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Antibody Therapies for Alzheimer's Disease

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by

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Lay Summary

Alzheimer's Disease (AD) is the leading cause of dementia worldwide. Patients with this condition first experience mild cognitive impairment, followed by the loss of memory, cognitive skills, identity, and the ability to perform daily tasks unassisted, eventually culminating in death (Kepp et al., 2023). Despite decades of research, the cause of the most common form of the disease is largely unknown and the mechanism through which Alzheimer's progresses continues to be highly debated among researchers. The symptoms of Alzheimer's dementia are diagnosed and tracked using cognitive tests performed by a patient's doctor. Additionally, the physiological markers of the disease can be detected using brain imaging and blood tests. These tests screen for accumulation of two different proteins - aggregated forms of tau protein and beta-amyloid (Aβ) protein peptides derived from Amyloid Precursor Protein (APP). The healthy versions of these proteins are present throughout the brain and are believed to be necessary for the normal functioning of the nervous system. However, certain versions of these proteins (Aβ fragments and hyperphosphorylated tau) can accumulate in the brain and disrupt neurons, eventually killing them. The brain cells that normally destroy defective cells and foreign bodies (microglia) fail to clear these protein aggregates, which apparently overwhelm this protective system.

The dominant hypothesis for the mechanism of Alzheimer's, the amyloid cascade hypothesis, suggests that amyloid plaques formed by Aβ peptides cause a cascading effect involving an increase in toxic tau protein, which is correlated with the disease progression of Alzheimer's patients. While the amyloid cascade hypothesis does not fully explain the cause of Alzheimer's Disease and researchers are still working to better understand the disease, the current hypothesis has been used as a framework to develop drug therapies. These therapies did not prove effective until the development of a handful of monoclonal antibody therapy drugs within the past five years. These drugs target amyloid plaques by marking them with antigens that microglial cells are able to recognize, destroying the plaques and

clearing them from the brain. However, there can be serious side effects to these drugs including bleeding in the brain. This paper will discuss the state of research on antibody therapies and the relevance of the amyloid cascade hypothesis in Alzheimer's research. First, I will provide a brief background on Alzheimer's Disease and the amyloid cascade hypothesis. I will then discuss my methods in choosing articles in order to gain an understanding of the scholarly conversation around antibody therapies. This is followed by an explanation of the diagnostic criteria for Alzheimer's with which these antibody therapies are evaluated. Then I will discuss the benefits and risks associated with antibody therapies. There are alternative and supplemental hypotheses to the amyloid cascade hypothesis, which may change the perception of antibody therapies. Finally, I will discuss the implications of these therapies on Alzheimer's research and patient outcomes.

Keywords: Alzheimer's Disease, neurodegeneration, amyloid hypothesis, antibody therapies, alternative models

Background on Alzheimer's Disease

Alzheimer's Disease (AD) is a form of dementia affecting an estimated 30-40 million people worldwide (Kepp et al., 2023). Patients with this condition first experience mild cognitive impairment, which progresses to the loss of memory, cognitive skills, identity, and the ability to perform daily tasks unassisted (Kepp et al., 2023) eventually culminating in death. Two forms of AD exist: sporadic Alzheimer's (SAD) and familial Alzheimer's (FAD). SAD or late-onset Alzheimer's accounts for most cases of AD and usually occurs after the age of 65 (Long & Holtzman, 2019). FAD is early-onset, usually between the ages of 30 and 65, and is typically caused by autosomal dominant mutations in the genes encoding presenilin-1 (PS1), presenilin-2 (PS2), and the amyloid-β precursor protein (APP) (Kepp et al., 2023). There are many pathological characteristics of Alzheimer's, including neurological, cardiovascular,

and metabolic abnormalities. On a microscopic level, the two primary signs of Alzheimer's within the brain are extracellular plaques of β-amyloid (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau protein (Watts & Prusiner, 2018). Amyloid plaques are formed by aggregates of Aβ peptide fragments cleaved from the Amyloid Precursor Protein (APP), a transmembrane protein. These cleaved peptide fragments do not contribute to the normal function of the transmembrane protein, but monomeric β-amyloid peptides might have biological activity under some circumstances, and they may also interfere with the normal signaling properties of the transmembrane protein. Oligomers, which are molecules made up of multiple peptide fragments, are precursors to plaques and are more toxic and active in the disease process (Kepp et al., 2023).

Alzheimer's is not the only disease that is associated with these structures. Similar extracellular amyloid plaques (formed by other peptide fragments) are also present in Transmissible Spongiform Encephalopathies, a group of neurodegenerative diseases including Creutzfeldt-Jakob Disease (Jankovska et al., 2020; Yamaguchi & Kuwata, 2017). All amyloid plaques share certain characteristics, including β-sheet secondary structure and fibrillar morphology (Kepp et al., 2023). However, the symptoms and etiology of the disease vary with the type of protein that forms the amyloid plaque. In the case of Alzheimer's Disease, the plaques are formed by 42-amino acid long peptides cleaved from APP. This protein in its complete form is not associated with Alzheimer's Disease. However, problems can arise when the protein is cleaved into shorter segments. In the non-amyloidogenic pathway for APP cleavage, the protein is first cleaved by the enzyme α-secretase and then by the enzyme γ-secretase. In an amyloidogenic pathway, however, APP is instead first cleaved by β-secretase and then γ-secretase, producing Aβ-42 peptides (Kepp et al., 2023; Watts & Prusiner, 2018). The Aβ peptides can then form short oligomers which in turn aggregate into amyloid plaques, which can be imaged in the brain. However, current research indicates that oligomers themselves are active in the disease process rather

than the plaques. The plaques are not fully inert, especially along the margins, where some exchange of Aβ oligomers and monomers occurs into the surrounding spaces.

Methods For This Perspective

For this perspective, I have selected a handful of pertinent articles with the help of my advisor. This thesis will not attempt to critically review the literature or primary research, as extensive reviews on this topic already exist. Rather, I will provide a summary of the current state of the amyloid cascade hypothesis and the use of its conceptual framework in the formation of new pharmaceutical treatments for Alzheimer's Disease. The articles selected were published within the last 25 years, but there are no further constraints. The articles were chosen based on their relevance in the field and the comprehensiveness and accessibility of their reviews. I aim to provide a broad summary of the amyloid cascade hypothesis in order to contextualize the recent antibody therapies for a non-specialized audience.

Amyloid Cascade Hypothesis

The current leading hypothesis of the mechanism of Alzheimer's Disease is the amyloid cascade hypothesis, which emerged in the 1980s (Kepp et al., 2023). The hypothesis has changed and expanded as new research has been generated, but the central concept remains that amyloid plaques are an early biomarker detectable in AD, and that the accumulation of toxic amyloid deposits disrupt neurons and normal functioning of the brain, contributing to a cascade of events that eventually leads to neuronal death and dementia. Amyloid plaques are present in both SAD and FAD, but only in familial cases are they closely correlated to the progression of the disease. Moreover, the genetic mutations that cause FAD directly lead to higher concentrations of Aβ-42, which is strong evidence that toxic forms of Aβ cause FAD.

In contrast, the etiology of SAD is not as clear. The timing and placement of amyloid plaques within the brain do not correlate with the onset of symptoms that SAD patients experience. Amyloid plaques appear in PET scans many years before patients develop symptoms. Therefore, the current amyloid cascade hypothesis does not view Aβ plaques as the cause of AD, but rather as one factor in the disease progression. First, Aβ fragments and oligomeric Aβ begin to accumulate, followed by increased microglial and astrocyte activation (Long & Holtzman, 2019). This is followed by the progressive accumulation of pathological tau neurofibrillary tangles, which do correlate with disease progression, as illustrated in Figure 1. Other factors have been proposed that likely play a role in modifying the disease process, such as interactions between tau and Aβ as well as the deleterious effects of the APOE ε4 allele (which is the most prominent risk factor associated with AD). It is still unclear if the amyloid cascade hypothesis is the best model for sporadic AD. Nevertheless, research does indicate that Aβ is involved in the disease progression, which has led to the development of treatments that target Aβ in order to interrupt this process. However, these treatments have a limited scope because the underlying cause of sporadic AD is unknown and, therefore, cannot be targeted. Alternative hypotheses are currently being explored and may open up new avenues for treatment.

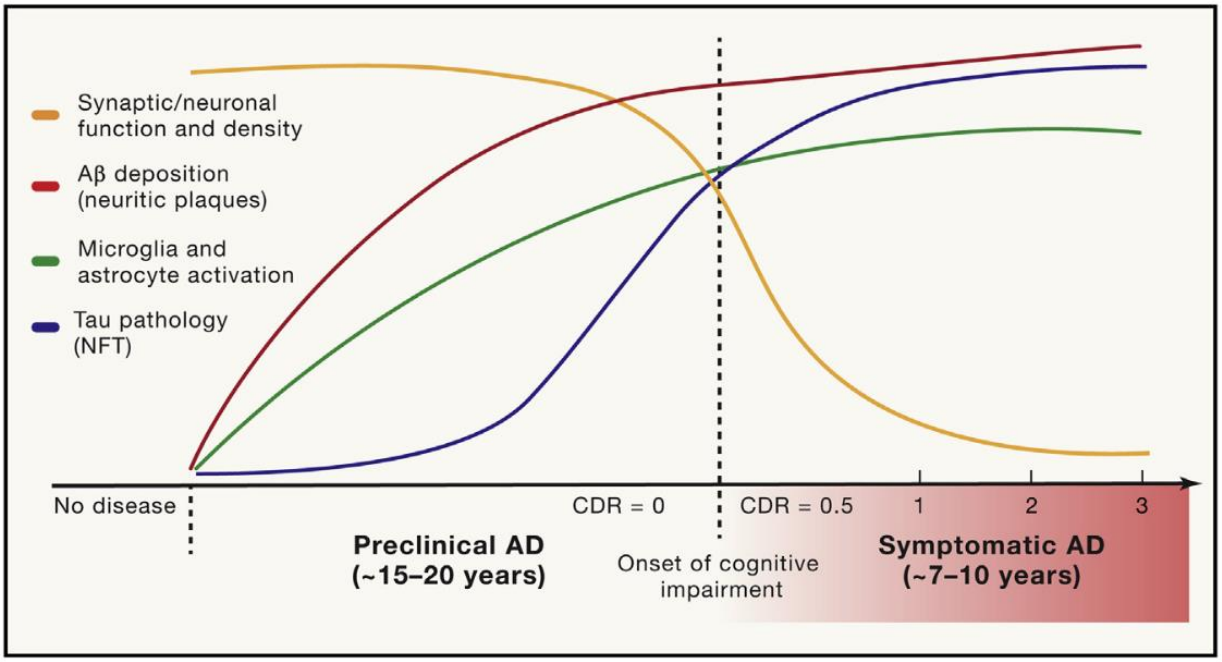

Figure 1. Timeline for the appearance of characteristic pathologies in AD (Long & Holtzman, 2019).

Antibody Therapies

The framework of the amyloid cascade hypothesis has been used to guide the development of different therapies for Alzheimer's Disease. After decades of research, none had been approved for clinical use until aducanumab and lecanemab were given accelerated approval by the FDA in 2021 and 2023 respectively (Kepp et al., 2023). A third drug, donanemab, was recently granted approval in June of 2024 to treat the early stages of Alzheimer's disease (Terao & Kodama, 2024; Cummings et al., 2024). These drugs are all monoclonal antibody therapies which target different versions of Aβ and are administered intravenously. Aducanumab targets a broad range of Aβ configurations but especially larger aggregates (Cummings et al., 2024). Lecanemab targets protofibrils with some effect on plaques and an even lesser effect on monomers, while donanemab targets plaques. These Aβ species are marked by the antibodies for destruction by microglia, specialized innate immune cells within the central nervous system that phagocytose microbes, damaged cells, and other debris. Theoretically, according to the amyloid cascade hypothesis, these antibody drugs should result in a reduction in the

volume of amyloid plaques without affecting healthy tissue or brain function. They have indeed been demonstrated to reduce signs of Aβ accumulation on PET scans and slow cognitive decline by approximately 25-40%, according to the Clinical Dementia Rating–Sum of Boxes and the Alzheimer's Disease Assessment Scale-cognitive subscale (Cummings et al., 2024; Terao & Kodama, 2024).

PET scans are a useful tool in the evaluation of therapies, as they are minimally invasive, though expensive and difficult to access. Patients are injected with an imaging compound that has specificity for Aβ and is detected by the scanner in order to visualize Aβ in the brain (Chapleau et al., 2022). Aducanumab, lecanemab, and donanemab trials have all produced a significant reduction in amyloid PET (Cummings et al., 2024). Other biomarker used in AD research are the ratios of Aβ-42 to Aβ-40 in the cerebrospinal fluid (CSF) and blood. A higher ratio of toxic Aβ-42 peptides over non-toxic Aβ-40 peptides is indicative of a further stage in disease progression. However, as there is not strong evidence of causation between Aβ plaques and dementia symptoms, a reduction in Aβ is not sufficient to demonstrate the efficacy of new drugs (Kepp et al., 2023). Besides relying on cognitive tests, a new biomarker test in development is a blood test for phosphorylated tau (Blennow & Zetterberg, 2018). As phosphorylated tau (P-tau) is more closely associated with neuronal loss and AD progression than Aβ, this marker has the potential to be an effective and minimally invasive test. Some drug trials have tracked phosphorylated tau levels in the cerebrospinal fluid. Aducanumab produced a significant reduction in levels of p-tau protein (Cummings et al., 2024). P-tau blood tests could also be used to screen patients for the early detection and treatment of AD.

Researchers dispute the claim that these therapies have shown a clinically significant effect on cognitive function (Terao & Kodama, 2024). In studies that assessed efficacy using the Mini-Mental State Examination, aducanumab and donanemab were less effective and presented more risks than lithium, which is another potential treatment option for Alzheimer's (Matsunaga et al., 2015; Terao & Kodama,

2024). Differences between the many cognitive tests used to diagnose and assess AD present issues in generalizing the results of clinical trials.

Additionally, Aβ antibody therapies present the risk of serious side effects referred to as amyloid-related imaging abnormalities (ARIA), which include cerebral edema, effusion, intracerebral hemorrhage, and loss of brain volume (Terao & Kodama, 2024; Cummings et al., 2024). ARIA occurred in 20-30% of participants in antibody therapy clinical trials, with fewer instances among those receiving a placebo (Cummings et al., 2024). ARIA can sometimes be accompanied by hemosiderin deposits, which are deposits of iron from blood cells outside the blood vessels and indicate hemorrhage. Symptoms such as headaches and confusion can also be associated with ARIA, although many patients with ARIA do not report experiencing noticeable side effects. Symptoms of ARIA are not fully understood and require further research, but some studies suggest they are caused by the removal of Aβ from around blood vessels, resulting in abnormal vascular permeability. In addition, individuals carrying the ε4 allele of APOE (involved in lipid trafficking) are at an increased risk of developing AD, and clinical trials for Aβ antibody therapies have found that they are also have an increased risk of developing ARIA. Patients homozygous for APOE ε4 are at the highest risk, followed by heterozygotes, with noncarriers at the lowest but still non-zero risk. Biogen, the pharmaceutical company that had ownership of aducanumab, discontinued the drug after it failed to perform well on the market, reflecting its controversial accelerated approval by the FDA (Robbins, 2024). The initial approval was based on the reduction of Aβ visible via PET scan rather than efficacy in slowing cognitive decline as measured by cognitive tests (Kepp et al., 2023). While aducanumab did demonstrate significant efficacy on the Alzheimer's Disease Assessment Scale, it did not have significant efficacy on the Clinical Dementia Rating-sum of boxes (Terao & Kodama, 2024). Donanemab and lecanemab are both currently under full approval for the treatment of mild cognitive impairment and early AD after demonstrating sufficiently significant efficacy in multiple tests.

Several other antibody therapies are in clinical trials, but it is unclear if they will be safer to use than existing therapies. Numerous other therapies targeting Aβ, including the recently developed drugs bapinezumab and gantenerumab, have undergone clinical trials and did not demonstrate sufficient clinical efficacy or safety to continue. Therefore, there is strong interest in developing alternate or complementary therapies that might be beneficial, particularly at earlier stages in the disease.

Alternative Hypotheses

Many promising alternatives to the amyloid cascade hypothesis exist that have not been studied adequately to dispute the amyloid cascade hypothesis. One hypothesis is that the production of Aβ-42 results in pathology due to an interference in the normal function of Aβ-40. As noted above, a better understanding of the normal functions of APP might lead to novel therapies. In addition, microglia are a source of many different avenues of AD research. They may play a protective role early in the disease process and a damaging role in later stages (Gao et al., 2023; Hansen et al., 2018). A recent study (Huang et al., 2024) indicated that astrocytes, a type of cell within the brain that is involved in maintaining the blood brain barrier, might affect the activation of microglia around Aβ plaques. Huang et al. proposed that neuroinflammation associated with AD could be reduced and Aβ plaques could be compacted by targeting guidance receptors like Plexin-B1 (Huang et al., 2024). At the same time, other researchers are focusing their attention on investigating if outside factors could influence the mechanism of the amyloid cascade. Some hypothesize that Aβ and tau could function as protective factors against pathogens, and therefore be triggered to aggregate by viral, bacterial, and fungal infections (Abbott, 2020; Li et al., 2018). As more research comes out, it is likely that the amyloid cascade hypothesis will shift or even be replaced. These alternative hypotheses open up new possibilities for the treatment and, ideally, prevention of AD.

Implications and Conclusion

AD is a terminal disease that affects millions of patients and their families. In addition to the personal cost, AD puts a large strain on the healthcare system, dominating the resources available for patients with high care needs. This in turn results in AD patients receiving limited care, decreasing their quality of life. Despite decades and billions of dollars spent in research, researchers still have a very limited understanding of sporadic AD. Many have been skeptical about the amyloid cascade hypothesis due to the historic lack of success of antibody therapies developed based on the hypothesis that Aβ plays a large role in the cascading disease process. However, the recent relative success and FDA approval of lecanemab and donanemab have renewed interest in antibody therapies and the amyloid cascade hypothesis as a whole. It is important that these therapies are contextualized properly and are not marketed as a cure for AD. They target one factor of a poorly understood disease process and result in a slowing of dementia progression by months when administered to patients with early symptomatic AD. These benefits may well be worth the risks for many patients and their families, but all affected participants must be fully informed of the benefits and risks. ARIA risks are substantial, with the most extreme cases resulting in death. Patients should be screened for risk factors and consistently monitored for ARIA. Careful monitoring of ARIA may help identify additional risk factors and help patients make more informed decisions. Another downside to antibody therapies are the high costs associated with these treatments. While Medicare now covers antibody therapies with standard approval by the FDA, a 12-month course of donanemab costs $32,000 before insurance and patients' out-of-pocket cost varies (Brooks, 2024). Lastly, the route of delivery (time-consuming intravenous injections) will present additional challenges for many patients and their families.

The success of anti-Aβ therapies is a positive development in AD research, but these therapies alone cannot fully treat AD, at least in their current iterations. There is speculation by researchers that treatment in earlier stages could help prevent cognitive decline for longer periods of time. The

biomarker tests in development may assist with earlier diagnosis and therefore higher efficacy of antibody therapies. More research is also needed on alternatives to antibody therapies and those that could complement the current therapies available. Alternatives to the amyloid cascade hypothesis focused on other promising targets include the normal function of APP, the role of microglia, the role of APOE ε4, and tau therapies. Further investigation into the mechanism of AD outside of the amyloid cascade hypothesis will open up more treatment options that could change the lives of millions worldwide.

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