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Effectivity of Aβ Immunotherapies on Amyloid Plaque in Alzheimer's Patients: A Close Examination

Rithwik Tamilselvan[1], Jothsna Kethar[#] and Jobin Varkey[#]

[1]Alliance Academy for Innovation, USA
[#]Advisor

ABSTRACT

Alzheimer's disease, alternatively named senile dementia, is a progressive neurodegenerative disease that affects 55 million people worldwide. As of this moment, the disease has no cure, with treatments being targeted towards the symptoms; specifically, slowing down clinical decline. Important treatments called Aβ immunotherapies are being developed right now. Due to the severity of this disease, efficiently researching and quickly finding cures that are effective is crucial. This paper will be focused on reviewing current passive Aβ immunotherapies and determining the effectiveness through the immunotherapy's effects on amyloid plaque concentration and clinical decline. Through this, it can be determined if research on further passive Aβ immunotherapies is warranted. Through reviewing numerous studies and cases from multiple hospitals and institutions, it is found that Donanemab and Lecanemab are effective, with both being shown to reduce clinical decline and amyloid plaque concentration. Crenezumab is shown to have potential, with further studies required to confirm efficacy. The other three immunotherapies, Bapineuzumab, Ponezumab, and Gantenerumab, were found to be ineffective lowering amyloid plaque and slowing clinical decline. Future research should focus on further studying the efficacy and safety of these passive immunotherapies. Through these results, further research on passive Aβ immunotherapies is warranted, and should be focused on in the future. Using these findings, the route in which further research on passive Aβ immunotherapies can be determined and be as efficient as possible.

Introduction

Alzheimer's disease, also known as senile dementia, is a progressive neurodegenerative disease that destroys memory and other important functions. An estimated 6 million people have Alzheimer's in the US, with 55 million having this disease worldwide (Alzheimer's Association, 2014). As of this moment, Alzheimer's disease has no cure. However, there are treatments that are targeted towards slowing down the disease and treating the symptoms which are being developed right now. Right now, crucial treatments called Aβ immunotherapies are being developed. This paper will examine the effectiveness of these experimental immunotherapies, which are being developed to break down amyloid plaque in the brain, slowing down the progression of Alzheimer's. If it is determined that this is not an effective way of slowing down the progression of Alzheimer's, research should be conducted on alternative treatments instead of these immunotherapies. This will be determined by examining the results of each trial, and deciding whether each immunotherapy is decreasing amyloid plaque levels in the brain or slowing down the Neurodegeneration process. If enough immunotherapies, at least a third of those developed or being developed, are shown to have significant effects on slowing down the neurodegeneration process, then further research on immunotherapies is warranted.

In a study conducted by multiple MD and PhD scientists from the First Hospital of Jilin University in Changchun, China, they have recorded the effects of both aducanumab and lecanemab in Alzheimer's disease.

Aducanumab and Lecanemab are two of the experimental Aβ immunotherapies being developed to treat Alzheimer's by targeting the amyloid plaques in the Alzheimer patients' brains. They discovered that, among the different immunotherapies being developed, these two specific immunotherapies have good effects. However, many things are still unknown, and further studies are needed to confirm the efficacy. Further study should focus on cognitive decline (Shi et al., 2022).

As documented in the New England Journal of Medicine, a team of distinguished medical professionals spearheaded a comprehensive investigation on the effects of donanemab in early Alzheimer's disease. Donanemab is another one of the experimental Aβ immunotherapies being developed to treat Alzheimer's by targeting the amyloid plaques in the Alzheimer patients' brains. The findings of the study revealed that patients with early Alzheimer's disease had a better score for cognition and were able to perform better in daily activities because of Donanemab at 76 weeks. However, they note that secondary outcome results were mixed (Mintun et al., 2021).

Research led by a cadre of scientists from the Neurology department in Emory University explored the field of immunotherapies with a specific focus on immunoprevention in treating Alzheimer's disease. The study identified that recent trials testing Aβ-immunotherapies showed evidence that the progression of Alzheimer's disease can be slowed by removing amyloid plaque. However, the benefits achieved in these clinical trials have been modest, showing that a more in-depth understanding of the disease mechanisms and importance of early intervention is key to treating Alzheimer's. In addition, the study also found that an immunoprevention strategy for Alzheimer's disease is required (Walker et al., 2023).

The purpose of this paper is to determine whether this is the most effective way to go about treating Alzheimer's disease. As millions of people around the world have this disease, with the symptoms being severe, finding effective treatments is crucial. By examining whether these experimental Aβ immunotherapies are effective, it can be determined if this is an effective way of treating Alzheimer's, or if alternatives should be researched in its place. Additionally, this paper can be used to optimize research, and develop treatments quicker. It is hoped that this research will be used as a tool in developing a treatment for Alzheimer's, by determining the route in which further research should take place.

Methodology

This paper primarily focuses on passive Aβ immunotherapies, and the effects of these immunotherapies on amyloid plaque concentration in the brain of patients. Moreover, the research paper will be using related literature, specifically sources from multiple hospitals and institutions. The research paper will analyze these sources and articles, discussing results and explaining concepts. First, articles will be used to provide a background on the different aspects of passive Aβ immunotherapies, starting with antibodies, then antibody-antigen interaction, then specificity, then monoclonal antibodies, and finally passive Aβ immunotherapies compared to active. Second, studies and papers from institutions and hospitals will be used to discuss each specific passive immunotherapy. Finally, conclusions and analysis will be drawn from all these sources.

Alzheimer's Disease

Alzheimer's disease is a progressive type of dementia affecting cognitive function and behavior. The greatest known risk factor for this disease is aging, with most of the affected population being those over 65. This disease is progressive, meaning the symptoms that are associated with this disease worsen over time. The disease starts off with mild memory loss and progresses to the individual losing the ability to carry out a conversation and respond to their environment. Most people only live up to 8 years after the initial diagnosis, but some can live up to 20 years depending on certain factors. The two main factors that scientists believe lead to Alzheimer's

disease are amyloid plaque and tau clusters, which scientists believe play a role in blocking cell signals, communication, and processing, directly leading to the death of the nerve cells. While this disease has no cure, treatments, like immunotherapies, have been shown to remove amyloid plaque, directly correlating to a lower rate of clinical decline (Alzheimer's Association, 2007).

Importance of Antibodies

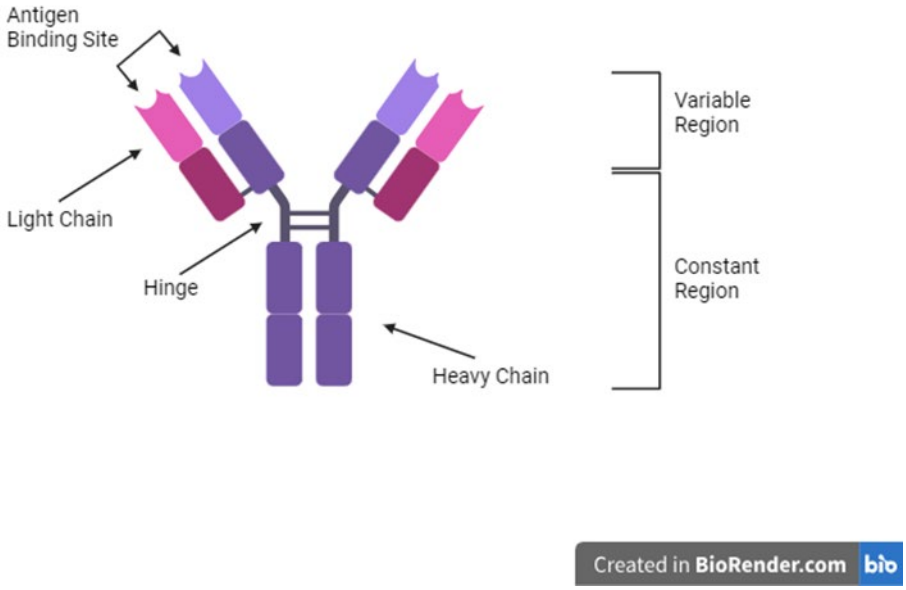

Figure 1. Antibodies are parts of the immune system; specifically, they are the protein components that circulate through the blood, recognize foreign substances, and neutralize the foreign substances. Antibodies are created by B cells, which are a type of specialized white blood cells (NIH, 2023). The structure of antibodies consists of four polypeptide chains in a Y-shape, two heavy and two light, connected by a di-sulfide bridge called the hinged. This structure allows it to carry out its functions in the most efficient manner. Additionally, Antibodies contain both a variable and constant region. The unique specific antigen binding site, the area in which the antibody binds to, is located in the variable region. This antigen binding site binds to the epitope, which is the region of the antigen that is recognized by the immune system. Finally, the two regions both have different functions. The constant region determines which immunoglobulin class the antibody belongs to, while the variable region determines the binding domain (Forst, 2018). Source: Created in BioRender.com by Tamilselvan (2024)

There are three main functions that antibodies carry out. First, antibodies are secreted out by B cells into the blood and mucosa of the body, where they bind to and neutralize foreign substances, like pathogens and toxins. Second, antibodies use and activate something called the complement system. The complement system are proteins that are a part of the immune system that destroy foreign invaders. This is through lysis, which happens

through rupture of the cell wall of the foreign invader. Third, antibodies use phagocytic cells to facilitate a process called phagocytosis. The antibodies activate the phagocytic cells using opsonization, which is a process where a pathogen is marked for phagocytosis. After the pathogen is marked, the pathogen is ingested by phagocytes and destroyed (Mbl Bio, 2017).

Antibody-Antigen Interaction

An antibody is able to complete its functions due to its interaction with an antigen, called the antibody-antigen interaction. The affinity of an antigen for the antigen it binds to determines the strength of the interaction. At the antigen binding site, the antibody interacts with the antigens at numerous sites through weak, covalent forces. The greater the interaction of the antibody with antigens at these sites, the greater the interaction between the two (Millipore Sigma, 2023).

The antigen binding site is located in the variable region of the antibody. Binding between this area and the epitope of the antigen occurs with a few processes and characteristics. First, the bond between the antigen and the antibody are reversible, which is due to the fact that these bonds are noncovalent. Second, these bonds can be either electrostatic bonds, hydrogen bonds, or bonds caused by Van der Waals forces. Third, tight bonding occurs due to numerous different bonds forming. Fourth, the binding that occurs between the epitope and the paratope, the region on the antibody that binds to the epitope, is made up of only a few amino acids. Fifth, the bonding sites are very important, as the binding must overcome the repulsion between the two molecules. Sixth, when the antibody and the antigen first come into contact, ionic and hydrophobic forces cause attraction, which help overcome the hydration energies and allow for water molecules to be expelled. Finally, Van der Waals forces are used later on to make the attraction between the antibody and the antigen stronger (Millipore Sigma, 2023).

The interaction between the antibody and the antigen can be affected by multiple different factors. First, temperature can affect this interaction. There is no specific temperature, as conditions vary depending on the epitope and paratope. For example, the formation of hydrogen bonds is usually exothermic. This means the bonds are more stable at lower temperatures. Second, pH can affect the antibody-antigen interaction. The effective functioning range of antibodies lies between 6.5 and 8.4 pH. Below or above this pH, the interaction is strongly inhibited. At very extreme pH conditions, either very basic pH or very acidic pH, the antibodies can change in shape, destroying the function and the antibody-antigen interaction. Finally, ionic strength can affect the antibody-antigen interaction. This strength is influenced by both sodium and chlorine ions. At lower ionic strengths, the reaction is usually faster, but effects can vary across different antibodies (Millipore Sigma, 2023).

Specificity of Antibodies

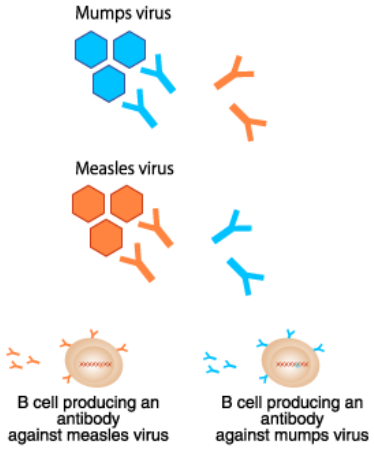

Figure 2. Antibodies display specificity, by which each antibody recognizes specific antigens. In the image above, there are two different antibodies produced by B cells. The first is an antibody against the measles virus, while the second is an antibody against the mumps virus. Due to the specificity of antibodies, the first antibody can recognize the measles virus, while the second antibody can recognize the mumps virus. However, the first antibody cannot recognize the mumps virus, and the second antibody cannot recognize the measles virus. Source: (MBL, 2017)

Each antibody is able to bind to one specific antigen. Specifically, each antibody is able to bind to specific epitopes, the region of the antigen that is recognized by the immune system, because of its unique Antigen Binding Site, located at the tip of its variable region. This allows precise detection of target epitopes, while avoiding other substances not of interest (Pacific Immunology, 2014). Monoclonal antibodies bind to a single epitope. However, if this antigen is not unique, the monoclonal antibody will bind to other proteins that contain the epitope. Polyclonal antibodies bind to multiple specific epitopes on one antigen (Aeonion Biotech, 2021). Due to the specificity of antibodies, the immune system can efficiently deal with foreign intruders.

Anti-Amyloid Monoclonal Antibodies Based on Aβ

Anti-amyloid monoclonal antibodies (mAbs), are the main disease modifying treatments that are being used for Alzheimer's disease. These antibodies specifically target the amyloid plaque in the brain. All of these antibodies all share some characteristics but have their own unique features. In function, they all demonstrate a lowering of marked Aβ, target high molecular weight fibrillar Aβ concentrations, and lead to imaging abnormalities that have to do with amyloid. The antibodies differ in what they target, specifically the type and range of amyloid species.

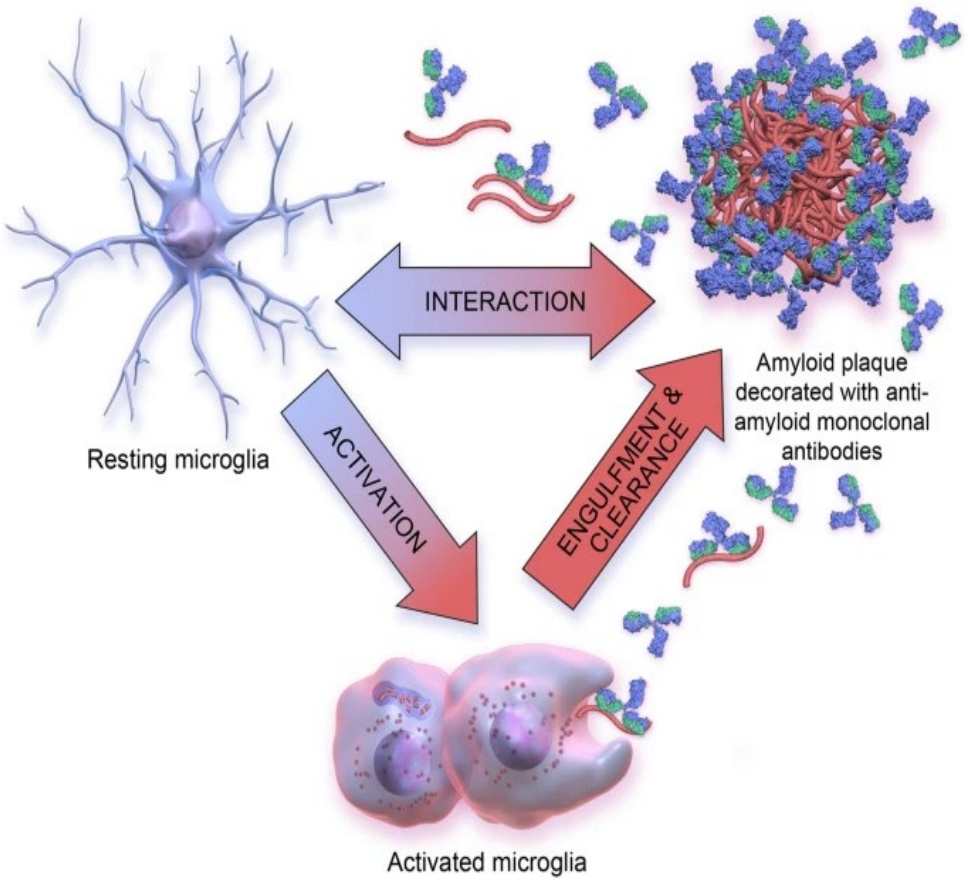

Figure 3. For all these antibodies, the way Aβ plaque is reduced is thought to be through two different things, the degradation through the endosomal/lysosomal system, and through the activation of microglia with phagocytosis of fibrillar Aβ. Each of these antibodies target a different type of Aβ species. For example, Lecanemab targets protofibrils with a higher preference over plaque Aβ, specifically protofibrils with higher affinities. On the other hand, Donanemab targets pyroglutamate Aβ that is present on plaque. This difference in the antibodies leads to a wide range of uses. Source: (Cummings et al., 2023)

Plaque Aβ, which is the amyloid plaque that is visualized through a machine called an amyloid PET, is reduced by all the anti-amyloid monoclonal antibodies that have been approved so far. Through this, the effectiveness of these antibodies in treating Alzheimer's has been seen, through reduction of amyloid plaque. Overall, approved antibodies have shown a 30% decline in clinical decline in Alzheimer's patients, suggesting that the benefits of this treatment may outweigh the risks. These anti-amyloid monoclonal antibodies demonstrate the first step in disease modifying treatments and are an important step in the road to curing Alzheimer's disease.

Passive Aβ Immunotherapies as Opposed to Active Aβ Immunotherapies

Passive immunotherapies and active immunotherapies are different, specifically in the way they influence the patient's immune system. Active immunotherapy is a drug that produces a long response to create immunological memory, which is the ability of the immune system to work faster and more efficiently with pathogens that have entered the body before. Opposed to this, a passive immunotherapy drug is one that administers immune-cell factors for the purpose of causing immediate action (Beckman, 2018)

Generally considered methods of passive immunotherapies in Alzheimer's disease include multiple things. First is the antibody opsonization of the antigen, in which the antibodies tag the pathogens for phagocytosis. Second is the reduction of Aβ, specifically mediated by antibodies in favor of Aβ efflux from the central nervous system. Third is the antibody-catalyzed modification of the monomers of Aβ for the purpose of blocking the formation of either oligomers or fibrils (Song et al., 2022). Through these methods, passive immunotherapies can directly target and lower amyloid plaque in the brain, leading to slower rates of clinical decline.

Effectiveness of Passive Aβ Immunotherapies

Donanemab

A major study published in the National Library of Medicine by numerous medical professionals tested the efficacy and events of Donanemab, a passive Aβ immunotherapy drug, on patients with Alzheimer's disease. By conducting an 18-month trial with 1736 participants, they were able to conclude that Donanemab slowed down clinical progression of patients with early symptomatic Alzheimer's disease. Specifically, they found that clinical progression was significantly slowed down at 76 weeks in low to high tau populations (R Sims et al., 2023).

In addition, a systematic review of clinical trials pertaining to Donanemab, done by the departments of research of multiple distinguished institutes, studied the efficacy of Donanemab. By reviewing trials of Donanemab in 396 patients, all with different degrees of Alzheimer's, they were able to conclude that there was an overall decrease in amyloid plaque levels in the brain in the patients tested. Additionally, they found that other favorable outcomes included a reduction in the accumulation of tau levels and lower cognitive decline with Donanemab (Rashad et al., 2022).

Finally, an evaluation done by a professor at the Queensland University of Technology analyzed the effectiveness of Donanemab on Alzheimer's patients. By evaluating a phase 2 trial of Donanemab, they concluded that it was not known whether this medicine specifically caused the outcomes of the trial. Finally, they stated that since there is no clear proof that using Aβ antibodies to remove amyloid plaque improves cognition and other activities of those with the disease, clinical trials testing using these antibodies should be abandoned, and money should be spent on studying the underlying cause of Alzheimer's disease (Doggrell, 2021).

Lecanemab

A study documented by the New England Journal of Medicine tested the effects of Lecanemab, a passive Aβ immunotherapies drug, on patients with early Alzheimer's disease. By conducting an 18-month study on persons 50-90 years old, they were able to conclude that Lecanemab was able to reduce the effects of amyloid plaque in the brain, causing a slower decline of mental functions. However, they gathered that longer trials are necessary to test the safety and efficacy of this immunotherapy on those with early Alzheimer's disease (Dyck et al., 2022).

Another study published in the BMC by multiple medical professionals also tested Lecanemab, analyzing the effectiveness of this immunotherapy. By conducting a placebo-controlled study of 856 patients, they were able to determine that this treatment resulted in a significant reduction of amyloid plaque in the brain, slowing clinical decline in the patients. They also determined that the data demonstrated that there is potential in using plasma biomarkers to monitor treatment using lecanemab (McDade et al., 2022).

Bapineuzumab

A study documented in the National Library of Medicine studied the effects of Bapineuzumab, a passive Aβ immunotherapy drug, on Alzheimer's patients. By conducting phase 1-3 randomized clinical trials, they were able to conclude that the drug failed to show efficacy, stating that no clinical benefit to using Bapineuzumab to treat Alzheimer's disease is visible (Khorassani et al., 2013).

Another, larger study, published in the National Library of Medicine evaluated the efficacy and safety of Bapineuzumab in Alzheimer's patients. By conducting 2 phase 3, placebo controlled, 18-month trials, they were able to conclude that Bapineuzumab was not effective. Specifically, they stated that these trials confirmed the lack of efficacy in patients with mild to moderate Alzheimer's disease at the doses being tested (Vandenberghe et al., 2016).

Another study documented in the New England Journal of Medicine, done by a group of medical professionals studied the effectiveness of Bapineuzumab on Alzheimer's patients. By conducting 2 placebo-controlled phase 3 trials, they were able to conclude that this drug did not have any effect in the clinical outcomes of patients with Alzheimer's disease, despite differences in biomarkers seen in *APOE ε4* carriers (Salloway et al., 2014).

Finally, a study published in JAMA by a group of distinguished scientists evaluated the effect of Bapineuzumab on neuronal degeneration in patients with Alzheimer's. By conducting 2 phase two placebo-controlled, 12-month trials, they were able to discover that Bapineuzumab decreases the neurodegeneration process. Specifically, the trial found that decreases in CSF T-tau and P-tau were seen as a result of Bapineuzumab (Blennow et al., 2012).

Crenezumab

A study documented in the National Library of Medicine evaluated the safety and efficacy of Crenezumab, a passive Aβ immunotherapy drug, on adults with early Alzheimer's disease. By conducting two phase 3 placebo-controlled trials, they were able to conclude that the immunotherapy was well tolerated but had no effect on clinical decline in patients with early Alzheimer's disease (Ostrowitzki et al., 2022).

Another study published in the BMC by a group of medical professionals investigated the effect of Crenezumab on disease progression in Alzheimer's patients. By conducting two phase 2 placebo-controlled trials, they were able to conclude there is a possible slower accumulation of amyloid plaque. However, the primary goal and endpoint was not met with this trial (Salloway et al., 2018).

Finally, a study documented in the Journals of Alzheimer's Disease investigated the safety and effects of Crenezumab in patients with Alzheimer's disease. By conducting a trial using people with mild to moderate Alzheimer's disease, they were able to conclude that doses of less than 120 mg/kg intravenously q4w were well tolerated (Guthrie et al., 2020).

Ponezumab

A study published in the National Library of Medicine characterized the safety and effects of Ponezumab, a passive Aβ immunotherapy drug, on patients with mild to moderate Alzheimer's disease. By conducting trials with patients over 50 years old with Mini-Mental State Examination scores 16-26, they were able to conclude that the drug was generally well tolerated. However, there was no observable effect on amyloid plaque, mental cognition, and function (Landen et al., 2017).

Next, a study by Clinical Neuropharmacology investigated the safety and pharmacology of Ponezumab in mild to moderate Alzheimer's disease patients. By conducting randomized, double-blind trials, they were able to conclude that Ponezumab alters Aβ levels, showing it could be effective in treating Alzheimer's disease. Additionally, they found that "a 2-hour infusion of 0.1 to 10 mg/kg Ponezumab" was tolerated well by subjects with mild to moderate Alzheimer's disease (Zhao et al., 2013).

Gantenerumab

A major study documented in the New England Journal of Medicine investigated the effects of Gantenerumab, a passive Aβ immunotherapy drug, on participants with mild Alzheimer's disease. Through conducting two phase 3 trials on participants aged 50-90 years, they were able to deduce that the use of Gantenerumab lowered the amyloid plaque in the brains of the patients compared to the placebo. However, they found that this did not lead to a slower rate of clinical decline in participants (Bateman et al., 2023).

Next, a study published in the BMC by a cadre of medical professionals characterized the efficacy and safety of Gantenerumab. By conducting a randomized, double-blind, placebo-controlled phase 3 study, they were able to conclude biomarkers suggested that higher dosing may be necessary to achieve efficacy. However, they found that Gantenerumab was overall ineffective, and this study was stopped early for futility (Ostrowitzki et al., 2017).

Results and Discussion

Examining these studies, it can be concluded that Donanemab is effective in decreasing amyloid plaque levels in patients and slowing clinical decline. While further study of the safety of this immunotherapy is necessary, the drug is successful overall, with the approval application having been submitted to the FDA. Action is expected in early 2024 (Alzheimer's Association, 2023). In addition, based on the studies, it can be determined that Lecanemab is effective in reducing amyloid plaque and slowing clinical decline. While further tests are necessary to test safety and further test efficacy, passive immunotherapy is shown to be successful. Additionally, based on the results of the studies, it can be determined that Bapineuzumab is overall unsuccessful in treating Alzheimer's patients, with very little effect on amyloid plaque and clinical outcomes. Out of 5 studies, only one showed any change, with no specific effects on clinical outcomes. Furthermore, it can be determined that Crenezumab is not effective in treating Alzheimer's disease, with very little effect on amyloid plaque and clinical decline. As this drug is a newer immunotherapy, further studies are required to confirm this lack of effectiveness; however, current studies have shown that Crenezumab is not successful. Moreover, it can be determined that Ponezumab is overall unsuccessful in treating Alzheimer's disease, with no definite outcomes on amyloid plaque and clinical decline. As there are very few studies on this drug, further testing is required, but the drug is shown to be ineffective as of now. Finally, it can be determined that Gantenerumab is not effective in lowering amyloid plaque and slowing clinical decline, with multiple organizations confirming this through independent studies. Testing for this drug has come to a near end due to futility in past studies.

Out of all six immunotherapies, Donanemab is the most effective immunotherapy. With multiple documented cases of success in lowering amyloid plaque level and slowing clinical decline, along with submission for FDA approval, Donanemab is shown to be the most effective out of the six. The second most effective is Lecanemab. Being the only other immunotherapy with clear effects on slowing clinical decline and lower amyloid plaque levels, Lecanemab is proven to be effective, albeit less effective than Donanemab. Crenezumab is the third most effective. While there are no definite results showing this drug is effective, studies have shown possible slower accumulation of amyloid plaque, with the drug being well tolerated. With this drug having the potential to be effective, it is more effective than the other three, but less effective than both Donanemab and Lecanemab. The fourth most effective is Ponezumab. With the drug shown to alter amyloid-beta levels, no observable effect is shown on brain function and amyloid plaque levels, which is why the drug is ineffective. However, with the potential to help, this drug is more effective than both Gantenerumab and Bapineuzumab. The fifth most effective is Bapineuzumab. With only one trial showing the drug having any effect on clinical

decline, this drug is ineffective, with most studies showing no effect on amyloid plaque levels and clinical decline. Finally, the sixth most effective, or the least effective, is Gantenerumab. With no study finding any effect on either amyloid plaque levels or clinical decline, the drug is ineffective, with many trials being stopped short for futility. For this reason, Gantenerumab is the least effective of the six immunotherapies.

Conclusion and Recommendation

By examining all six of the most relevant passive Aβ immunotherapies, it can be determined that two out of the 6 are proven to be effective in lowering amyloid plaque in the brain, and slowing down the neurodegeneration process, namely Donanemab and Lecanemab. Crenezumab is found to have possible effectiveness in lowering amyloid plaque and is well tolerated by participants. As Crenezumab is a relatively new immunotherapy, further testing is required to quantify and establish the effectiveness of this immunotherapy. The other three, Bapineuzumab, Ponezumab, and Gantenerumab, were found to be ineffective in lowering amyloid plaque and slowing clinical decline. As at least one third, 2 out of the 6, are proven to lower amyloid plaque or slow down the neurodegeneration process, it can be stated that further research on Aβ immunotherapies is warranted. With this, Aβ immunotherapies are shown to be effective and instrumental towards developing a cure for Alzheimer's disease. In addition, Donanemab is the most effective, with most studies finding effects on amyloid plaque levels and clinical decline, even awaiting FDA approval after submission in 2023. Gantenerumab is the least effective with no studies finding any effect on amyloid plaque levels and clinical declines, and studies even being shut down early for futility.

Based on all prior study and analysis, further research on Aβ immunotherapies is warranted and is an effective way of treating Alzheimer's disease, and further research should be conducted on both existing and new immunotherapies. Developing these immunotherapies should be prioritized, and further study of the safety and efficacy of existing and new immunotherapies should be conducted. Specifically, research should focus on Donanemab, Lecanemab, and Crenuzumab, along with creating new immunotherapies.

Limitations

This paper is focused on passive Aβ immunotherapies, and the effectiveness of these immunotherapies. Out of the six immunotherapies mentioned, Donanemab, Lecanemab, and Crenuzumab should be further explored. While immunotherapies are only one of the many Alzheimer's disease treatments being developed, results have shown that this treatment is a key instrument in the road towards curing Alzheimer's disease.

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