

# Is Aducanumab a Miracle Drug?

Sanjana Ananthula<sup>1</sup>, Dr. Rajagopal Appavu<sup>1#</sup> and Josthana Kethar<sup>1#</sup>

<sup>1</sup>Gifted Gabber

#Advisor

## ABSTRACT

A new drug called Aducanumab has been circulating the medical news for a while along with many questions. To answer these questions, it is imperative to understand Alzheimer's disease. This research was done by reading other articles and observing scans to truly comprehend the premise of the problems. It was found that Alzheimer's is caused by the clumping of amyloid-beta proteins and tau proteins which kill the neuron. The drug, that is in question, is an immunotherapeutic drug that is prescribed for moderately severe cases of Alzheimer's. The trials were done on a variety of people and different stages of Alzheimer's. They tested different doses and compared the values to a placebo. This was all monitored by MRI scans to any decrease in amyloid plaque and to monitor the possible systems. Through the observation of different trials and testing, it is still not clear if the drug truly works and is worth taking. In some studies, Aducanumab has been seen to work positively and had a substantial difference in the amount of plaque reduced compared to the placebo values. However, some of the later studies say otherwise because there is not much plaque reduction and the symptom called ARIA-E. This drug is different in its approach from other drugs in the sense that it actually targets the amyloid plaques. According to a neuro physician, many doctors are willing to give this medication a try and closely monitor a patient if the patient falls under the right category for treatment. Overall, questions about this drug are still yet to be answered.

## Introduction

Around 4.5 million Americans have Alzheimer's disease. In 2001 it was the 8th leading cause of death in the US. 12.8 percent of those over 65 years old and 40 percent of those over 80 years old are affected. Currently, more than 6 million people have Alzheimer's disease solely in the United States. So many years have passed, and people are still affected yet there still is no cure. Anyone diagnosed with Alzheimer's feels that they are given a death sentence. After many years, a revolutionary drug created by Biogen will change our future: a treatment that manages Alzheimer's disease and hopefully lengthens many elders' lives. After this drug was approved by the FDA, many questions arose such as what this miracle drug is, how it works and why it is considered influential.

## What is Alzheimer's Disease?

Discovered in 1906, Alzheimer's disease is a neurodegenerative disease, also known as senile dementia. This disease results in a continuous decline in thinking, behavioral, and social skills which disrupt a person's ability to function independently. People with Alzheimer's have a dominant-negative genetic mutation in their twenty-first chromosome which means that it is more likely to be passed down from generation to generation. Those who carry the APOE gene are more likely to be at risk for Alzheimer's when they are older. However, many carry the gene and don't get Alzheimer's. People can also get Alzheimer's early in their life with the mutation in the APP, PSEN1, or PSEN2 gene, but this mutation is uncommon. Unhealthy diets, high blood pressure, smoking, and diabetes are also ways that can increase the risk of getting Alzheimer's disease.

Simply put, the mutated gene creates an excess of a protein called amyloid-beta ( $A\beta$ ). Amyloid-beta is made up of peptides that are bonded together through hydrogen bonds. These amyloid-beta proteins start clumping together and form plaques around the neurons. Another protein called Tau builds up inside neurons forming dense, thread-like molecules. Both protein clumps inhibit transmissions of neurotransmitters and provide a disconnect. This process usually occurs ten to twenty years before the symptoms appear. As more and more of this occurs, the neurons start to die and unlike our body cells like skin cells, neurons cannot renew themselves. The death of the neurons occurs at memory-associated parts such as the amygdala and hippocampus. This is why the first symptom of Alzheimer's is dementia.

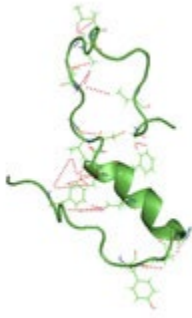


Figure 1: Picture of the Amyloid-Beta Protein

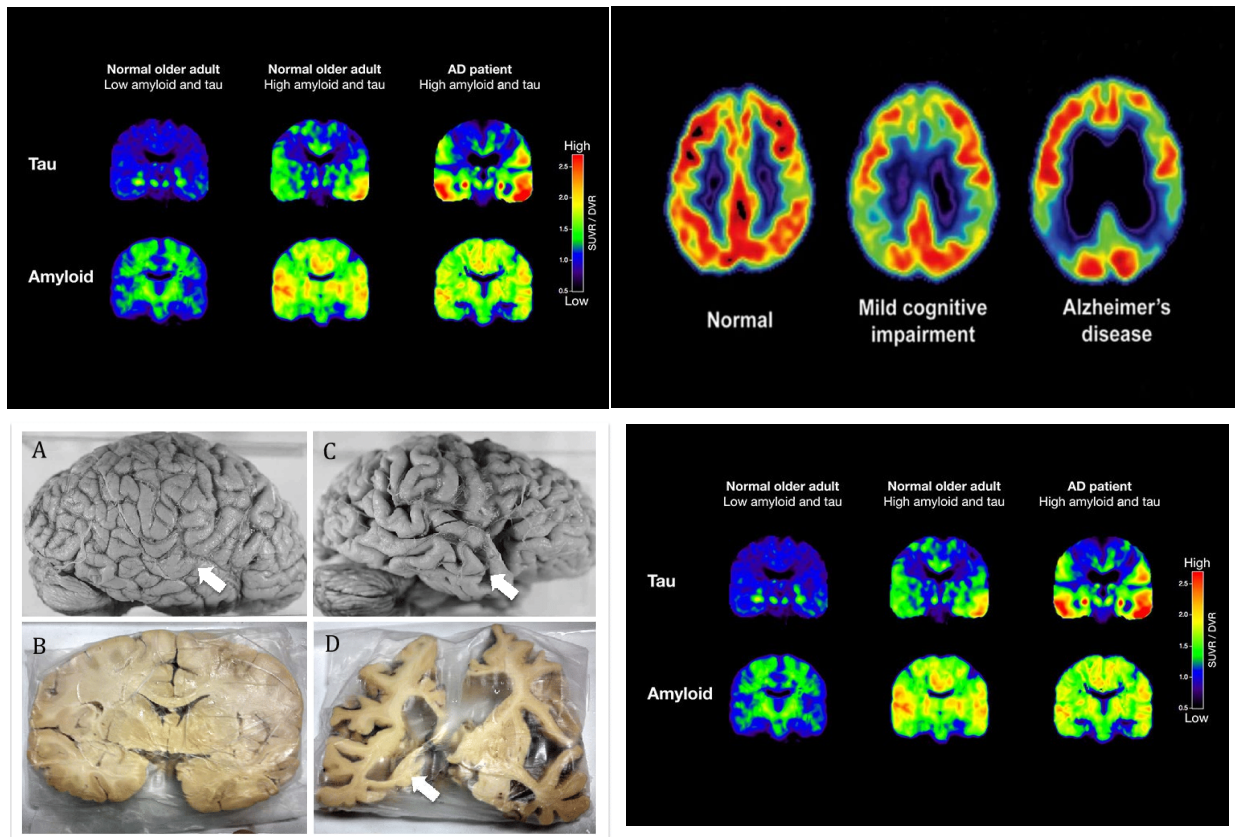


Figure 2,3,4: PET scans and Coronal plane cut. Compares patients that have severe Alzheimer's to those with either moderate or has no disease.

As more and more neurons die, gray matter in the brain slowly decreases to roughly a third of its size. To diagnose patients quickly, doctors use a PET scanner or positron emission tomography to assess the plaques and size of the brain. In the first PET scan, it is observable that the density of the brain increases as the number of amyloid and tau clumps increases since the pictures get progressively greener. In the second picture, there is a lot of activity in a normal brain and the colors are spread around the; however, the patient with Alzheimer’s disease has less brain activity and is more focused on the outside. In the real-life version of the brain, it is clear that it becomes smaller and less smooth. The lack of neurons makes the brain look decomposed and shriveled. Prominent atrophy is visible on the frontal lobes and the ventricles are enlarged.

## What is Aducanumab and How Does it Work?

Aducanumab is a recombinant human immunoglobulin gamma monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid-beta. Essentially this drug uses external antibodies from Chinese hamster ovary cells to attack the clots. These monoclonal antibodies are attracted to the bonds between proteins in the amyloid-beta due to their protein’s specific molecular geometry. Those antibodies mark those plaques signaling the immune system to destroy the plaques. B lymphocytes, a type of immune cell, produce more antibodies to further mark more plaques, and the T-Cells, specialized white blood cells, try to break apart the plaque by dissecting its proteins. Since these developments in plaques occur fifteen to twenty years ahead of clinical recognition, the drug is focused on people who have the mildest symptoms of Alzheimer’s disease. The dosing is 10mg/kg is registered into the body as an IV infusion for an hour every month.

## Clinical Tests for Aducanumab

The first trial consisted of 3,078 patients where 1105 patients received Aducanumab while the rest were given a placebo. 1105 patients were diverse in age and race. Specifically, reports say that approximately 52% were female, 76% were White, 10% were Asian, and 3% were Hispanic or Latino. Of the 3,078, 5% of patients withdrew from the trial due to unfavorable effects. Each participant was given some amount of Aducanumab and monitored through MRI scans. Some were given low doses such as 1mg/kg, 3mg/kg, and high doses such as 6mg/kg, 10mg/kg. Each person was infused monthly for an hour and monitored for over a year. As previously mentioned, 5% of patients withdrew due to the symptoms in the chart below. The main symptom was ARIA-E. This is a symptom where the brain is inflamed and causes exponentially more damage to the already deteriorating brain.

**Table 1:** Table of the symptoms that were observed when testing with Aducanumab and the Placebo

Common Symptoms and Reactions	Aducanumab 10 mg/kg (%)	Placebo (%)
ARIA-E	35	3
Discomfort with headache	21	16
ARIA-H micro hemorrhage	19	7
ARIA-H superficial siderosis	15	2
Fall	15	12
Diarrhea	9	7
Confusion/Delirium/Altered Mental Status	8	4

Through PET Scans scientists observed changes in the amyloid-beta clumping in the majority at low and high doses. Towards weeks 26 through Weeks 78 the amount of amyloid-beta plaque was comparable to the ones in those with a placebo. By week 132 the amyloid-beta plaque continually decreased. The tests observed that Aducanumab reduced markers of tau pathophysiology and neurodegeneration. Aducanumab reduced a specific type of Tau called p-Tau in the cerebrospinal in sub-studies conducted. When comparing the baseline levels of Tau in the cerebrospinal fluid to the placebo, the low and high dosages of Aducanumab were favorable. The graphs below show that the drug works effectively and seems to be doing what it is supposed to do. It is clear to see that the amount of plaque did not decrease at all with the placebo group. In fact, in the second graph, the plaque amounts increased. It is also shown that through the second study the low dosage started to change its rate in the reduction of the plaque after 26 weeks of being administered. Similarly in the third study after the 26th week of the drug being administered the rate of change decreases. However, the titration to 10mg/kg increased its rate of change. Therefore, when Aducanumab is given to patients, they are given an initial titration and then given the 10mg/kg since the rate is similar and steadier than the higher doses. Therefore, this drug is a marvel since it functions differently and has shown promising results in patients with milder symptoms of Alzheimer's. It is a miracle that it is reversing the effects of this troubling disease.

Figure 3: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 2

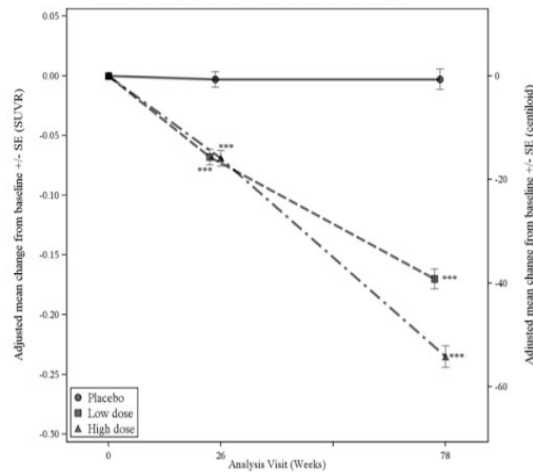


Figure 4: Reduction in Brain Amyloid Beta Plaque (Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 3

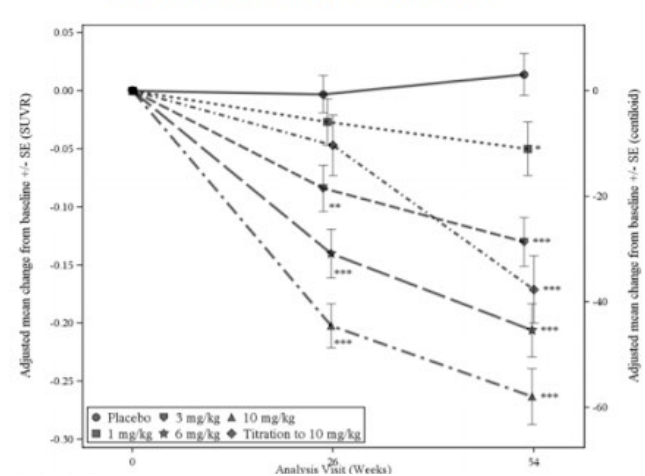


Figure 3 and 4: Graph of the reduction in Brain Amyloid Beta Plaque compared to the placebo in trials two and three.

However, another trial did not achieve such successful results as the ones that were previously produced. In this trial, 3285 people that were in the mild stages of Alzheimer's participated at 348 different sites across 20 countries. There were equal amounts of placebo and actual participants in the trial. In this trial, people were infused with 10 mg/kg monthly for 18 months. Compared to the 30% percent that received ARIA-E in the previous trial, around 41% experienced ARIA-E in this new one. There were not any new symptoms observed but the percentage increased from the older trial to the new one. After the results, researchers noticed that many were prone to ARIA-E if they had the APOE-4 gene defect. They also noticed that there was no significant difference in the percent decrease across and placebo and variable groups. The trial ultimately concluded that it is a drug worth trying but people should be cautious of the risks it poses.

## What do Physicians Think?

When consulting a neuro physician about this drug, he explained that in order to actually prescribe this medication, patients must go through a PET scan or must have the levels of amyloid checked through extraction from the spinal fluid. Only people within the mild stage are recommended to receive this drug and must be willing to pay out of pocket

as insurance will not be covered. After asking him about the potential risks with ARIA-E and with the uncertainty of the success, he noted that it is worth the shot. He said that the patient will be closely monitored for any adverse effects and the moment they see negative symptoms they will stop the treatment.

## **Difference between Aducanumab and other Drugs**

Now, this brings up the question “Why Aducanumab and why is it different?”. So far there are a couple of drugs in the market that appease the pain and hardship of Alzheimer’s disease. Some of these drugs include Galantamine, rivastigmine, donepezil, and memantine. There are more drugs to treat Alzheimer’s, but these are the most common ones that are used in America. All of these drugs are different from Aducanumab since they aren’t classified as immunotherapeutic drugs. Instead, they all deal with neurotransmitters. For example, galantamine, rivastigmine, and donepezil are drugs that are classified as cholinesterase inhibitors. The neurotransmitter Acetylcholine is vital for the brain to function. As Alzheimer’s progresses, the brain produces less and less of this degenerating the brain exponentially. In order to slow down this degeneration and to increase the output of acetylcholine, cholinesterase inhibitors are prescribed because they break down Acetylcholinesterase. This enzyme essentially breaks down acetylcholine and the cholinesterase inhibitors prevent acetylcholinesterase from releasing. This then leads to more output of acetylcholine since nothing is breaking it down. Memantine is another drug used to treat Alzheimer’s but it is for severe cases. Memantine is prescribed only to make the patient’s life at ease and comfortable before they pass. Memantine regulates the flow of glutamate, another neurotransmitter. While too much can be harmful, glutamate is a messenger transmitter that helps patients with their dementia. While it is not a cure, it prolongs the patient’s life. When compared with these drugs Aducanumab is different because it isn’t targeted towards the symptoms. Instead of increasing the flow of transmitters, Aducanumab attacks the main thing that blocks the flow. The approach of aducanumab is very different and its main goal is to reverse the effects that the disease has caused. While the other medications ignore the plaques, Aducanumab addresses it head-on. This type of medication is revolutionary since it shows the progression of finding a cure. Since it is nothing like the other disease and addresses the plaques head-on, it is a miracle drug because nothing like this has ever existed.

In conclusion, it is clear to see that aducanumab is a revolutionary drug. Alzheimer’s will continue to increase and progress until a cure is found. It is important to realize how all the medications mentioned aren't a cure but a treatment. This is critical to remember as Alzheimer's is a genetic disease. The only way to cure the disease is to correct the mutation in the gene. Aducanumab proved to work well compared to the placebo tests and has been successful so far. Even after comparing Aducanumab to other drugs, it is easier to understand how it works. Although Aducanumab doesn't cure Alzheimer's disease, it shows the progression of technology and gives light to a cure that may come shortly. The statistics for Alzheimer's are terrifying and it will continue to get worse. Unless we find a cure we will continue to suffer. Watching a family member deteriorate is difficult, and if there isn't a cure soon, it may be multiple members. In the future, it is important to make a change to prevent the tears and suffering of many faces due to genetic disease.

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