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MINI-REVIEW

Innovative approaches and challenges in antibody-based therapeutics for Alzheimer's disease

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Abstract

Neurological conditions, such as Alzheimer's disease (AD) and tau-related pathologies, represent a substantial worldwide health dilemma. This review explores recent advancements and challenges in single-domain antibody (VHH)-based strategies targeting beta-secretase 1 (BACE1) inhibition and tau-related therapeutics. The methodology adopted in this study involved a comprehensive search of databases (e.g., Scopus, PubMed, and Google Scholar), with recent articles cited to provide an up-to-date overview. The research examines the limitations of current AD treatments, emphasizing the need for innovative techniques. We, further, discuss potential gene transfer methods using adeno-associated virus-based vectors for central nervous system delivery of single-domain immunoglobins/antibodies (VHHs) to inhibit BACE1. In addition, insights into anti-tau therapeutics, including passive immunization and active vaccines, offer novel insights into research. These findings hold implications for the redesign of therapies for neurodegenerative disorders and the advancement of clinical understanding.

Keywords: Neurological condition; Single-domain antibodies; BACE1 inhibition; Tau-related therapeutics

1. Introduction

Neurodegenerative diseases, such as Alzheimer's disease (AD) and tau-related pathologies, present a growing global health issue. AD predominantly afflicts the

elderly, causing dementia characterized by abnormal protein deposits leading to plaques and tangles. These manifestations result in gradual nerve cell degeneration and impaired communication.[1] Clinical studies focusing on immunotherapy targeting amyloid beta (Aβ) face challenges due to the observed lack of correlation between Aβ levels and dementia severity, which raises questions about the capabilities of Aβ-focused interventions.[2] Current United States Food and Drug Administration-approved drugs, including acetylcholinesterase inhibitors (e.g., donepezil and rivastigmine) and aducanumab, which target Aβ plagues, offer temporary relief by delaying the progression of AD. However, they fail to reverse neuronal loss, brain atrophy, or cognitive decline.[3] Aβ, derived from amyloid precursor protein cleavage, is a central focus of therapeutic research, with drugs targeting β- or γ-secretase and Aβ aggregation.[4-6] However, these approaches provide limited benefits and may lead to adverse effects. Recent findings suggest that Aβ immunotherapy not only reduces Aβ but also lowers tau levels in animal models. This discovery has prompted researchers to explore tau immunotherapy as a promising avenue, particularly in early-stage AD, given the evident interaction between Aβ and tau.[7-9] The development of single-domain antibodies (VHHs) stemmed from the limitations of conventional antibodies, such as their larger size, limited tissue penetration, and susceptibility to denaturation and aggregation, which hindered their effectiveness in targeting specific epitopes, particularly in the central nervous system (CNS).[7]

Antibody-based therapies offer a promising alternative to small-molecule drugs, especially when comparing inhibitors of beta-secretase 1 (BACE1) to VHHs targeting BACE1. However, the development of BACE1 inhibitors has faced challenges leading to their failures, highlighting the need for further exploration and understanding of these therapies. Despite recent developments in monoclonal antibody research and the emergence of disruptive therapeutics such as variable heavy chain domains, which are VHHs (Table 1), their potential application in CNS disorders remains underexplored due to the inherent challenge of these agents crossing the blood–brain barrier (BBB).[10] Recent setbacks, such as the termination of the variable heavy chain domains B (VHH-B) clinical trial, underscore the critical need for innovative systems and a comprehensive understanding of the molecular mechanisms involved in targeting key proteins such as BACE1 and tau.[11] The proposed gene transfer method using adeno-associated virus (AAV)-based vectors offers a novel avenue for effectively delivering therapeutic antibodies into the CNS. Moreover, investigating the system of anti-tau therapeutics, including passive immunization, active tau-targeted vaccines, and tau aggregation inhibitors, is imperative for advancing the field and addressing the challenges posed by tau-related disorders. Therefore, this review aims to address these gaps by elaborating on current studies exploring gene transfer methods to deliver therapeutic agents directly into the CNS, with the goal of offering insights into therapies inhibiting BACE1 and advancing our understanding of their therapeutic potential. This article holds significant implications for both preclinical and clinical studies. For instance, it could contribute to the broader understanding of antibody-based therapies in neurodegenerative disorders, shedding light on the challenges and opportunities associated with VHHs in applications. In addition, discussions on tau-related therapeutics offer a comprehensive overview, laying a foundation for refining existing scientific models and developing innovative methods.

Table 1. Studies and clinical trials on VHH-based therapeutics for CNS disorders

Study/ Clinical trial	Focus	Findings	Implications
Singh *et al.*[10]	Monoclonal antibody research and VHHs in CNS disorders	Underexplored potential due to BBB challenge	Highlights the need for innovative approaches
Das and Yan[11]	Molecular intricacies of targeting BACE1 and tau	Termination of the VHH-B trial emphasizes the need for understanding	Calls for a comprehensive approach in targeting key proteins
Marino *et al.*[14]	Gene transfer method using AAV-based vectors to deliver VHHs into CNS	Promising results in inhibiting BACE1	Offers novel avenue for effective CNS delivery
Yadav *et al.*[15]	Infusion of anti-BACE1 antibodies via i.c.v. administration in primates	Significant reduction in Aβ peptides in CSF and brain parenchyma	Highlights potential of direct CNS injection for uniform antibody distribution
Burns *et al.*[16]	VHH-B clinical trial termination due to safety concerns	Emphasizes the need for further refinement of VHH-based therapeutics	Caution in translating to human CNS disorders

Abbreviations: AAV: Adeno-associated vector; Aβ: Amyloid beta; BACE1: Beta-secretase 1; BBB: Blood–brain barrier; CNS: Central nervous system; CSF: Cerebrospinal fluid; i.c.v.: Intracerebroventricular; VHH: Single-domain antibody.

2. Innovative approaches and challenges in variable heavy chain domains-based therapeutics for CNS disorders

Monoclonal antibodies have emerged as an important field in research, offering targeted interventions against specific molecules such as lipids and proteins.[12] Within this realm, VHHs, known for their potential as revolutionary treatments, are gaining scientific recognition.[13] Despite their versatility in addressing medical challenges, these antibodies have seen limited application in neurological disorders due to the formidable obstacle posed by BBB.[14] In a recent study, researchers devised a gene transfer strategy utilizing vectors equipped with BBB-crossing capabilities to deliver therapeutic molecules directly into the CNS of mammals. Specifically, the study aimed to inhibit a key enzyme in the brain using a developed VHH named VHH-B9.[14] The results indicated a high selectivity of VHH-B9 for BACE1, with a single systemic dose demonstrating enduring benefits such as improved cognition in mice lasting up to 12 months.[14] This innovative protocol holds promise for exploring therapeutic interventions in neurological disorders.

In another investigation by Yadav *et al.*,[15] anti-BACE1 antibodies were infused into primate subjects through intracerebroventricular administration, resulting in a substantial and sustained reduction of up to 70% in Aβ peptides within the cerebrospinal fluid (CSF). Notably, direct CNS injection achieved uniform antibody distribution (20 – 40 nM) in the brain parenchyma, leading to a 50% reduction in Aβ in cortical parenchyma. However, intravenous administration in nonhuman primates yielded non-significant changes in cortical or CSF Aβ levels, accompanied by a low brain concentration (approximately 0.6 nM) of anti-BACE1 antibodies.[15]

Despite promising results in preclinical studies, the translation of VHH-based therapies to clinical trials has faced challenges. The VHH-B clinical trial, terminated in 2021, was deemed unsafe for human subjects due to unforeseen changes in cognitive function, brain volume loss, and body weight loss.[16] This finding highlights the imperative for further investigation and refinement of VHH-based therapeutic methods before their application in human CNS disorders.

3. Advancements and strategies in anti-tau therapeutics

Tau, a microtubule-associated protein crucial for stabilizing axonal microtubules, becomes problematic when deposited abnormally, leading to various diseases, including dementia.[17] Figure 1 illustrates the pathogenesis of tau, highlighting the complexities involved. Current therapeutic approaches target intracellular and extracellular tau to hinder pathological tau formation, accumulation, and spread.[18] The strategies involved encompass protein kinase inhibition, inhibition of tau aggregation, antisense oligonucleotides, as well as active and passive immunotherapies.[18] Notably, numerous small molecules directly or indirectly modify tau aggregation.[19]

The efficiency of tau immunotherapies was initially demonstrated in the Janus kinase- and nucleotide-binding oligomerization domain-like receptor protein 3 mouse model, also known as JNPL3 in 2007, demonstrating reduced tau pathology in various brain regions.[21] At present, the majority of tau-targeted therapies in preclinical

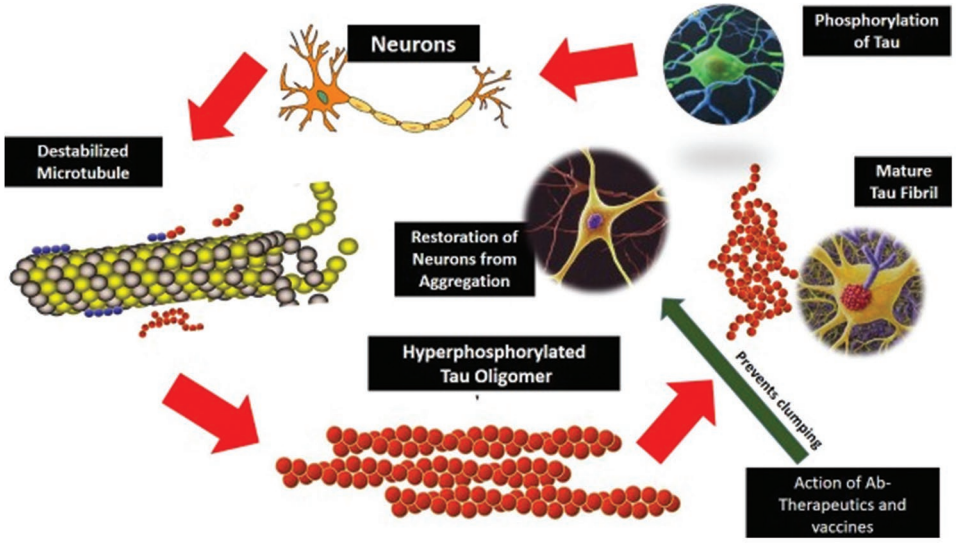


Figure 1. Proposed mechanism of pathogenesis of Tau.[20]

investigations revolve around immunotherapies.[17] In addition, passive immunization, which involves administering monoclonal immune-proteins, has marked a significant growth.[17] The development of passive immunization techniques such as the JNJ-63733657 and UCB0107 marks a significant improvement in the quest for effective anti-tau treatment, offering hope in the fight against tau-related neurodegenerative diseases.

JNJ-63733657 is a humanized IgG1 monoclonal antibody that targets the temperate region of tau and exhibits potential to prevent tau's cell-to-cell propagation and aggregation.[22] Janssen Research and Development conducted two phase 1 clinical trials, demonstrating safety and tolerability, pharmacokinetics, and pharmacodynamics of a drug candidate in a small group of healthy volunteers or patients.[23] In a 2019 phase 1 trial, dose-dependent increases in exposures were reported, with CSF concentrations of approximately 0.2% of serum levels, and dose-dependent reductions in p217+ tau in CSF were observed.[24] A phase 2 study commenced in January 2021, involving 420 patients with the early AD symptoms and a positive tau PET scan, set to conclude in 2025.[25] Similarly, UCB0107 is a humanized monoclonal IgG4 antibody that exhibits an affinity for binding to paired helical filaments of tau, recognizing amino acids 235–250 near tau's microtubule-binding domain.[22] Union Chimique Belge (UCB) completed a phase 1 trial in March 2019, assessing adverse events and pharmacokinetics in 24 healthy Japanese men who received a single, unspecified UCB0107 dosage or placebo.[26] The ongoing phase 2 trial aims to randomize 450 individuals with mild cognitive impairment or mild AD dementia to different doses or a placebo for 80 weeks, concluding in 2025.[25]

3.1. Active tau-targeted vaccines

At present, ACI 35 and AADvac-1 are two active anti-tau vaccines undergoing clinical research. ACI 35, a liposome-based vaccine, consists of 16 copies of synthetic tau fragments phosphorylated at S396 and S404. These fragments are anchored into a lipid bilayer to stimulate the immune system and generate antibody proteins.[17] In July 2019, AC Immune and Janssen initiated a small phase 1b/2a trial to assess the safety and immunogenicity of ACI-35 in individuals with early AD. By July 2020, the lowest-dose cohort had completed the trial, revealing favorable safety, tolerability, and immunogenicity data.

In February 2022, interim data from the trial confirmed the consistent safety and potent immunogenicity of the p-Tau Alzheimer's vaccine in a high-dose cohort in early AD. AADvac-1, an active vaccine, is designed to provoke an immune response against a pathologically altered form of tau pathology.[17] This first-generation active immunotherapy targets 12 amino acid sequences in the microtubule-binding region of the tau protein.[27] Axon neuroscience initiated a phase 1 trial in May 2013 with 30 patients with mild-to-moderate AD. The results from the trial indicate high immunogenicity, with IgG antibodies against tau peptides induced in 29 out of 30 patients. Overall, AADvac-1 demonstrated encouraging safety and tolerability profiles. The subsequent phase 2 trial involved 196 patients with mild-to-moderate AD, meeting the major objectives and secondary objectives, including the evaluation of immunogenicity and treatment efficacy.

3.2. Tau aggregation inhibitor

The primary direct tau binder is methylene blue, also known as methylthionine chloride.[26] Variants of methylene blue have demonstrated particular promise in blocking tau clumping.[26] TRx0237 (LMTM), a second-generation tau aggregation inhibitor for AD and frontotemporal dementia, is the purified form of methylene blue. Wilcock and colleagues explored the effectiveness of LMTM as monotherapy in a non-randomized cohort during an 18-month phase 3 trial in mild AD. The results supported the hypothesis that it could be effective as monotherapy, particularly when administered at a dose of 4 mg twice a day. Although the phase 3 trial did not slow cognitive or functional decline in mild-to-moderate AD, re-investigation of the data revealed a significantly lower brain atrophy rate in patients receiving monotherapy compared to those receiving placebo. A phase 3 trial with a lower dose has been conducted and concluded in December 2022.[25]

4. Implications of findings

The ever-evolving nature of research addressing neurological conditions presents promising avenues and challenges for future exploration. The change from a singular focus on Aβ in AD to an exploration of alternative targets such as tau highlights the need for novel advancements in therapeutic methodologies. Innovations in VHH-based therapies, such as the gene transfer method using AAV-based vectors, offer the potential to overcome challenges associated with BBB penetration. However, setbacks in clinical studies, such as the termination of the VHH-B trial, indicate the imperative for rigorous preclinical investigation and improvement of methodology. In addition, utilizing VHH-based therapy is accompanied by limitations, including potential immunogenicity, limited epitope diversity, and challenges in large-scale production and formulation for therapeutic use. In addition, their small size may lead to rapid renal clearance, necessitating modifications to improve their pharmacokinetic properties. Therefore, this comprehensive review of anti-

tau interventions, encompassing passive immunization, active vaccines, and aggregation inhibitors, suggests that current drawbacks may soon be transformed into research advantages, driving progress in this field. Future directions may encompass personalized therapies, multi-modal systems, advancements in gene editing, and innovative tactics for BBB penetration. Longitudinal studies, biomarker identification, and considerations of neuroinflammation and immune modulation will be crucial. As the field advances, a patient-centric focus and global collaboration for data sharing will be paramount for accelerating advancement in understanding and treating neurodegenerative disorders.

5. Conclusion

The detrimental impact of tau phosphorylation on neurons underscores the urgent need for effective therapies targeting this pathway. Antibody-based therapeutics, particularly those utilizing VHH antibodies, hold immense promise for future research and applications, due to their potential to overcome BBB limitations. As research progresses, further investigation into VHH-based therapies and their efficacy in clinical trials will be crucial for developing successful antibody-based therapies for neurodegenerative disorders. The advancement of these therapies will pave the way for personalized treatment options and improved patient outcomes.

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Conflict of interest

The authors declare that they have no competing interests.

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