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Strategies for Treating Alzheimer's: Current Approaches and Future Perspectives

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ABSTRACT

Introduction and Purpose:
Alzheimer's disease is the most common cause of dementia, affecting millions of people worldwide and posing a significant challenge to modern medicine. This review explores the available treatment options, their limitations, and the future directions of research that may bring breakthroughs in combating this devastating condition.

Materials and Methods:
This article is a comprehensive review based on a detailed analysis of peer-reviewed studies obtained from major scientific databases, such as PubMed. The selected articles focus on modern methods of treating Alzheimer's disease, chosen for their relevance and importance to the subject.

Results:
This review highlights the complex pathogenesis of Alzheimer's disease (AD), driven by amyloid-β accumulation, tau protein abnormalities, cholinergic deficits, and neuroinflammation. Current treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, provide only temporary symptom relief, while emerging therapies, including immunotherapy and gene therapy, offer promising new directions. Advances in disease-modifying approaches targeting Aβ, tau, and genetic factors have shown potential, though challenges remain in achieving long-term efficacy and accessibility.

Conclusion:
Despite significant progress in understanding AD and developing new treatment strategies, an effective cure remains elusive. Immunotherapies and gene therapy represent promising avenues for disease modification, but further research is needed to optimize their effectiveness and accessibility. A multidisciplinary approach combining pharmacological, genetic, and lifestyle interventions is essential to improving patient outcomes and combating this devastating disease.

Keywords: Alzheimer's disease, amyloid, tau, inflammation, dementia, acetylcholinesterase inhibitors, immunotherapy, gene therapy

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that develops gradually, leading to progressive impairment of cognitive and behavioral functions. Approximately 55 million people are affected by dementia and Alzheimer's disease is the most common form of dementia, responsible for at least two-thirds of cases in individuals aged 65 and older. The disease primarily affects key cognitive abilities, including memory, language, comprehension, attention, reasoning, and decision-making, making daily activities increasingly difficult for those affected. As AD progresses, individuals may experience severe disorientation, personality changes, and a decline in their ability to perform basic self-care tasks. While it is not a direct cause of death, it significantly increases the risk of complications that may ultimately lead to a person's death [1]. This devastating neurodegenerative disease is believed

to affect approximately 50 million people globally, while also having a profound impact on the lives of tens of millions who witness the prolonged cognitive decline of their family members. AD is the sixth leading cause of death in the United States and ranks fifth among the primary causes of death for Americans aged 65 and older [2]. Approved symptomatic drugs improve cholinergic function and regulate excessive glutamatergic activity to support cognitive stability. In contrast, experimental disease-modifying treatments aim to reduce or eliminate brain amyloid buildup, though their clinical benefits remain limited.

Risk Factors

A small proportion of Alzheimer's disease (AD) cases are associated with dominant genetic mutations in three specific genes: APP (amyloid precursor protein), PSEN1 (presenilin 1), and PSEN2 (presenilin 2). These mutations are typically linked to early-onset AD, where clinical symptoms manifest before the age of 65. However, the majority of cases involve late-onset Alzheimer's disease (LOAD), which develops later in life and occurs sporadically. While this form of AD is not inherited and lacks a single genetic cause, research suggests the presence of multiple genetic risk factors. Among them, the E4 allele of the APOE - APOEε4 (apolipoprotein E) gene which was found in approximately 16% of the population is considered the most significant [3].

The risk of developing Alzheimer's disease (AD) can be influenced by various modifiable factors, many of which are linked to lifestyle choices and general health. Cardiovascular health plays a key role, as conditions such as high blood pressure, diabetes, elevated cholesterol levels, and obesity are associated with an increased likelihood of Alzheimer's. These issues negatively impact brain vascular health, making it crucial to manage heart and circulatory health to reduce AD risk. Another important factor is physical activity. Leading a sedentary lifestyle has been shown to raise the risk of Alzheimer's, while engaging in regular exercise supports brain health and may help reduce the buildup of amyloid-beta plaques, a characteristic feature of the disease.

Likewise, diet has a significant impact. Diets rich in saturated fats and sugars, often typical of Western eating patterns, may heighten the risk, whereas adopting a Mediterranean diet including rich in fruits, vegetables, whole grains, and healthy fats can provide protective benefits for the brain. Smoking and excessive alcohol consumption also contribute to Alzheimer's risk. Smoking increases oxidative stress and damages blood vessels, impairing brain function, while heavy, long-term alcohol use can accelerate cognitive decline and brain degeneration. Sleep health is another critical factor. Disorders such as chronic sleep deprivation or sleep apnea are linked to a greater risk of Alzheimer's, as poor sleep can contribute to the accumulation of amyloid-beta in the brain [4]. Prioritizing good sleep hygiene is an important preventive measure.

Traumatic brain injuries (TBIs) are another modifiable factor. Head injuries have been shown to increase the risk of neurodegenerative disease like Alzheimer's later in life, making it essential to take precautions, such as wearing helmets during activities and preventing falls [5]. Cognitive engagement and mental stimulation also play protective roles. A lack of intellectually challenging activities or mental engagement is associated with a higher likelihood of developing Alzheimer's. Activities such as reading, solving puzzles, or learning new skills help build cognitive reserve, potentially delaying the onset of symptoms. Social connections are equally important, as social isolation has been linked to cognitive decline, whereas maintaining regular social interactions can support brain health.

Pathogenesis of Alzheimer's Disease

The complex pathological processes of Alzheimer's disease primarily involve the accumulation of amyloid-beta (Aβ) plaques and tau protein tangles in the brain. These hallmark features lead to progressive neuronal loss and synaptic dysfunction, resulting in cognitive decline and behavioral changes [6]. Amyloid-beta (Aβ) is a 4 kDa fragment derived from the amyloid precursor protein (APP), a larger molecule that is abundantly produced by neurons in the brain, as well as by vascular and blood cells, such as platelets, and to a lesser degree, by astrocytes. The amyloid hypothesis suggests that the overproduction or reduced clearance of Aβ peptides contributes to plaque formation, triggering a cascade of neuroinflammation and oxidative stress that exacerbates neuronal damage [7].

Abnormal accumulations of the misfolded microtubule-associated protein tau (MAPT) have been identified in the brains of patients with tauopathies, a diverse group of neurodegenerative disorders. Among these, Alzheimer's disease (AD) is the most prevalent. Misfolded tau is considered a central pathological hallmark of AD, playing a crucial role in disease progression. Insoluble tau aggregates, known as neurofibrillary tangles (NFTs), primarily accumulate within the cell bodies and dendrites of neurons, leading to widespread neurodegeneration. Research has demonstrated a strong correlation between the density of NFTs and the severity of clinical symptoms, including cognitive decline and memory impairment. The formation of NFTs results from hyperphosphorylation of tau proteins, which disrupts microtubule stability, compromises intracellular transport mechanisms, and ultimately contributes to neuronal dysfunction and cell death. This progressive accumulation of pathological tau is thought to be a key driver of neurodegenerative processes in AD and other tauopathies. [8].

Cholinergic dysfunction is a key feature of Alzheimer's disease, driven by the degeneration of cholinergic neurons in the nucleus basalis of Meynert and their projections to the cerebral cortex. This results in reduced cholinergic signaling, affecting critical brain regions like the cerebral cortex, hippocampus, and amygdala, which are essential for memory, attention, and emotional regulation. Additionally, both nicotinic and muscarinic acetylcholine receptors in the cortex are disrupted, with studies showing a significant loss of postsynaptic nicotinic receptors [9]. The progressive degeneration of basal cholinergic neurons leads to widespread cortical and hippocampal deafferentation, contributing to cognitive decline.

Emerging evidence highlights the role of chronic neuroinflammation mediated by microglial activation in perpetuating the disease process. Acute neuroinflammation is a protective immune response to harmful stimuli like infections, toxins, or injury, crucial for brain repair. However, when pro- and anti-inflammatory signals become imbalanced, chronic neuroinflammation arises. This persistent activation of glial cells and excessive release of cytotoxic molecules impairs brain function and plays a significant role in the development of neurodegenerative disorders, including Alzheimer's disease.

Additionally, vascular dysfunction and blood-brain barrier disruption are recognized as contributors to impaired clearance of toxic proteins and neuronal health. Recent studies have also identified the gut-brain axis and gut microbiota alterations as potential modulators of neuroinflammation and Aβ deposition, adding another layer of complexity to AD pathogenesis [8][10]. Further research into these interconnected mechanisms is essential to developing targeted therapies that address the underlying causes of Alzheimer's disease.

Treatment

Currently, there is no cure for Alzheimer's disease; however, various treatments are available to help ease and manage certain symptoms. In recent years, significant progress has been

made in developing medications designed to slow the progression of the condition, largely driven by the identification of new disease biomarkers

Acetylcholinesterase Inhibitors (AChEIs)

The cholinergic system plays a key role in the pathogenesis of Alzheimer's disease, with its dysfunction contributing significantly to the cognitive and behavioral symptoms of the condition. This understanding underpins the use of cholinergic therapies, such as acetylcholinesterase inhibitors (AChEIs), which work to boost acetylcholine levels and provide partial relief of symptoms. Acetylcholinesterase inhibitors (including donepezil, rivastigmine, and galantamine) function by blocking the enzyme acetylcholinesterase, which is responsible for breaking down acetylcholine in neural synapses.

This mechanism has significant therapeutic effects in Alzheimer’s disease. Normally, acetylcholine is broken down by acetylcholinesterase into choline and acetic acid after it has transmitted its signal. This process ends its activity in the synapsę (figure 2) [9]. By inhibiting this enzyme, AChEIs increase acetylcholine levels, allowing it to remain active in the synapse for a longer period. By prolonging the presence of acetylcholine in the synapse, these inhibitors amplify its action on cholinergic receptors. This can improve neuronal communication, which is often impaired in Alzheimer’s disease, thereby supporting cognitive functions [9][11].

In summary, acetylcholinesterase inhibitors boost acetylcholine levels in the brain, enhancing its effects. While they do not slow or stop disease progression, they can enhance the quality of life for patients and support cognitive functions, offering relief from some of the symptoms of Alzheimer’s disease.

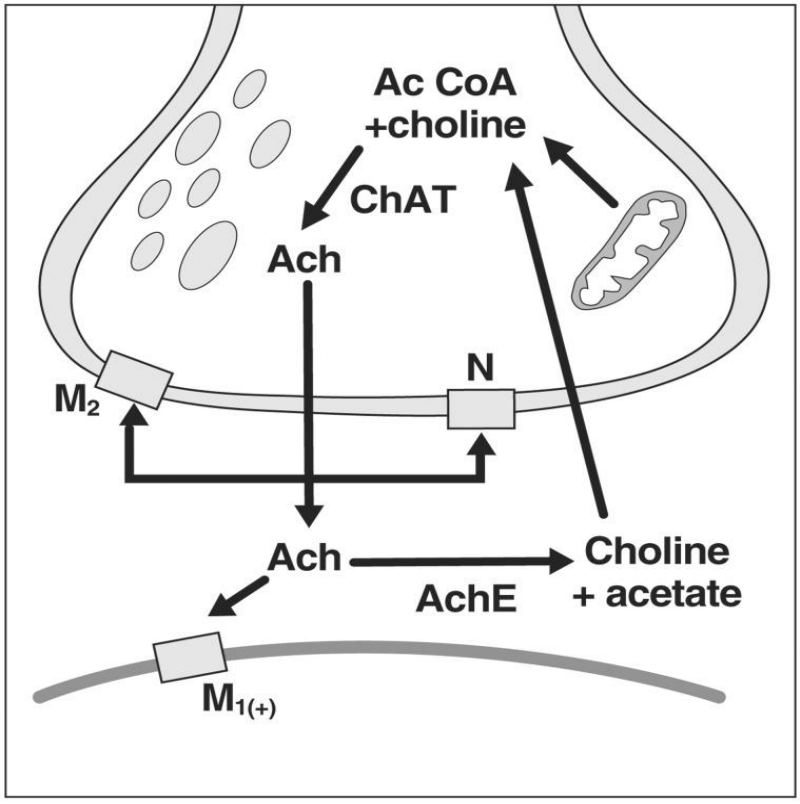

Figure 1. Physiology of the cholinergic synapse. Adapted from Hampel H, Mesulam MM, Cuello AC, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain*. 2018;141(7):1917-1933. doi:10.1093/brain/awy132 [9]

Memantine

Memantine is a medication that works by blocking N-methyl-D-aspartate (NMDA) receptors, which are involved in the regulation of glutamate, a neurotransmitter crucial for learning and memory. In Alzheimer's disease (AD), glutamate activity becomes dysregulated, leading to excitotoxicity, which can damage neurons and worsen cognitive decline. By inhibiting NMDA receptors, memantine helps to protect neurons from this damage, thereby improving cognitive function and reducing symptoms associated with moderate-to-severe stages of Alzheimer's disease.

Memantine has been approved by the U.S. Food and Drug Administration (FDA) for use in patients with moderate-to-severe dementia, including Alzheimer's disease. It can be prescribed either as a monotherapy, when used alone, or in combination with acetylcholinesterase inhibitors. When used in combination, these medications work synergistically to target different pathways involved in the disease, further enhancing the management of cognitive symptoms [11].

Although memantine does not cure Alzheimer's disease or stop its progression, it plays a crucial role in alleviating symptoms and helping patients maintain their independence for a longer period.

Immunotherapy

In recent years, a wide range of agents have been studied for their potential to reduce the production of amyloid-beta (Aβ) and prevent the aggregation of these toxic proteins, which are believed to play a crucial role in the progression of Alzheimer's disease. As a result, immunotherapy has gained significant attention as a promising approach to promote the clearance of Aβ from the brain. This has led to a surge in research focused on developing effective anti-Aβ therapies.

Among the most advanced and extensively researched immunotherapies are vaccines and exogenous antibodies. Vaccines, which are designed to stimulate the body's immune system to recognize and clear Aβ, are classified as active immunotherapy. On the other hand, exogenous antibodies, which involve the direct administration of antibodies to target and neutralize Aβ, fall under passive immunotherapy (figure 2) [12]. Both approaches aim to reduce the burden of Aβ plaques in the brain and have shown potential in preclinical and clinical studies, although further research is needed to fully understand their efficacy and safety profiles. These immunotherapeutic strategies represent a major step forward in the search for disease-modifying treatments for Alzheimer's disease [13].

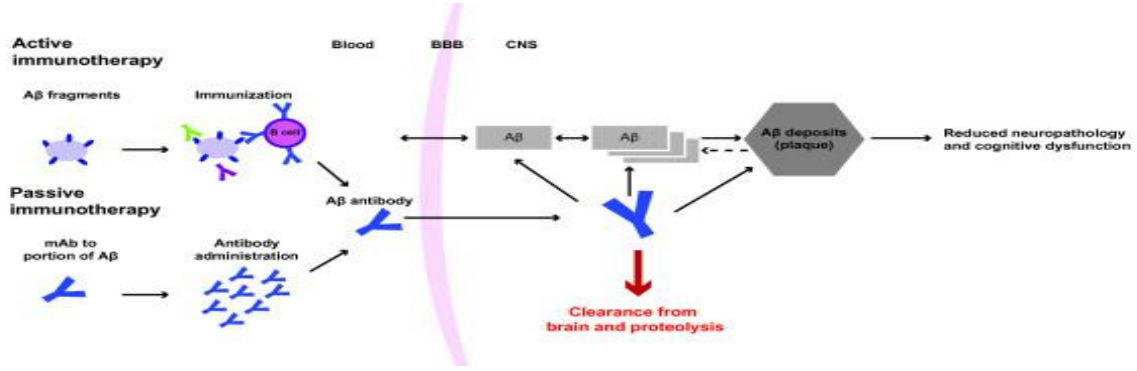

Figure 2. Immunotherapy approach to beta-amyloid clearance. Adapted from Winblad B, Graf A, Riviere ME, Andreasen N, Ryan JM. Active immunotherapy options for Alzheimer's disease. *Alzheimers Res Ther*. 2014;6(1):7. Published 2014 Jan 30. doi:10.1186/alzrt237 [12]

- **Passive Immunotherapy – targeting amyloid-beta**

Despite numerous challenges and setbacks faced by the pharmaceutical industry in the development of effective anti-amyloid beta (Aβ) immunotherapies, several monoclonal antibody (mAb) drugs (such as gantenerumab, aducanumab, lecanemab and donanemab) have demonstrated promising results in phase III clinical trials. Some of these therapies have received conditional or full approval from the FDA.

Gantenerumab, a human monoclonal IgG1 antibody, binds aggregated amyloid-beta (Aβ) with high affinity, promoting its clearance via Fc receptor-mediated phagocytosis. Despite showing significant reductions in amyloid plaques and cerebrospinal fluid (CSF) biomarkers such as phospho-tau181 and total tau, gantenerumab has struggled to demonstrate cognitive benefits in Alzheimer's disease (AD) clinical trials. In phase III trials like Scarlet Road and Marguerite Road, gantenerumab showed limited efficacy at lower doses and transitioned to open-label studies using higher doses (up to 1200 mg/month). These higher doses achieved a 51% amyloid-negative rate after 104 weeks. However, in the larger Graduate I and II trials, gantenerumab failed to significantly slow cognitive decline despite reducing amyloid levels by up to 57.6 CL over two years [14].

In inherited early-onset AD trials, gantenerumab also reduced Aβ plaques and biomarkers but did not improve cognition. Ongoing phase III trials continue to assess its long-term safety and potential in broader AD populations [13]. While promising in amyloid reduction, gantenerumab's clinical efficacy in slowing Alzheimer's progression remains uncertain.

Aducanumab, a humanized IgG1 monoclonal antibody, targets aggregated amyloid-beta (Aβ) including soluble oligomers and insoluble fibrils. Initial trials, such as the phase Ib PRIME study, demonstrated significant reductions in brain amyloid levels in a dose- and time-dependent manner, with cognitive benefits reflected in delayed declines in Clinical Dementia Rating-Sum of Boxes (CDR-SB) and MMSE scores [14]. Two phase III trials, EMERGE and ENGAGE, aimed to evaluate aducanumab's efficacy in patients with mild cognitive impairment or early-stage Alzheimer's disease. While both trials were terminated early due to futility, subsequent analysis revealed contrasting outcomes. EMERGE showed a 22% reduction in clinical decline in the high-dose group, while ENGAGE failed to meet its primary endpoint. The discrepancy is attributed to protocol changes, with EMERGE enrolling more patients at higher doses [15].

In 2021, the FDA granted accelerated approval for aducanumab, despite objections from advisory committee members and ongoing debate about its inconsistent clinical results. Approval was based on its ability to reduce amyloid plaques, a surrogate endpoint, requiring a phase IV confirmatory trial. Aducanumab became the first Alzheimer's therapy approved since 2003, offering hope to patients despite criticism of the decision [13][14]. The drug remains controversial, with limited insurance coverage and its clinical efficacy still under scrutiny.

Lecanemab is a humanized IgG1 monoclonal antibody targeting soluble Aβ protofibrils, which are more neurotoxic than Aβ monomers and fibrils. Drug was fully approved for AD by FDA in 2023 It exhibits activity across oligomers, protofibrils, and fibrils, contributing to its potential disease-modifying effects.

The phase III Clarity AD trial (NCT03887455), completed in September 2022, included 1,795 early AD patients randomized to receive 10 mg/kg lecanemab or placebo every two weeks for 18 months. Lecanemab significantly slowed cognitive decline on the CDR-SB

scale by 27% ($p < 0.001$), with benefits observed as early as six months. Secondary endpoints, including ADAS-Cog14, ADCOMS, and ADCS-MCI-ADL scores, were also met. Amyloid levels decreased significantly, and biomarker improvements were noted in CSF and plasma, along with reduced tau accumulation on PET imaging [12] [13].
Regarding safety, ARIA-E incidence was 12.6% (2.8% symptomatic) in the lecanemab group versus 9.9% in placebo. ARIA-H occurred in 17.3% versus 9.0%, with higher rates in ApoE ε4 homozygotes. While lecanemab-associated ARIA rates were lower than other Aβ mAb trials, safety concerns persist due to three reported deaths linked to brain hemorrhages or swelling. Further research will clarify its role in slowing disease progression [13].
Donanemab is a humanized IgG1 monoclonal antibody designed to target the N-terminal pyroglutamate Aβ epitope, found exclusively in established Aβ plaques. In the phase II TRAILBLAZER-ALZ study (NCT03367403), patients received either a placebo or donanemab, initially at 700 mg for three doses followed by 1400 mg every four weeks for 72 weeks. Donanemab showed a significant reduction in amyloid plaque levels, with 67.8% of treated patients reaching amyloid negativity. The study demonstrated cognitive decline reduction, as measured by the Integrated Alzheimer's Disease Rating Scale (iADRS) (Mintun et al., 2021) [14].
Further, in the phase III TRAILBLAZER-ALZ 2 trial (NCT04437511), which included 1736 patients with mild cognitive impairment (MCI) or mild AD dementia, donanemab met its primary endpoint, showing a 35.1% slowed clinical decline on iADRS and a 36.0% reduction in decline on CDR-SB in the low/medium tau population. When including patients with high tau expression, clinical decline slowed by 22.3% and 28.9% on iADRS and CDR-SB, respectively. Additionally, at 76 weeks, donanemab reduced brain amyloid plaques by 88.0 CL in the low/medium tau group and by 87.0 CL in the combined population, with over 76% of patients reaching amyloid clearance. However, PET imaging showed no significant differences in tau deposition changes across groups. Plasma phosphorylated-tau217 (P-tau217) levels significantly declined in donanemab-treated patients.
Regarding safety, ARIA-E was reported in 24.0% of donanemab recipients, with 6.1% experiencing symptoms, and ARIA-H occurred in 31.4% of treated participants. Unfortunately, three patients suffered fatal ARIA-related events. To further assess its long-term effects - extension study is ongoing [13] [14].

- **Passive Immunotherapy – targeting tau protein**

Passive immunotherapy targeting tau protein represents a promising approach for Alzheimer's disease treatment. Anti-tau monoclonal antibodies (mAbs) are designed to inhibit tau aggregation, seeding, and spreading, aiming to reduce tau pathology by targeting both intracellular and extracellular tau. However, the clinical development of anti-tau mAbs remains in its early stages. So far, four such antibodies (semorinemab, tilavonemab, gosuranemab, and zagotenemab) have progressed to phase II clinical trials [14].
Gosuranemab, an IgG4 monoclonal antibody targeting N-terminal tau fragments (amino acids 15–22), was the first anti-tau therapy tested in clinical trials. It demonstrated the ability to significantly reduce free N-terminal tau fragments in cerebrospinal fluid (CSF) and was safe and well-tolerated in early trials. However, gosuranemab showed no clinical efficacy in multiple phase II trials. In the PASSPORT trial (NCT03068468), conducted in patients with progressive supranuclear palsy (PSP), it failed to meet the primary endpoint despite reducing free tau in CSF by 98%.

Similarly, the TANGO trial (NCT03352557) in patients with mild cognitive impairment (MCI) or mild Alzheimer's disease (AD) also failed to show significant cognitive improvements or reductions in brain tau accumulation as measured by PET imaging. Moreover, cognitive outcomes in treated groups were sometimes worse than in the placebo group. Though gosuranemab effectively reduced extracellular tau levels in CSF, it did not impact tau pathology in brain tissue or improve clinical symptoms. Consequently, its development was terminated in 2021 [14][16].

Semorinemab is a humanized IgG4 monoclonal antibody that targets the N-terminus of monomeric and oligomeric tau. It binds all six human tau isoforms and is designed to protect neurons by neutralizing extracellular tau. Preclinical studies demonstrated that the mouse version reduced a specific phospho-tau epitope in brain sections but showed no effect on tau levels in western blots from a tauopathy mouse model. Its impact on insoluble tau and behavioral outcomes was not assessed. Notably, the effector-function version cleared tau at a lower dose than the effectorless variant, though neither form triggered astrogliosis or microgliosis. Nevertheless, the effectorless version was chosen for clinical trials to mitigate the risk of microtubule-associated protein 2 fragmentation, which is essential for maintaining neuronal microtubule stability [14].

Semorinemab's safety profile has been documented by AC Immune SA, though clinical trials have yet to show meaningful efficacy in Alzheimer's disease. Nonetheless, ongoing research includes a study in patients with moderate AD, which aims to further evaluate its therapeutic potential [16].

Tilavonemab is an IgG4 monoclonal antibody targeting an N-terminal tau epitope and is designed to recognize aggregated, extracellular pathological tau. Developed by C2N Diagnostics and AbbVie, tilavonemab demonstrated promising preclinical results. In vitro studies showed it blocked tau seeding and prevented tau pathology propagation when preincubated with tau seeds. In mouse models of tauopathy, it significantly reduced p-tau and insoluble tau levels, improved motor function, and alleviated contextual fear conditioning deficits. Additionally, it was associated with decreased brain atrophy and enhanced neuroprotection [14] [16].

Zagotenemab is a humanized anti-tau antibody derived from the MC1 antibody, originally developed by Peter Davies. MC1 targets an early pathological conformation of misfolded tau. Preclinical studies in tau transgenic mice demonstrated that chronic administration of zagotenemab reduced insoluble phosphorylated tau (p-tau) levels in the spinal cord, decreased tau immunoreactivity in the brainstem and spinal cord, and improved motor function. Additionally, its single-chain variable fragment (scFv), delivered via an AAV-based gene therapy, also reduced tau pathology. Two phase I clinical trials assessed the safety and pharmacokinetics of zagotenemab. The first (NCT02754830) investigated its safety profile and serum drug concentration in healthy participants and individuals with mild cognitive impairment (MCI) or mild-to-moderate Alzheimer's disease (AD). The second (NCT03019536) examined the effects of multiple ascending doses in the same patient group. While adverse effects and pharmacokinetics were evaluated, the trial results remain unpublished. A phase II efficacy trial (NCT03518073) enrolled 285 patients with at least six months of gradual and progressive memory decline by August 2019. The study, which ran until August 2021, assessed cognitive and functional outcomes, along with the presence of anti-drug antibodies. However, in October 2021, Eli Lilly announced that the trial failed to meet its primary endpoint, leading to the discontinuation of zagotenemab's development [12] [14] [16].

Active Immunotherapy

The first Aβ peptide vaccine, AN-1792, was composed of the Aβ1–42 peptide combined with the QS21 adjuvant. Its purpose was to stimulate the immune system to produce antibodies targeting endogenous Aβ, aiming to prevent Aβ plaque formation in the brain and associated cognitive decline. Although the AN-1792 vaccine demonstrated promising safety and tolerability in a phase I clinical trial, it was discontinued two years later during a phase II trial due to cases of meningoencephalitis caused by Th-1 response.

Despite the failure of the AN-1792 peptide vaccine in clinical trials, it laid the groundwork for the development of second-generation Aβ peptide vaccines. Since then, nine Aβ peptide vaccines have entered clinical trials. Four of the most promising candidates are CAD-106, ACI-24, ABvac40, and UB-311 - all tested in at least phase II trials. These vaccines target specific regions of Aβ as antigens, using various methods of antigen presentation. Most second-generation vaccines focus on the N-terminus of Aβ to elicit a Th-2 immune response while avoiding a Th-1 response, incorporating lessons from AN-1792's failure [13][17].

Gene Therapy

Gene therapy offers a groundbreaking approach to address diseases at their root cause by repairing faulty DNA, genes, or proteins, allowing cells to resolve the underlying problem. With the identification of various genes involved in Alzheimer's disease pathology, gene therapy presents a promising avenue for intervention. This approach typically involves introducing new genetic material into living cells using viral vectors, such as recombinant adeno-associated viruses (rAAVs). Recent advancements in rAAV technologies have opened the door to potential treatments for AD in humans.

One notable breakthrough occurred in June 2018 when scientists at the Massachusetts Institute of Technology demonstrated the possibility of addressing the APOEε4 gene, the strongest genetic risk factor for AD. The APOEε4 variant is associated with an increased production of amyloid beta proteins in the brain, significantly raising the risk of AD. Individuals with one copy of the APOEε4 gene face a twofold increased risk, while those with two copies face up to a twelvefold increase. In contrast, the APOEε2 variant appears protective, lowering AD risk[18][19].

Gene-editing techniques have been proposed to mitigate the impact of APOEε4 by converting it into the neutral APOEε3 variant or introducing the protective APOEε2 variant. For example, Crystal and colleagues have developed an rAAV vector to deliver the APOEε2 gene directly to the central nervous system (CNS). Administered intracisternally in non-human primates, this approach achieved widespread APOEε2 expression in the CNS, reduced amyloid beta levels, and avoided vector-related inflammation or adverse effects. A Phase 1 clinical trial is currently underway, representing a significant step forward in leveraging gene therapy to combat Alzheimer's disease [19][20].

One of the main challenges in gene therapy for Alzheimer's disease (AD) is the limited efficiency of gene transfer to the central nervous system (CNS). Research has shown that modifying the AAV capsid structure, such as introducing specific tyrosine mutations in AAV2 or engineering variants like AAV-PHP.B and AAV-B1, can significantly enhance CNS transduction while minimizing peripheral distribution. Additionally, approaches like Cre recombinase-based evolution (CREATE) and targeted mutagenesis have led to the development of improved vectors with higher neurotropism and transduction efficiency.

Recent studies have demonstrated that variants such as AAV-PHP.B and AAV-PHP.eB improve gene delivery to neurons and astrocytes, while engineered AAV2g9 shows enhanced selectivity for the CNS with minimal off-target effects. Other strategies, including CRISPR/Cas9-mediated gene editing via optimized AAV vectors, offer potential for precise genetic interventions in neurodegenerative diseases. However, further research is needed to validate the effectiveness of these vectors in primates and humans to ensure their safety and long-term efficacy in AD therapy[21].

Conclusions

Alzheimer's disease is the most prevalent neurodegenerative disorder and the leading cause of dementia in older adults, characterized by cognitive decline and limited treatment options. Its pathology is marked by amyloid-β (Aβ) plaques, tau neurofibrillary tangles, synaptic loss, and neuronal degeneration, ultimately resulting in cognitive impairment. Although the exact mechanisms underlying AD remain unclear, evidence suggests that Aβ-triggered cascades, cholinergic deficits, abnormal tau phosphorylation, and neuroinflammation play critical roles in disease progression. Current treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, provide only temporary symptomatic relief. However, recent advances in disease-modifying therapies, particularly immunotherapies targeting Aβ and tau, offer promising avenues for intervention. Passive immunotherapy, which involves administering Aβ antibodies, has been the most extensively studied strategy. While these approaches represent significant progress, challenges remain in terms of treatment efficacy, early diagnosis, and accessibility. Additionally, gene therapy is emerging as a potential approach, with research focusing on modifying genes associated with AD risk, such as APOEε4, or delivering neuroprotective genes to slow disease progression. Over the past four decades, research has greatly expanded our understanding of AD, paving the way for novel diagnostic tools and therapeutic options. A comprehensive strategy combining pharmacological and non-pharmacological interventions, alongside continued scientific innovation, is essential to improving patient outcomes and ultimately finding a cure for this devastating disease.

Disclosures

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