Immunotherapy as a treatment strategy for Alzheimer's and Parkinson's Disease

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Abstract

Every day millions of individuals are affected by Alzheimer's and Parkinson's disease. Currently available treatments solely treat the symptoms of these neurodegenerative diseases, rather than targeting the underlying causes. Immunotherapy has emerged as a possible treatment, targeting the protein aggregates associated with the pathogenesis of these diseases. Passive or active immunotherapy can be used to administer target specific antibodies, which are able to bind and remove AB plaques, tau protein, alpha synuclein and inflammatory mediators involved in neurodegeneration. This literature research provides an overview of the immunotherapeutic strategies currently studied in clinical trials for AD and PD. While results of most study outcomes show the ability of these drugs to reduce the levels of their target proteins, in many cases this does not translate to a significant effect on the clinical progression of the disease. This might be due to the lack of knowledge on the interactions between the involved proteins and the insufficient understanding of the main disease driving pathways. Additionally, more research should be done on developing methods for early diagnosis before the onset of clinical symptoms of AD and PD. Nevertheless, immunotherapy as a treatment for AD and PD is a promising strategy which could lay the foundation for future research into the treatment of these neurodegenerative diseases.

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most prevalent neurodegenerative diseases worldwide, affecting millions every day (Chopade et al, 2022). Therefore, the demand for treatment strategies treating the cause of these diseases is high. This literature research will focus on summarizing the immunotherapeutic strategies which are currently being studied in clinical trials for Alzheimer's and Parkinson's disease.

Alzheimer's disease is the main cause of dementia and is characterized by a decline of memory and cognitive functioning. According to the World Health Organisation (WHO, 2023), over 55 million people have been diagnosed with dementia today, of which between 60- and 70% is caused by AD. The main driver of Alzheimer's Disease remains an ongoing debate, with several hypotheses offering explanations for the onset of this disease. Firstly, the amyloid-cascade hypothesis states that the aggregation of amyloid- β and thereby the formation of Aβ plaques is the main cause of neurodegeneration leading to the cognitive decline observed in AD (López et al, 2019). A second hypothesis states that the aggregation of tau proteins is the leading cause of neurodegeneration found in Alzheimer patients (Muralidar et al, 2020).

Parkinson's disease is a chronic neurodegenerative disease which is characterized by the death of dopamine producing neurons in the substantia nigra (Reich et al, 2019). Reduced dopamine levels caused by this neuron loss disrupt the signal transduction needed for normal movement and coordination, which results in motor symptoms visible in PD patients such as tremor, rigidity and a crouched posture. Non-motor systems such as cognitive impairment, dementia, depression and anxiety are also often observed in PD patients (Reich et al, 2019). The leading theory on the cause of neurodegeneration in Parkinson's disease is the aggregation of alpha-synuclein protein (Chatterjee et al, 2019). Additionally, neuroinflammation in the central nervous system (CNS) is thought to play an important role in the neurodegeneration observed in both AD and PD (Wang et al 2023).

The treatments currently available for Alzheimer's and Parkinson's disease primarily target the symptoms of the diseases, rather than affecting the underlying causes of these conditions (Passeri et al, 2022, Reich et al, 2019). Examples of available treatments for AD are drugs which increase glutamatergic signalling; the primary excitatory neurotransmitter in the brain, and cholinergic signalling; a neurotransmitter involved in memory and cognitive functioning (Passeri et al, 2022). Treatment options for motor symptoms in PD are mainly based on administering dopamine to compensate for the loss of dopaminergic neurons (Reich et al, 2019). Given the strong demand for treatments targeting the cause of these neurodegenerative diseases, many studies are being conducted on this topic, such as research on gene therapy (Tuszynski et al, 2015), whole body vibrations (Arauz et al, 2020) and immunotherapy.

Immunotherapeutic treatment has attracted much attention in the last years. In this treatment strategy, target specific antibodies are used which bind and remove the toxic protein aggregates found in PD and AD (Song et al, 2022, Chatterjee et al, 2019). Two types of immunotherapy, passive or active, can be used to produce antibodies in the patient. During active immunotherapy, a vaccine containing fragments of the target protein is given. This induces a humoral response of the immune system, in which B cells are activated and start the production of specific antibodies to the target protein. This type of immunotherapy is beneficial due to its ability to provide a sustained production of antibodies, without the need for repeated injections (Song et al, 2022). Passive immunotherapy, in which predesigned protein specific antibodies are injected directly, does not induce immune memory and therefore needs to repeatedly be given to the patient (Song

et al, 2022). However, a greater risk of generating an autoimmune response is present with this treatment strategy. Another drawback of active immunotherapy is the chance of failure to activate an immune response in the patient (Song et al, 2022).

The aim of this literature study is to provide an overview of the immunotherapeutic treatments available for Alzheimer's and Parkinson's disease which have been approved or are currently being developed in clinical studies. The main drug target, mechanism of action and results of each study will be discussed and compared for all drug treatments. Furthermore, the future perspectives of using immunotherapy as a treatment for AD and PD will be explored.

Methods

A literature research was conducted to provide an overview of the currently existing immunotherapeutic treatments for AD and PD, by finding and comparing the relevant research articles for each study on PubMed or ClinicalTrials.gov. The findings of each study were organized into tables in the appendix for a clear overview. A detailed elaboration was provided for all therapeutic strategies which showed an effect on cognitive function in phase 2 or phase 3 trials. No further elaboration was given on immunotherapeutic studies which showed no effect on disease progression or slowing of cognitive decline in their most recent trial, or on therapies currently studied in preclinical or phase 1 studies. An overview of the different phases of clinical trials, used to test the safety and efficacy of drug treatments, is given in figure 1 (MD Anderson Cancer Center, n.d.).

Figure 1: *An overview of the focus of each clinical trial used to test the safety and efficacy of medical drug treatments Note.* Phases of clinical trials. (n.d.) From MD Anderson Cancer Center.(https://www.mdanderson.org/patients-family/diagnosis-treatment/clinical-trials/phases-of-clinical-trials.html)

Overview current immunotherapy treatment strategies

a. *Immunotherapeutic strategies based on Aβ*

i. Amyloid-beta cascade hypothesis

According to the amyloid-beta cascade hypothesis, the formation of Aβ plaques is the main cause of neurodegeneration in Alzheimer's disease (López et al, 2019). Amyloid plaque formation is caused by the cleavage of amyloid precursor protein (APP) (López et al, 2019). APP is part of a family of single-pass transmembrane proteins, of which the exact function is still unknown. Once this protein is synthesized it is inserted into the surface of the cell. This step is followed by two possible cleavage pathways of APP. In the first, non-amyloidogenic pathway, APP is cleaved by α- and γ-secretases. During the second amyloidogenic pathway, the cleavage of APP is done by β- and γ-secretases. Only this second pathway leads to the formation of amyloid-β peptides, which then get released into extracellular space (López et al, 2019). The length of this peptide varies, but research has shown that peptides made up of 40 or 42 amino acids are most likely to aggregate into amyloid-β fibrils (López et al, 2019). These fibrils have been shown to cause apoptosis of neurons, thus leading to cell death (López et al, 2019). There are multiple possible reasons for the increase of amyloid-β plaques in the brain with age. For instance, the clearance of Aβ from the brain decreases with age and an increase in β-secretases, leading to increased production of Aβ, is seen as well (Song et al, 2022). Targeting Aβ plaques with immunotherapy could therefore be a promising strategy to treat Alzheimer's Disease.

ii. Passive and active immunotherapy strategies based on *A*β

Lecanemab

The passive humanized IgG monoclonal antibody Lecanemab binds to soluble amyloid-beta aggregates (Swanson et al, 2021). The antibody was tested in a phase 2 study (Clinical Trials [CT], NCT01767311) involving 854 participants with early Alzheimer's disease, in which the primary endpoint was not met. However at 18 months, a decrease in amyloid-beta plaques and slowing of disease progression were measured (Swanson et al, 2021). The results of the following phase 3 study (CT, NCT03887455), where Lecanemab's effect on 50 patients with early Alzheimer's disease was studied, showed a slowed disease progression compared to the control group as well as a decrease in Amyloid-Beta plaques (Van Dyck et al, 2023 & McDade et al, 2022). However, Amyloid related imaging abnormalities (ARIA) were observed, an adverse effect which is often seen in immunotherapy treatments (Hampel et al, 2023). Two types of ARIA can occur; ARIA-H and ARIA-E. During ARIA-H, or ARIA haemorrhage, blood vessels in the brain are damaged by accumulated protein and the binding of the target specific antibodies to these aggregates, resulting in small bleedings. The second type of ARIA, ARIA-edema, is caused by the accumulation of fluid in the tissues of the brain due to these aggregated proteins and antibodies (Hampel et al, 2023). In both cases, ARIA can lead to side effects such as head ache, nausea and confusion. Due to the outcomes of the previous studies, a longer trial to test the safety and effectiveness of Lecanemab was suggested by the researchers involved in this study (Van Dyck et al, 2023).

Aducanumab

The use of the passive immunotherapeutic drug Aducanumab as a treatment strategy for Alzheimer's disease has been a controversial topic over the past few years (Heidebrink et al 2024). In a phase 1 trial (CT, NCT01677572) including 165 patients with early symptomatic AD, a significant decrease in amyloid beta levels was measured as well as slowing of disease progression (Sevigny et al, 2016).

During this study the main side effect was ARIA-E, which occurred more with an increase of aducanumab dosage (Sevigny et al, 2016). Due to the promising results of the phase 1 trial and the urgent demand for a treatment strategy for AD, two phase 3 trials were announced immediately after (Haeberlein et al 2024). Again, these studies involved patients with early symptomatic AD, this time including 1638 test subjects (Haeberlein et al, 2022). However, both trials were terminated early due to a prediction of having ineffective results (Heidebrink et al 2024). After half a year, it was announced that the predictions of one of the two studies (CT, NCT02484547) had been wrong and that this study had in fact shown significant effects of aducanumab. Results of EMERGE showed significantly less cognitive decline in aducanumab treated groups compared to the control group after a treatment period of 78 weeks. However, no meaningful effect of aducanumab was found in the second phase 3 study (CT, NCT02477800) (Haeberlein et al, 2022). In 2021, aducanumab got accelerated approval from the US Food and Drug Administration (FDA) to be used as treatment for patients with mild cognitive impairment or mild dementia (Heidebrink et al 2024). Although aducanumab had now been approved, this authorization process raised a lot of concern (Heidebrink et al, 2024). Due to these concerns about the safety and efficiency surrounding aducanumab, many health systems refused to offer the treatment , resulting in the drug's failure to be launched (Heidebrink et al 2024).

Donanemab

The passive humanized monoclonal igG1 antibody Donanemab underwent a phase 2 study (CT, NCT03367403), involving 257 patients diagnosed with early stage Alzheimer's Disease. These results showed an increase in cognitive performance as well as a reduction in the amount of Aβ plaques in patients treated with Donanemab after 76 weeks of treatment (Mintun et al, 2021). Following this, an 18-month phase 3 study (CT, NCT04437511) was performed on 1736 patients diagnosed with early symptomatic AD (Sims et al, 2023). The outcomes of this study indicated that treatment with Donanemab slowed progression of the disease. In 24% of patients who received Donanemab, ARIA-E was observed, whereas the incidence of this adverse effect was only 2.1% in the placebo group (Sims et al, 2023). The results of a subsequent follow-up study, testing the safety of Donanemab usage, are expected to be available in November 2027 (CT NCT05026866).

b. Immunotherapeutic strategies based on tau

i. Tau hypothesis

In patients with Alzheimer's Disease, high levels of hyperphosphorylated tau can be observed in the CNS (Muralidar et al, 2020). Tau is a protein involved in the stabilization of microtubules, which are structures with multiple important functions in the cell such as stability, signal transduction and intracellular transport (Muralidar et al, 2020). Hyperphosphorylation of tau leads to a change in charge and conformation of the protein, which increases the risk of its aggregation. Aggregated tau proteins will eventually form neurofibrillary tangles (NFT's). As a result, tau loses its stabilizing function and the microtubules will collapse, which causes impaired axonal transport and neurotoxicity (Muralidar et al, 2020).

It is clear that tau plays an important role in the onset of neurodegenerative diseases such as Alzheimer's disease. Therefore, using immunotherapy as a strategy to decrease tau protein aggregates is currently being studied in many clinical trials as a potential treatment for Alzheimer's Disease.

ii. Passive and active immunotherapy based on tau

All immunotherapeutic strategies based on removing tau protein aggregates are currently in preclinical, phase 1 or phase 2 studies. For more information on these studies see table 4 and 5 in the appendix.

c. Immunotherapeutic strategies based on alpha-synuclein

i. Alpha-synuclein hypothesis

Alpha-synuclein aggregation is thought to play an important role in the onset of Parkinson's Disease. AS is a protein found at presynaptic terminals, where it is involved in regulating snare complex formation and vesicle fusion (Chen et al, 2020) . Misfolding of αS proteins leads to the formation of protein aggregates, which can induce nuclear dysfunction, synaptic dysfunction and lead to neuronal cell death (Chen et al, 2020). This protein misfolding can have multiple potential causes, such as mitochondrial dysfunction, the production of reactive oxygen species (ROS) and malfunctioning clearance pathways (Chatterjee et al, 2019). Since αS is suggested to play an important role in the neurodegeneration observed in PD, targeting these protein aggregates with immunotherapy could be a promising strategy to treat this disease.

ii. Passive and active immunotherapy based on alpha-synuclein

All immunotherapeutic strategies based on removing alpha-synuclein aggregates in AD and PD patients are currently undergoing preclinical, phase 1 or phase 2 studies. For more information on the outcomes of these studies see table 6 ad 7 in the appendix.

d. Immunotherapeutic strategies based on neuroinflammation

i. Neuroinflammation hypothesis

Inflammation in the central nervous system is associated with both Alzheimer's and Parkinson's disease (Mortada et al, 2021). The inflammatory response in the CNS is activated as a protective response to damage. This response is mainly regulated by microglia, the primary immune cells in the spinal cord and the brain (Mortada et al, 2021). Microglia can shift their physiological state from a ramified, surveillant form to a amoeboid, phagocytotic state in case of damage (Vidal-Itriago et al, 2022). Once activated, the main type of microglial cells named astrocytes, start producing proinflammatory cytokines and induce the recruitment of peripheral immune cells to the CNS. To enable the entry of these immune cells into the brain, astrocytes cells break down the blood brain barrier (BBB). Once the infection or injury in the brain has been removed, typically the homeostasis will be restored (Mortada et al, 2021). Neuroinflammation is therefore a beneficial response to protect the neurons of the CNS against permanent damage. In some cases, certain mutations can cause an abnormally low level of immune cell activation (Mortada et al, 2021). In this situation, immunotherapy can potentially be used to increase microglial activity in order to trigger a sufficient immune response to the aggregated proteins associated with neurodegenerative diseases (Mortada et al, 2021). However, in neurodegenerative diseases such as AD and PD, permanent activation of the immune system leading to neuroinflammation is often observed in the brain (Mortada et al, 2021). Protein aggregates associated with these diseases were shown to act as a persistent stimulus by binding to the pattern recognition receptors (PRRs) on the immune cells, causing a chronic activation of microglia and a continuous elevation of cytokine levels (Wang et al, 2019). This chronic immune cell activation does not only remove the present DAMP's, but can lead to phagocytosis of synapses and other cell parts as well (Wang et al, 2019).

Therefore, targeting these inflammatory mediators involved in the immune response, in order to prevent neurodegeneration, could potentially be used as a treatment for Alzheimer's and Parkinson's disease.

ii. Immunotherapy targeting inflammatory mediators

GV-971

Disruption of the gut microbiome has been shown to increase microglial activity and proinflammatory cytokine production, thus contributing to neuroinflammation associated with Alzheimer's disease (Wang et al, 2019). A phase 3 study (CT, NCT0229391) was performed to test the safety and efficacy of GV-971, an oligosaccharide derived from brown algae which is thought to reconstruct gut microbiota (Xiao et al , 2021). This trial consisted of 818 patients with mild to moderate AD, of which 408 received GV-971, and was continued for a total of 37 weeks. The results of the study showed that GV-971 administration had the ability to reconstruct the gut microbiome, reduce neuroinflammation in the brain and significantly increase cognitive function (Xiao et al, 2021 & Wang et al, 2019). Furthermore, the incidence of adverse effects was not higher in the GV-971 treated group than in the placebo group (Xiao et al, 2021).

Not only has GV-971 been studied as a strategy to treat Alzheimer's disease, but research on its effect on Parkinson's disease is currently also being done (Yu et al, 2023). A study (Yu et al, 2023) showed that GV-971 protects neurons from damage associated with αS aggregation. A phase 2 study of the effect of GV-971 on Parkinson's Disease has been approved in the US, but this study has not been started yet (Yu et al, 2023).

Sargramostim

Sargramostim is a synthetic form of GM-CSF, designed to mimic it's activating effect on microglial and regulatory T cells (Mortada et al, 2021). By activating these immune cells, GM-CSF promotes the clearance of Aβ plaques. Sargramostim is currently being studied as a treatment for both neurodegenerative diseases, so far with promising results. In a preclinical study in AD mouse models, GM-CSF administration for a short period of three weeks showed a significant increase in microglial activity. Additionally, a decrease in the amount of Aβ plaques and an increase in cognitive function were measured (Sanchez-Ramos et al, 2009). In a phase 2 study (CT, NCT01409915), Sargramostim's ability to reduce symptoms of Alzheimer's disease in a safe manner was assessed (Potter et al, 2021). The study contained 40 patients with mild to moderate Alzheimer's disease, which received placebo or Sargramostim injections for 3 weeks (Potter et al, 2021). Results of this study showed a significant decrease in Aβ and tau biomarkers, as well as an increase in cognitive function and no drug related adverse effects. A phase 3 study on Sargramostim's effect in AD patients has not yet been started.

Sargramostim as a drug against neurodegeneration is currently also being studied in Parkinson's disease. Results of a phase 1 study (CT, NCT01882010), containing 17 healthy subjects and 20 PD patients, showed improved cortical motor activities and increased Treg numbers after Sargramostim administration (Gendelman et al, 2017).

T3D-959

T3D-959 is an agonist of PPAR- γ, a receptor regulating the storage of fatty acids and glucose production (De La Monte et al, 2016). The brain is highly dependent on glucose as an energy source and therefore impaired PPAR-y signalling can lead to low energy availability which causes neuronal cell death (De La Monte et al, 2016).

The use of T3D-959 to increase PPAR-y signalling has been studied in a preclinical trial (De La Monte et al, 2016), which found that drug administration reduced Aβ and tau levels and decreased neuroinflammation in rat AD models. These promising results led to a phase 2 trial (CT, NCT04251182), in which 34 test subjects with mild to moderate AD were given different doses of T3D-959 for two weeks (Chamberlain et al, 2020). The results of this trial showed cognitive improvement in the test subjects, with no serious adverse effects, but further investigation in a larger study is necessary.

Table 1: Overview of all immunotherapeutic strategies for AD or PD which have shown to improve cognitive functioning in a phase 2 or phase 3 trial

Drug	Disease	Immunization type (passive vs active)	Drug target	Study Subjects	Most recent phase of trial	Status recent trial	Results	Source study
Lecanemab	AD	Passive	*A*β plaques	Early AD	Phase 3 Clarity AD (NCT03887455)	Completed	- Decrease in Aβ levels - Slowing of cognitive decline - Terminated due to adverse effects	105
Aducanumab	AD	Passive	*A*β plaques	Early symptomatic AD	Phase 3 EMERGE (NCT02484547)	Completed	- Decrease in Aβ levels - Slowing of cognitive decline	61
Donanemab	AD	Passive	*A*β plaques	Early symptomatic AD	Phase 3 TRAILBLAZER-ALZ 2 (NCT04437511)	Completed	- Decrease in Aβ levels - Slowing of cognitive decline	92
GV-971	AD	Passive	Gut microbiome reconstruction	Mild to moderate AD	Phase 3 (NCT0229391)	Completed	- Reduced Th1 related neuroinflammation - reconditioned gut microbiota - Reverse cognitive impairment	112
Sargramostim	AD	Passive	Immune cell activation	Mild to moderate AD	Phase 2 (NCT01409915)	Completed	- Effect on cognitive and memory function	86
T3D-959	AD	Passive	PPAR- γ activation	Mild to moderate AD	Phase 2b (NCT04251182)	Completed	- improved cognitive function	9

Discussion

Many of the previously discussed clinical trials showed the ability of immunotherapeutic drugs to bind their target proteins, resulting in a decrease of these protein aggregates in the CNS. However, in most cases the removal of these aggregates through drug administration does not translate into an increased cognitive function or slowed disease progression (see table 2-8). Additionally, even in drug strategies which were able to increase cognitive function, the progression of the disease is only slowed slightly, when comparing the immunotherapy treated group to the control. For instance, results of the phase 3 Lecanemab study (Van Dyck et al, 2023) showed a change of 1.21 from the baseline value in Lecanemab treated patients and 1.66 in the control group, a 27% slowing of decline (figure 2, Van Dyck et al, 2023). This score is measured on the clinical dementia rating sum of boxes scale (CDR-SOB), which is used to score the severity of dementia (O'Bryant et al, 2008). According to a study by (Andrews et al, 2019), a minimum change of 1 point on the CDR-SOB scale over a year is necessary for a significant effect on cognitive decline, suggesting that Lecanemab would not have a meaningful effect on disease progression. Similar CDR-SOD scores were measured in the Donanemab phase 3 study, where cognitive decline was slowed by 32% (Sims et al, 2023). Another example is the approval of aducanumab. Initially, phase 3 trials of aducanumab were halted due to a lack of clinical efficacy. However, later observations of slowed disease progression lead to a reversal of this decision (Heidebrink et al 2024). The observed disease progression was slowed by a total of 0.39 on the CDR-SOD scale after 18 months of treatment, an outcome which again lies below the threshold typically associated with meaningful clinical improvement (Andrews et al, 2019). While Lecanemab, Donanemab and Aducanumab have been proven to effectively reduce Aβ levels, these examples highlight the complex pathophysiology of AD and PD and raise the question of whether targeting only one potential driver is enough to treat these diseases.

Another fact to consider is that there might be a reciprocal relationship between the aggregated proteins involved in neurodegenerative diseases. Evidence of a study (Gerson et al, 2018) showed that targeting tau oligomers in PD mouse models additionally caused a decrease in levels of alpha-synuclein and resulted in less synaptic damage. Another study by (He et al, 2017) found that injections of tau into mouse models containing Aβ plaques without any tau overexpression, lead to toxic tau aggregate formation. The tangle formation seemed to be induced by the presence of amyloid-beta plaques, suggesting interactions between these two proteins in neurodegenerative diseases. Considering this potential relationship between aggregated proteins, as well as the low efficacy of drugs targeting one disease driver, a combination of multiple immunotherapy treatments could potentially be an interesting treatment strategy to study further. Additionally, since chronic neuroinflammation is caused by protein aggregates (Wang et al, 2019), combining immunotherapy which targets inflammatory mediators together with antibodies which bind and remove protein aggregates could be a beneficial treatment strategy. Thus, further research on the safety and efficacy of using mixed immunotherapy as a treatment strategy is necessary.

Furthermore, studies should focus on minimizing the occurrence of adverse effects. Autoimmune T cell activation is one of the main risks present for active immunotherapeutic strategies (Song et al, 2022). For instance, the phase 2 study of AN1792 showed improved memory and cognition in AD patients, but got terminated due to the occurrence of T cell mediated meningoencephalitis in 6% of the test subjects (Gilman et al, 2005). In order to avoid inflammatory T cell activation, studies should focus on the development of drugs able to cause B cell activation or selective activation of a T cell response. One example is the active immunotherapy UB-311,

which consists of helper T cell epitopes and therefore only activates a Th2 response. This selective T cell activation reduces the chance of T cell mediated inflammation, and therefore decreases the amount of adverse effects seen in the study subjects (Yu et al, 2023). The safety of UB-311 was confirmed in the phase 2 trial of the vaccine, where there was no occurrence of T cell mediated meningoencephalitis (Yu et al, 2023). Additionally, amyloid related imaging abnormalities are common in all amyloid-beta based immunotherapeutic strategies, but not in strategies targeting neuroinflammatory mediators. For instance, ARIA-E occurred in 24% of Donanemab treated patients, compared to 2.1% in the control group (89). Similarly, 35% of the test subjects treated with high doses of Aducanumab showed ARIA-E, while only 2% of the placebo group showed this adverse effect (60). Despite these results, Aducanumab still got accelerated approval by the FDA (Heidebrink et al, 2024). Aducanumab's failure to launch, due to concerns regarding it's safety and efficacy, highlights the importance of doing thorough research despite the high demand for a disease treatment. Considering the low efficacy of most Aβ targeting drugs, as mentioned before, a high percentage of adverse effects might outweigh the small clinical effect of the drug treatment on disease progression (Heidebrink et al, 2024).

Moreover, treatment of AD and PD is mostly started at later stages of disease progression instead of prior to the onset of symptoms, due to a lack of strategies allowing preclinical diagnosis (Mortada et al, 2021). Especially in the case of Parkinson's disease, not as many reliable strategies used to determine αS levels and the stage of the disease progression are currently available as for AD (Song et al, 2022). As seen in figure 3 (Song et al, 2022), most treatments discussed in this paper focus on patients diagnosed with early- or mild-to-moderate stage AD. In order to prevent neuronal damage all together, treatment of patients during the preclinical stage is necessary (Song et al, 2022). Therefore, research should focus on the development of diagnostic strategies able to recognize neurodegenerative disorders in earlier stages, in addition to developing effective drug strategies.

Finally, based on the results of this literature study, passive immunotherapeutic strategies targeting Aβ and neuroinflammatory mediators have so far seemed the most effective in treating Alzheimer's Disease. Therapies based on αS as a treatment for PD have not shown the same success rate. Similarly, tau based immunotherapy and active vaccines targeting Aβ have not shown to be an effective treatment for AD yet. However, most of these drug therapies are still in earlier trial phases and have not yet reached phase 2 trials. For instance, Bepranemab, JNJ-63733657 and ACI-35 all showed promising results in the conducted phase 1 trials and are currently in phase 2 studies. Therefore, these drugs might show beneficial effects on neurodegenerative diseases in the future. However, the focus of this literature study lies mainly on drug therapies which have shown to effectively slow cognitive decline in phase 2 or phase 3 trials. This decision is based on the observation that positive outcomes of preclinical and phase 1 studies do not always translate to a meaningful effect of the drug in later trials. For example, ADDvac1 was shown to effectively decrease tau levels and slow cognitive decline in a phase 1 study but these results were not found in the following phase 2 study (Novák et al, 2021). At present, Lecanemab, Aducanumab and Donanemab have shown the highest efficacy as a treatment for AD, while targeting inflammatory mediators might be promising for both PD and AD. Currently, GV-971 has even been approved in China as a treatment strategy for mild to moderate AD (Syed, 2020).

In conclusion, the discussed immunotherapeutic drugs have shown promising results regarding target binding and reduction already. Although the effect on cognitive decline might still be small, it cannot be denied that these immunotherapies have an effect on disease progression.

However, future research for a better understanding of the multiple causes of these diseases as well as the interactions between different proteins, is needed in order to identify optimal drug targets. Additionally, minimizing adverse effects and providing diagnostic strategies for early disease detection is necessary for further development of effective immunotherapeutic strategies. Nevertheless, immunotherapy as a treatment for AD and PD is a promising treatment strategy which might provide the foundation for future research into the treatment of neurodegenerative diseases.

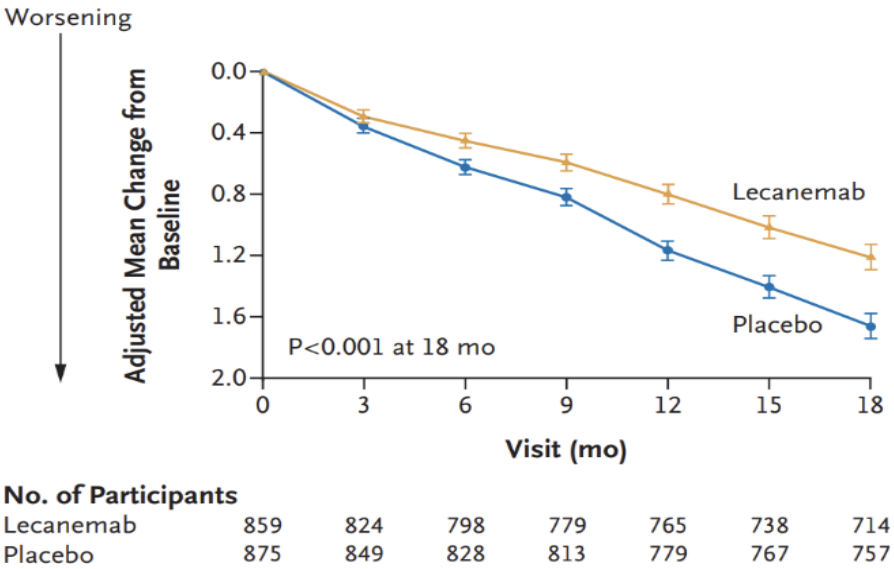

***Figure 2**: Change in disease progression over a period of 18 months, after treatment with Lecanemab vs Placebo, measured on the CDR-SOD scale.* From: "Lecanemab in early Alzheimer's Disease", by: Van Dyck, C.H., Swanson, C.J., Aisen, P., Bateman, R.J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L.D., and Iwatsubo, T., 2023, *The new England journal of Medicine, 388(1), p.14 (*DOI: 10.1056/NEJMoa2212948)

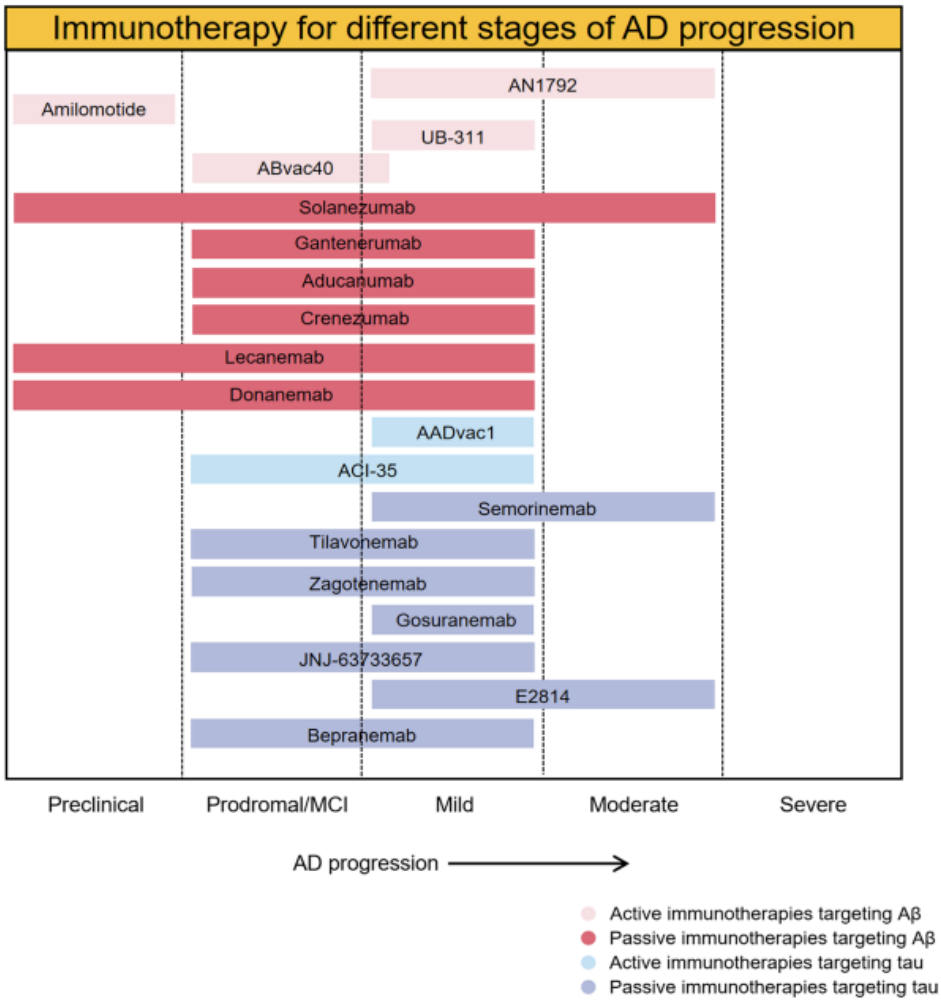

Figure 3: *Immunotherapy strategies for different stages of Alzheimer's Disease*.
From: " Immunotherapy for Alzheimer's disease: targeting β-amyloid and beyond", by Song., C., Shi, J., Zhang, P., Zhang, Y., Xu, J., Zhao, L., Zhang, R., Wang, H., & Chen, H., 2022, *Translational neurodegeneration,* 11(1), p.13 (https://doi.org/10.1186/s40035-022-00292-3).

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Appendix

Drug	Immunization type (passive or active)	Study Subjects	Most recent phase of trial	Status recent trial	Results	Source study
Lecanemab*	Passive	Early AD	Phase 3 Clarity AD (NCT03887455)	Completed	- Decrease in Aβ levels - Slowing of cognitive decline - Terminated due to adverse effects	105
Aducanumab*	Passive	Early AD	Phase 3 EMERGE (NCT02484547)	Completed	- Decrease in Aβ levels - Slowing of cognitive decline	61
Donanemab*	Passive	Early symptomatic AD	Phase 3 TRAILBLAZER-ALZ 2 (NCT04437511)	Completed	- Decrease in Aβ levels - Slowing of cognitive decline	92
Gantenerumab	Passive	Early symptomatic AD	Phase 3 GRADUATE 1 (NCT03444870) and GRADUATE 2 (NCT03443973)	Completed	- Decrease in Aβ levels - Decrease in tau levels - No effect on cognitive decline	3
Solanezumab	Passive	Preclinical AD	Phase 3 (NCT02008357)	Completed	No effect on cognitive decline	100
Crenezumab	Passive	Early AD	Phase 3 CREAD (NCT02670083) and CREAD2 (NCT03114657), CREAD OLE (NCT03491150)	Terminated	Unlikeliness to hit primary endpoint of slowing cognitive decline	80

Table 2: Passive immunotherapeutic drugs targeting amyloid-beta currently studied in clinical trials for Alzheimer's Disease

* All marked drugs are further discussed in the main part of this article

Drug	Immunization type (passive or active)	Study Subjects	Most recent phase of trial	Status recent trial	Results	Source study
AN1792	Active	Mild to moderate AD	Phase 2 (NCT00021723)	Terminated	- Decrease in Aβ levels - Slowing of cognitive decline - Low immunogenicity - Terminated due to development of T cell mediated meningoencephalitis	106,60
UB-311	Active	Mild AD	Phase 2 (NCT02551809)	Terminated	- High immunogenicity - No effect on cognitive decline	113
Amilomotide	Active	Participants at risk of onset of AD	Phase 3 (NCT02565511)	Terminated	- Terminated due to adverse effects - High immunogenicity - No effect on cognitive decline	24
ACI-24	Active	Prodromal AD	Phase 2 (NCT05462106)	Active	Results expected in June 2026	44
ACC-001	Active	Early AD	Phase 2 (NCT01227564)	Completed	- High immunogenicity - No effect on cognitive decline	104
ABvac40	Active	Patients with mild cognitive impairment or very mild AD	Phase 2 (NCT03461276)	Completed	Results not available yet	28

Table 3: Active immunotherapeutic drugs targeting amyloid-beta currently studied in clinical trials for Alzheimer's Disease

Drug	Immunization type (passive or active)	Study Subjects	Most recent phase of trial	Status recent trial	Results	Source study
Semorinemab	Passive	Mild to Moderate AD	Phase 2 (NCT03828747 and NCT02754830)	Completed	No effect on cognitive decline	73
Gosuranemab	Passive	Early AD	Phase 2 TANGO (NCT03352557)	Completed	No effect on cognitive decline	99
Tilavonemab	passive	Early AD	Phase 2 (NCT02880956)	Completed	No effect on cognitive decline	57
Bepranemab	Passive	Mild dementia	Phase 2 (NCT04867616)	Active	Results expected in July 2025	12
zagotenemab	Passive	Early symptomatic AD	Phase 2 PERISCOPE-ALZ (NCT03518073)	Completed	No effect on cognitive decline	56
JNJ-63733657	Passive	Early AD	Phase 2 (NCT04619420)	Active	Results expected in nov 2025	13
Lu AF87908	Passive	AD patients	Phase 1 (NCT04149860)	Active	No results available yet	15
E2814	Passive	Mild to moderate cognitive impairment due to inherited AD	Phase 1b/2 (NCT04971733)	Active	Results expected July 2025	14
PNT001	Passive	Healty adults	Phase 1 (NCT04096287)	Completed	High immunogenicity	68
APNmAb005	Passive	Healthy adults	Phase 1 (NCT0534989)	Active	Results expected in july 2024	17

Table 4: Passive immunotherapeutic drugs targeting tau protein currently studied in clinical trials for Alzheimer's Disease

Drug	Immunization type (passive or active)	Study Subjects	Most recent phase of trial	Status recent trial	Results	Source study
AADvac1	Active	Mild AD dementia	Phase 2 (NCT02579252)	Completed	- High immunogenicity - No effect on cognitive decline	78
ACI-35	Active	Mild to moderate dementia	Phase 1/2 (NCT04445831)	Completed	No results available yet	18

Table 5: Active immunotherapeutic drugs targeting tau protein currently studied in clinical trials for Alzheimer's Disease

Drug	Immunization type (passive or active)	Study Subjects	Most recent phase of trial	Status recent trial	Results	Source study
Prasinezumab	Passive	Early PD	Phase 2 (NCT03100149)	Completed	No effect on cognitive decline	81
BIIB054	Passive	Early PD	Phase 2 (NCT03318523)	Completed	No effect on cognitive decline	66
Lu AF82422	Passive	Healthy subjects and PD patients	Phase 1 (NCT03611569)	Completed	- Safe to use - decreases plasma αS level	8
MEDI-1341	Passive	Healthy subjects	Phase 1 (NCT03272165)	Completed	No results available yet	22
ABBV-0805	Passive	PD patients	Phase 1 (NCT04127695)	Completed	No results available yet	23

Table 6: Passive immunotherapeutic drugs targeting alpha-synuclein protein currently studied in clinical trials for Parkinson's Disease

Drug	Immunization type (passive or active)	Study Subjects	Most recent phase of trial	Status recent trial	Results	Source study
AFFITOPE	Active	Mouse model	Phase 1B (NCT02270489)	Completed	- High immunogenicity - Decrease in αS levels - Improved cognitive and memory function	85
ACI-7104.056	Active	Early PD	Phase 2 (NCT06015841)	Active	Results expected in January 2028	21

Table 7: Active immunotherapeutic drugs targeting alpha-synuclein protein currently studied in clinical trials for Parkinson's Disease

Drug	Disease	Mechanism of action	Study Subjects	Most recent phase of trial	Status recent trial	Results	Source study
Etanercept	AD	Inhibits TNF αlpha	Mild to moderate AD	Phase 2 (NCT01068353)	Completed	- No effect on cognition decline	7
Neutralizing p40-specific antibody	AD	Blocks IL-12 signalling pathway	Mouse model	Preclinical	Completed	- Decrease in Aβ levels - Effect on cognitive decline	4
AL002	AD	TREM2 microglial receptor	Early AD	Phase 2	Active	Results expected in September 2024	55, 20
GV-971*	AD	Reconditioning of gut microbiota in order to reduce neuroinflammation	Mild to moderate AD	Phase 3 (NCT0229391)	Completed	- Reduced Th1 related neuroinflammation - reconditioned gut microbiota - Reverse cognitive impairment	112
GV-971	PD	Reconditioning of gut microbiota in order to reduce neuroinflammation	PD patients	Phase 2	Not yet active	No results available yet	114
Daratumumab	AD	Antibody which targets CD38	Mild to moderate AD	Phase 2 NCT04070378	Completed	No results available yet	19

Table 8: Immunotherapeutic drugs targeting inflammatory mediators currently studied in clinical trials for Alzheimer's and Parkinson's Disease

Sargamostim*	AD	Synthetic recombinant form of GM-CSF which activates microglia and Treg cells	Mild to moderate AD	Phase 2 (NCT01409915)	Completed	- Effect on cognitive and memory function	86
Sargamostim	PD	Synthetic recombinant form of GM-CSF which activates microglia and Treg cells	Healthy subjects and PD patients	Phase 1 (NCT01882010)	Completed	- Reduction of motor symptoms - T-reg induction which causes protection of nigrostriatal dopaminergic neurons - safe to use	58
T3D-959*	AD	Increase of PPAR- γ signalling, to increase energy supply to the brain	Mild to moderate AD	Phase 2b (NCT04251182)	Completed	- improved cognitive function	9
Pioglitazone	AD	Activate PPAR receptors which play a role in glucose and lipid metabolism	Subjects at risk of developing AD	Phase 3 (NCT01931566)	Terminated	- Unlikeliness to hit primary endpoint of slowing cognitive decline	6

Table 8 (continued): Immunotherapeutic drugs targeting inflammatory mediators currently studied in clinical trials for Alzheimer's and Parkinson's Disease

* All marked drugs are further discussed in the main part of this article