the original version of Amyloid hypothesis, Amyloid β also experienced structural and functional changes that alone lead to their aggregation and deposition of Amyloid plaques [3]. When amassing into substantial amount, these proteins will lead to an inflammatory response and cause irreversible to the neurons [6].

2.2. Proposed Mechanism and Properties of Aducanumab.

Aducanumab works by selectively binding with aggregated forms of Amyloid β as oligomers and plaques [7]. Aducanumab can penetrate the brain an elicit phagocytotic response from Iba1+ [8]. Compared to other existing antibody drugs, aducanumab is favored by its flexibility and selectivity of targets and antibody surfaces [7]. The protein will denature from its original form of β-hairpin to monomers at the surface of aducanumab [7]. Also, the geometric surface and the space it provided are well suited for interacting with the flexible N-terminal β-sheet tops [7]. While on the other hand, other nonselective antibodies as Crenezumab and Bapineuzumab targets more monomer proteins [7]. The removal of monomers will add neurotoxicity to the cell and thus may be harmful and ineffective in curing the disease [7]. Due to the diversity in oligomers, it is difficult to derive an exact structural formation, but scientists believed that it is possible to increase its accuracy in targeting through further engineering [7].

Aducanumab is a human, immunoglobulin gamma 1(IgiG1) monoclonal antibody

2.3. Behavioural Measurement

Several behavioral measurements have been used to measure the efficacy and the proposed clinical benefits in each phase of clinical tests. These measurements are used to analyze the efficacy of the drug through interpretation of the patient's behavioral data and biological information about the concentration of possible target protein for AD in the brain.

2.3.1. CDR-SB

This is a test for cognitive impairment and dementia levels on people based on information offered by behavioral evaluation of the patient and collateral information provided by the patient's caregiver. It measures behavioral categories in 6 aspects: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care [9]. The informant rates the ability of the patient of daily skills and the participants are answered questions directly testing the abovementioned skills. The numerical values were calculated via algorithm (http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html) [10]. The score ranges from 0 to 18 (18 being the most severe) [10]. The patients that will be discussed below in clinical trials fell between questionable impairment (0.5-2.5), very mild dementia (3.0-4.0) and mild dementia (4.5-9.0) [10].

2.3.2. SUVR

Positron emission tomography (PET) is method for obtaining a three-dimensional model measuring numerous physiological activities in the brain. It is conducted by the injection of a molecule attached with a slightly radioactive signaling particle. Gamma rays will be emitted when the particle clashes with electrons. The scientists will then detect those rays and construct the model. Standard uptake value (SUV) is measured through PET scanning. It is calculated with the division of the activity level per unit volume of a specific area by the activity per unit whole body volume [11]. In measuring tumors, any number above 1 is abnormal; any number bigger than 2.5 is considered to be a sign of malignant tumor [11]. However, in the clinical trials that this passage will be discussing, the SUV values serve more as numerical reference of the concentration of protein aggregation instead

of direct implication of disease severity. The change in SUV values is calculated into a ratio called Standard Uptake Value Ratio (SUVR).

2.3.3. MMSE

MMSE is a set of questions that the doctor asks the patient to test his/her mental abilities. From a total of 30 points, 25 below is considered abnormal, and less than 10 is considered severe impairment [12].

2.3.4. Summary

These measurements were utilized in clinical studies of aducanumab to check for clinical benefits and effect of the drug. Table 1 provides a summary for the information of the three assessments.

2.4. Concerns for Amyloid Hypothesis

Between the two hypotheses (Figure 1), most arguments and evidence are pointing towards Tau instead of Amyloid β, weakening the stance of aducanumab which functions by inhibiting Amyloid β formation. Compared to Amyloid β, most evidence points to Tau accumulation as the more apparent and operatable cause of Alzheimer disease. To begin with, presently, clinical evidence had only indicated the correlation between disease symptoms with Tau pathology instead of Amyloid β accumulation [13]. Second, the accumulation of this protein is a gradually process that can take decades and result in a cascade effect. The delay in response offer scientists a chance to observe various stage of AD and correlate the change in structure to specific modification of the protein. Phosphorylated Tau will maintain their harmless soluble forms at first, then gradually grow in number with increase phosphorylation sites at carboxyl and amino ends of the protein [13]. Third, the origin of accumulation is fixed on particular brain regions as entorhinal cortex and hippocampus and gradually infect other part of the brain with its increase in number [14]. This feature, along with the detection of Tau in extracellular environments points to the feasibility of it as a more potent therapeutic target than Amyloid β [13].

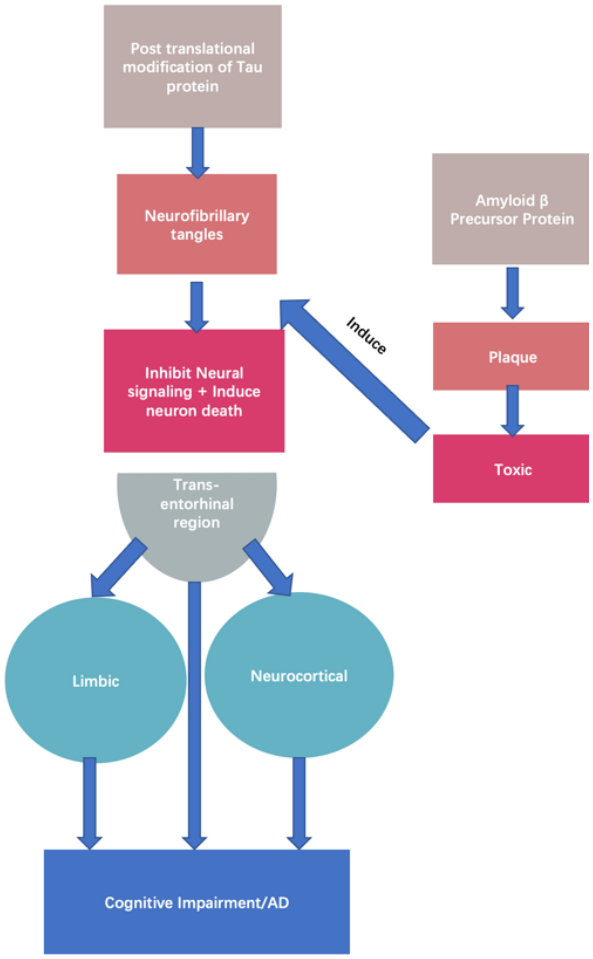


Figure 1. Two Theories of Alzheimer's disease Mechanisms

On the other hand, the exact role of Amyloid β on cognitive decline and AD is still open to interpretation. The hypothesis of Amyloid β plaque leading to symptoms of dementia have been questioned by few clinical studies. In a cohort experiment conducted tested the correlation between Amyloid β increase in the brain and symptoms of dementia. However, instead of exhibiting a linear proportional relationship between standard uptake ratio value of C-PiB (a measure of the amount of Amyloid β presented in the brain through PET scanning), the growth of Amyloid β staggered before severe symptoms of AD. In mild symptoms of cognitive impairment or health control, high C-PiB retentions are correlated with faster rates of episodic memory and non-memory decline, the reduction of grey matters in the brain and the hippocampal shrinkage. However, in the 18 patients tested for AD, symptoms as memory loss and brain shrinkage were more significant than the growth rate of Amyloid β deposition [15]. This may imply the subordinate position of Amyloid β in later stages of AD.

The cooperative mechanisms behind Tau pathology and Amyloid β had not yet been elucidated. Theories abound supporting different relationships between the two, as existing in a parallel relationship or one acting as a catalyst to accelerate the reaction of another. However, evidence did suggest that Amyloid β was not induced by Tau, since the gene coding for Tau does not lead to Amyloid plaques. Also, the role of Amyloid β in causing disease related symptoms were still unsupported as neurofibrillary Tau PET signaling was not affected by the presence of Amyloid β [16]. Amyloid β accumulation usually precedes the development of Tau pathology in both early and late-onset AD [13]. the aggregation of Amyloid β is a gradual process that can occur prior in time to all visible symptoms of AD [15]. Based on the above listed observation, it is most likely that Amyloid β assist in the formation of Tau pathology, that leads to neurofibrillary tangles and to neural death. In this case, the onset of this disease can take on two separate paths: the accelerated channel with the helper Amyloid protein and the regular one without it.

Table 1. Summary of Behavioral Measurements

Assessment	Aims	Score	Reference
CDR-SB	To determine cognitive impairment and dementia levels	Questionable impairment; 0.5-2.5 Very mild dementia: 3.0-4.0 Mild dementia: 4.5-9.0 Moderate dementia: 9.5-15.5 Severe dementia: 15.5+	[9-10]
MMSE	To test mental abilities	Mild Dementia: 25-20 Moderate Dementia: 15-19 Severe: 9-14	[11]
SUVR	To measure physiological activity	Normal: 1 Non-Malignant Pathology: 1-2.5 Malignant Pathology: 2.5+	[12]

Therefore, the obstruction of Amyloid β oligomer activity of aducanumab in hope of stopping further cellular activities is likely to be futile. To what extent do Amyloid β affect Tau pathology is still under investigation. Even if direct results are produced, will the effective dosage cause severe side effects as ARIA-E to the patients? Since Amyloid β accumulates through decade, what is the optimal timing of taking this drug? In the end, the uncertainty of the target devalues the drug by leading people to question its fundamental operating principles.

3. CLinical Trials and COntroversy

3.1. Clinical Efficacy Phase 1 PRIME

Aside from the inconsistency of Amyloid theory, insufficient clinical evidence is what undermined the argument for aducanumab. The claim of efficacy for aducanumab started the phase 1 trial conducted by Biogen at year 2016. The trial is denoted as PRIME. 197 participants ranging from 50 to 90 years old were recruited at the start. They were randomized into 5 groups: four receiving treatments of different dosage of this drug and one group serving as the placebo. Over the course of 52 weeks, participants were injected with a total of 14 doses of this drug [17]. Measurements of the patients' baseline data and their physiological response to their assigned treatment as SUVR, MMSE, and CDR-SB were measured at week 26 and 32 [17].

Results indicate that Amyloid β levels were significantly reduced through the session, in which the patients with the strongest dosage of 10mg/kg nearly passed through the threshold of positive and negative scans. Also, the changes of CDR-SB values at the end of 54 weeks exhibited dosage dependent response in which the strongest dose exhibited the smallest change. With the proven efficacy of Amyloid β removal, aducanumab successfully marched into phase III trial of EMERGE and ENGAGE.

3.2. Clinical Efficacy Phase 3 EMERGE and ENGAGE

EMERGE and ENGAGE studies are identical studies conducting phase III evaluation of aducanumab drug. An 18-month trial tested a total of 3285 patients diagnosed with early AD at 348 sites in 20 countries. The patients were equally divided into three proportions receiving high dose, low dose or placebo once every four weeks [18]. However, though working under the same conditions, the two trials produced astonishingly different results. This trial started from August 2015 and ended in July 2018 [18]. At the end of the study, a total of 1812 patients, 55.2% percent of the original population, completed the study [18]. Having the measurement of CDR-SB as the primary endpoint, after 78 weeks of trial, the EMERGE group demonstrated the efficacy of the drug with mental ability test showing little or no decline in cognitive abilities. On the other hand, ENGAGE trials

demonstrated no effect on preventing or decelerating the patient's degradation of abilities. The inconsistent results of phase III trial connect with the insufficient clinical effect at phase I.

3.3. Analysis of PRIME

In PRIME, there are several factors affecting the validity of the trial. To begin with, the trial involves less than 200 participants in total. When subdivided into sections, each of the group contained only about 30 people. In this case, the effects of specific outliers are significant to the generation of mean data and calculation of patients' response to the drug. Second, the working mechanism and the specific target of this drug is still unknown to the researchers [19]. The drug can be targeting monomers, oligomers, protofibrils, or plaques. In the group with the highest dosage, the side effects were so severe that 31 percent of the patients exit the study [20]. On the other hand, even the group with the strongest dosage was unable to pass the SUVR threshold for positive and negative scan of Amyloid β in the brain [20]. Additionally, the researchers' themselves even admitted that the trial was flawed because of the side effects of ARIA-E [20]. There is the possibility that severity of ARIA-E may let the researchers know who is in the placebo group, the low dosage group, and the high dosage group. This possible unblinding may lead to biased information and estimation from the investigators. For example, when conducting the CDR-SB examination, the performer may be influenced by the fact that the patient is applying the actual drug instead of the placebo group. This preconceived information may affect the performer's judgement in analyzing the patient's cognitive ability and cause inaccurate information in the experiment.

3.4. Analysis of EMERGE and ENGAGE

When comparing the data set of two trials, the discrepancy between EMERGE and ENGAGE trials is highly noticeable. The different results of changes in SUVR (0.019 for EMERGE and -0.005 for ENGAGE [21]) and CDR-SB results (EMERGE 1.74 and ENGAGE 1.55 [21]) all proved the randomization in the study. With that in mind, the produced effects for aducanumab on reducing Amyloid β seemed more authentic. In both trials, the two control groups of high and low dosage distinguish themselves from that of the control group by exhibiting decreases in SUVR values. On the other hand, the variety among individual patients can account for the difference the two trial's test results. Heterogeneity existed among AD of different patients in the different quantity of plaque and the causative agent of the disease: whether it is p-Tau and t-Tau pathways [19]. As hypothesized, there can be multiple pathways leading to similar symptoms of AD [15]. Therefore, the participants selected for ENGAGE may have included more individuals whose Tau pathology occur with little or no catalyzation of Amyloid β and were therefore little affected by the removal of it.

There are currently multiple versions of explanation trying to account for the incongruency in data. First, Biogen claimed that the difference in AD progression rate is responsible for the difference. However, estimations made by the Bayesian model announced that the model only "offered overwhelming evidence against Biogen's assumption." [22]. Though the model provides more of an evaluation than a prediction, the accuracy and validity of Bayesian analysis is tested in numerous trials, giving the generated statistic strong reference values [23]. Moreover, the EMERGE dataset did not analyze the full population of the initially tested patients, about half of them quitted the trial due to various reasons. Out of all the reasons, the two major reasons were adverse event and withdrawn consent [21]. The discontinued participants account for almost half of the total population at the start of the trial (49.8% in placebo group, 49.5% in low dose group, and 47.8% in high dosage group) [21]. The number of participants withdrew from the trial speaks against the safety of this drug. Aducanumab can lead to side effects as bleeds in the brain which is known as Amyloid related imaging abnormalities- microhemorrhages, macrohemorrhages, or superficial siderosis (ARIA-H) and swelling of blood vessels in the brain due to leakages from the sulcus known as Amyloid related imaging abnormalities- edema (ARIA-E) [24]. Incidence of ARIA-E and ARIA-H on patients with APOE4 gene is as seven and three times as great as those without APOE4 gene [25]. In this case, the patients with adverse side effects can most likely be comprised of people carrying the APOE4 gene

and the remaining are ones without it. When calculating only the population that completed the entire trial, Biogen is disregarding the side effects and the danger that can be induced on users of aducanumab. The company is neglecting the potential threats that the drug can cause to a proportion of its users.

Moreover, technical issues as in the inconsistency of methods and neglect of details in study can also account for the drug's inability to produce clinical efficacy. First, it is hypothesized that the researchers did not allow enough time for the drug to present its use [26]. The trial length is not enough for the disease to develop into serious conditions a so cannot offer an ability to fully testify the efficacy of this drug. The early termination of certain trials leads to a loss of 35% of participants in EMERGE and 30% percent in ENGAGE [16]. The disruption through the trial permitted the patients from conducting full dosage trials and impacted the incidence of side effects for the drug [18]. Noting that the accumulation of Amyloid β in the brain can occur 25 before the onset of the symptom, the 18 months design in EMERGE and ENGAGE trials seems rather hasty [27]. Additionally, the aim of heterogeneity of the study seemed to sacrifice the validity of it. Doctors that do not belong to the research team are recruited to test the patients as to assert the protocol of double-blind experiments [26]. Since active sites had a wide geographic span including but limiting to countries as Australia, South Korea, the Netherlands, Poland, and United States, biases and measurement error may occur through the evaluation of data. To be specific, CDR-SB requires subject information offered by the caregiver of the patients. In international settings, the native language spoken by the doctor and the informants may be different, resulting in misunderstanding or misinterpretation of statements and thus producing a less accurate evaluation [28]. Although translation in Asian countries proved to be dependable, but in countries less developed, the effect is still undetermined [29]. In this case, with different clinicians performing estimations in settings holding huge disparity from each other, it is natural that EMERGE and ENGAGE were unable to produce consistent data.

3.5. FDA approval

The FDA consented to accelerated approval on aducanumab based on the results produced in its phase 3 trials. The approval process is unnatural in multiple aspects as the lack of phase 2 trial, the use of Amyloid β decline as a surrogate to prove the drug's efficacy, the granted approval despite disagreement from multiple members, and the use of only one successful clinical trial as evidence for the drug's effect [30, 31]. Most drugs require a phase 2 trial to progress into phase 3. Phase 2 trials tests the effect of the drug on treating the disease. After safety is guaranteed in phase 1 trial, the researchers will be asked to select the most effective and safest dose of the drug to test on about 100 patients [20]. Only the stability and effect of this drug is confirmed can it move on to a larger population. Additionally, when conducting phase 1 trial, the team noted that the trials were not to investigate to effectiveness of the proposed clinical endpoints, so the clinical cognitive results is uncertain [20]. However, the reduction of Amyloid β detected by PET is used as a surrogate endpoint to support the clinical benefit of the drug.

Clinical effect of aducanumab cannot be testified by the data provided in clinical trials, further research is needed to clarify its precise working mechanism and impact on human body. Although there are diversified claims trying to account for the inconsistency of two trials or trying to prove the efficacy of this drug. However, in the end, the reason for controversy is due to murky and unclear data and insufficient evidence to guarantee the effectiveness and harmlessness of aducanumab. Acknowledged that aducanumab has great potential and value when further research is conducted, yet speeded approval and simplifying the process of examination is irresponsible to the patients. Aducanumab is currently estimated to cause 28,000 dollars a year [32]. However, the value of aducanumab may not be worth the overwhelming price of it. Aducanumab had brought hope to a lot of families as the termination of their sufferings of AD. As Amyloid β accumulation stems from decades before the eruption of the disease, there is no clear definition of when to apply this drug. When widely applied in the market without further clarification and examination, it is likely that

people will overly depend on this drug. Furthermore, since AD is a genetic disorder, people are likely to apply this drug as an early prevention of the disease. In this case, the side effect will be uncontrollable and will likely cause long term harm without providing effective cure to the patients.

4. Conclusion

Presently, aducanumab is still the only drug claiming to cure AD. CDR-SB, MMSE, SUVR, et al were used in clinical trials to determine metal and physiological activities of AD patients. Despite the controversial phase 1 and phase 3 clinical trials and the unsubstantiated clinical benefits of the reduction of aducanumab, aducanumab was still granted accelerated approval by the FDA department. The discrepancy in results points to the instability of the drug's efficacy and the severe side effects points to the potential harm of hasty approval of this drug. Mechanisms of aducanumab effects as well as its clinical benefits remain unclear. In the future, it is best to conduct further research aducanumab and conduct another phase 3 trial testing the efficacy of it. In this case, the gaps in clinical data for patients in long term studies and continuous monitoring of disease progression or regression can be filled and used to testify the efficacy of aducanumab.

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