Open Access

OBM Neurobiology

LIDSEN Publishing Inc.

Review

Tau-Targeted Immunotherapy for Alzheimer's Disease: Insight into Clinical Trials

Nadia El Kadmiri *

Molecular Engineering, Biotechnology and Environment Team, Bio-Geo-Environment Engineering and Innovation Laboratory, Polydisciplinary Faculty of Taroudant, IBN ZOHR University, Taroudannt City, Morocco; E-Mail: n.elkadmiri@uiz.ac.ma

* **Correspondence:** Nadia El Kadmiri; E-Mail: n.elkadmiri@uiz.ac.ma

Academic Editor: Francesco Amenta

Special Issue: Molecular Mechanisms of Alzheimer's Disease Pathogenesis

OBM Neurobiology
2024, volume 8, issue 3
doi:10.21926/obm.neurobiol.2403238

Received: August 16, 2023
Accepted: June 18, 2024
Published: August 07, 2024

Abstract

The use of immunotherapy as a therapeutic approach to Alzheimer's Disease (AD) is gaining rapid interest, with the primary goal of targeting abnormalities that impact neuronal viability through specific antibodies. Currently, clinical strategies focus intensively on targeting the two main pathologies associated with AD, beta-amyloid (Aβ) and tau. This review examines ongoing research in the realm of tau immunotherapy, including clinical trials that demonstrate promising potential for halting AD progression. Several trials are underway, focusing on improving tau-targeted immunotherapy tools based on passive and active immunization protocols. Tau-targeted therapies have proven relevant and demonstrated safety and efficacy in both animal models and human clinical trials. Some studies have demonstrated a reduction in tau protein aggregation in animal models, highlighting a potential mechanism by which these antibodies inhibit the spread of tau protein in the extracellular space. Recent discoveries have highlighted the potential role of tau-targeting therapy with antibodies and have revealed significant promise in treating pathological tau in AD.

Keywords

Tau; immunotherapy; clinical trials; Alzheimer disease

1. Introduction

Alzheimer's Disease (AD) is a complex neurodegenerative disorder influenced by genetic mutations, environmental factors, and aging. It is characterized by neuronal death and a progressive decline in cognitive functions, leading to progressive memory loss, spatial and temporal disorientation, and behavioral disorders [1]. Tau proteins are predominantly neuronal and show significant involvement in microtubule polymerization. In the human brain, the tau protein consists of six isoforms that originate from a gene located on chromosome 17 through the alternative splicing of exons 2, 3, and 10. These splice variants result in proteins that vary in length between 352 and 441 amino acids. In AD, tau phosphorylation is atypical, leading to tau hyperphosphorylation. Hyperphosphorylation and aggregation of the six isoforms generate paired helical filaments (PHF-tau) [2]. Evidence suggests that abnormal hyperphosphorylation and accumulation of tau protein induces irreversible neuronal damage in AD, making p-tau proteins attractive targets for treating AD. However, tau aggregation and neurofibrillary tangles are not unique to AD and constitute a family of neurodegenerative diseases, called tauopathies that include frontotemporal dementia with chromosome 17-linked parkinsonism (FTDP-17), corticobasal degeneration, Pick's disease, progressive supranuclear palsy, dementia pugilistica, and Chronic Traumatic Encephalopathy (CTE) [3]. As such, therapies targeting tau will have broader effects on neurological diseases.

Recent advances in treatment approaches have included targeted immunotherapies that have aligned themselves with the two neuropathological lesions seen in AD: senile extracellular plaques comprising of Aβ and intracellular neurofibrillary tangles (NFTs) consisting of abnormal hyperphosphorylated deposits of tau (p-tau) [4]. These strategies aim to alleviate progressive cognitive decline. Several trials are underway, investigating development tools for tau-targeted immunotherapy based on passive and active immunization protocols. Research into immunotherapies has highlighted the great potential of tau in animal models and patients with AD [2].

2. Methods

Three databases were explored: PubMed/Medline and EBSCOhost to identify relevant trials conducted over the past 13 years. A set of appropriate keywords was employed, including [Tau], [AD], [AD immuno-therapy], and [AD trials]. The initial selection was performed through the screening of abstracts. Sixty-six file records were selected. Three duplicate records were removed. The selection of articles was confined to Tau immunotherapies for AD and clinical trials. Sixty-three items were evaluated based on eligibility criteria. Twenty-six studies were analyzed and categorized into passive and active immunotherapies. Figure 1 illustrates the study process according to the PRISMA flow diagram.

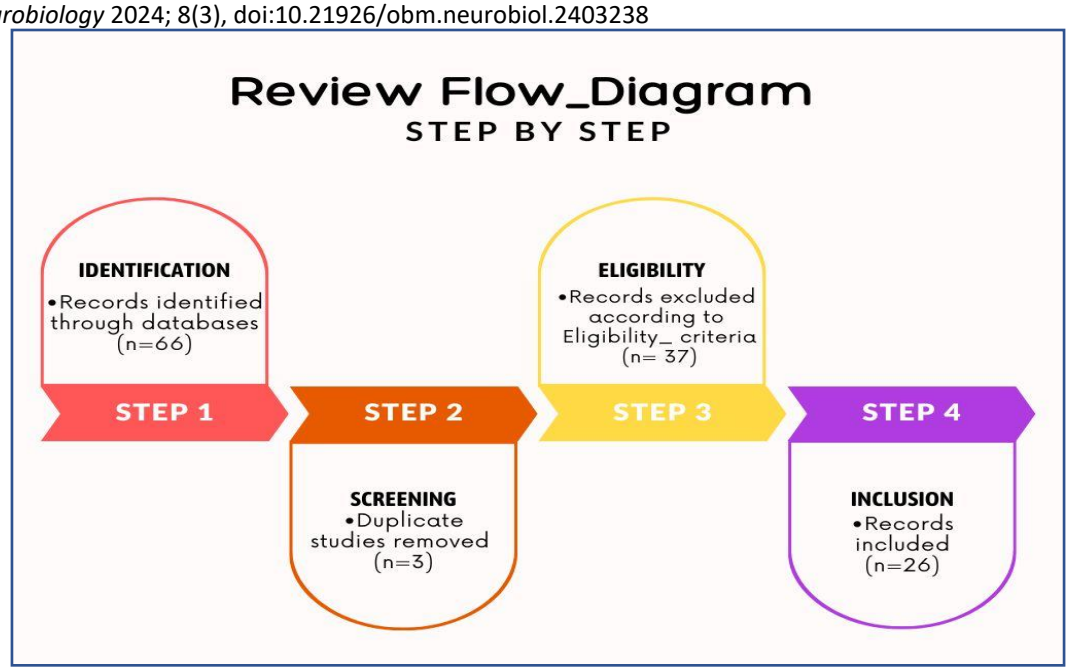

Figure 1 Study process according to the Prisma flow diagram.

The eligibility criteria were as follows:

- Available studies;
- Records published in English;
- Investigations focusing on tau-targeted immunotherapies for AD;
- Trials involving human and animal models;
- Ongoing clinical trials from 2011 to the present date.

3. Passive Immunotherapy

Passive immunotherapy trials involving the administration of phospho-tau-specific monoclonal antibodies in animal models have shown excellent safety, attributed to their potential to avoid the risk of autoimmune complications and transient effects. The first target was the pSer396/404 region in tau. The use of the PHF1 antibody in the JNPL3 mouse model significantly decreased tau pathology and reported functional enhancements in this mouse following treatment [5]. Sankaranarayanan et al., 2015 [6] found that p-tau antibodies targeting pT231 and pS396 decrease p-tau levels in the brain and cerebrospinal fluid (CSF) in aging tau transgenic mice. Subsequently, other monoclonal antibodies have emerged to target other tau regions that are effective in tauopathy models [7, 8]. Reports suggest that passive immunotherapy eliminates tau aggregation by targeting extracellular-tau protein [9, 10]. The administration of the RO6926496 antibody anti-tau/pS422 (RG7345) reduced the accumulation of tau in transgenic mice [11]. However, phase I was completed in healthy young individuals, and although the study was completed in October 2015, results have not been published [12]. In animal models, a humanized monoclonal antibody that bound to N-terminal regions of tau (BIIB092 (BMS-986168)), significantly reduced tau levels in the interstitial space and soluble $A\beta_{1\text{-}40}$ in the brain [13]. A Phase II investigation enrolled participants with mild cognitive impairment (MCI) or mild AD to test the effectiveness of different doses of BIIB092 in slowing cognitive and functional impairments [14]. However, this Phase II study (NCT03352557) was terminated due to a lack of efficacy.

C2N-8E12 (ABBV-8E12), a humanized anti-tau antibody showed a promising response in transgenic mouse models by decreasing levels of p-tau as well as its aggregation [10]. A phase II trial aimed to evaluate the safety and efficacy of ABBV-8E12 in subjects with early AD. However, the trial was terminated and discontinued due to a lack of efficacy in the parent study (Study M15-566; NCT02880956) [15]. A Phase I trial of RO 7105705 (MTAU9937A and RG6100) and an anti-tau antibody LY3303560, designed to assess the pharmacokinetics and safety in healthy volunteers and individuals with mild to moderate AD [16, 17] has been completed, but the study outcomes have not yet been disclosed. BIIB076 (NI-105 and 6C5 hulgG1/I); groups receiving a high dose of BIIB076 showed a significant decrease in total and free tau levels in CSF. Phase I was completed to evaluate the pharmacokinetics, tolerability, and safety of BIIB076 in healthy volunteers and AD cases [18]. Two novel antibodies, JNJ-63733657 and UCB0107, were developed to inhibit tau seeding, prevent the spread of pathological tau, and block the formation of pathogenic tau aggregates; trials for these antibodies are currently ongoing [19, 20] (Figure 2.P).

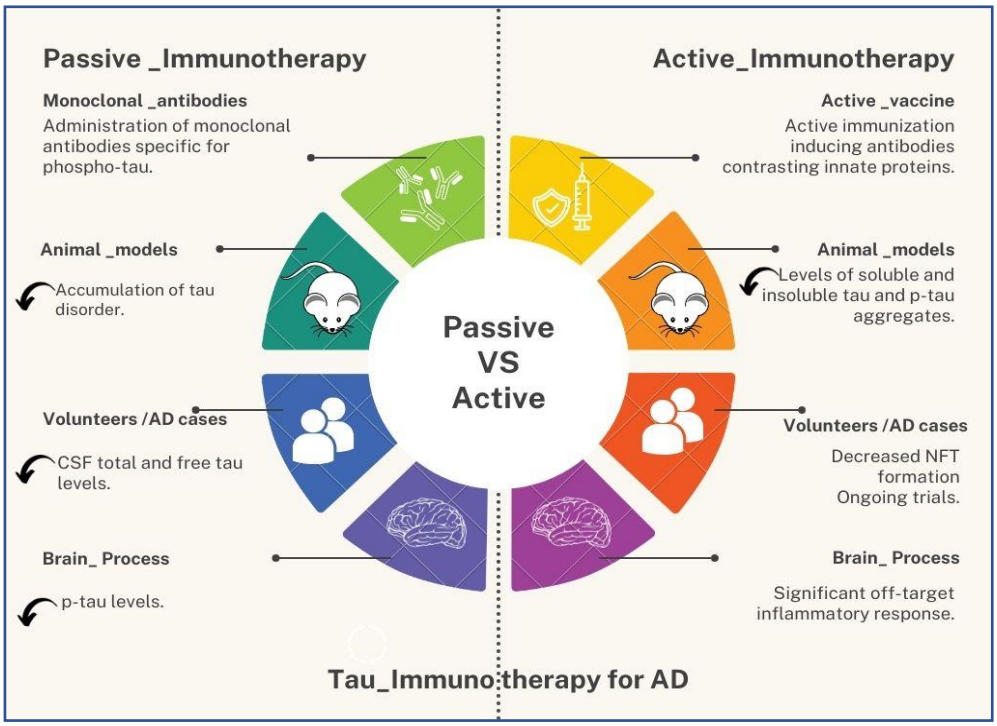

Figure 2 Key results of ongoing clinicals trials categorized into passive and active tau-immunotherapies for Alzheimer's disease.

4. Active Immunotherapy

Active immunization in animal models showed improvement in tau status by reducing both soluble and insoluble tau levels as well as p-tau aggregates, with limited adverse effects [21, 22]. However, the induction of antibodies contrasting innate proteins constantly carries the risk of unwanted immune responses [23]. AADvac1, an active vaccine targeting various epitopes in pathological forms of tau, has shown promising results. It decreased neurofibrillary tangle formation and inhibited tau aggregation, leading to significant behavioral improvements. Human trials of AADvac1 were initiated, and the findings revealed a safety profile that led to a larger phase II trial involving AD patients; Phase II was completed, and the results are pending [24]. Animals vaccinated with ACI-35 showed a significant reduction in a specific soluble p-tau Ser396 isoform and improved

longevity, devoid of any significant off-target inflammatory response [25, 26]; a phase 1b trial is underway for ACI-35 in patients with mild to moderate AD to assess effects and safety (Figure 2.A).

The involvement of the immune system in neurological disorders indicates that immunotherapy can prove effective in managing neurodegenerative diseases.

Immunotherapy as a therapeutic strategy for Alzheimer's disease is crucial, primarily aimed at identifying abnormalities that compromise neuronal viability through specific antibodies. This approach has emerged as a new therapeutic approach; the challenge is to inhibit abnormal hyperphosphorylation of tau, which widens prospects in the therapeutic management of AD and associated tauopathies. Targeting tau phosphorylation requires a thorough understanding of how tau functions are altered. Certainly, tau immunotherapy decreases tau pathology and may improve AD behavior. Ongoing clinical trials aim to develop safe, tolerable, and effective antibodies to inhibit the formation and progression of tau pathology in animal models and patients with AD. These trials have attempted to target hyperphosphorylated tau by passive or active immunotherapy based on direct antibodies against misfolded tau. Both passive and active immunotherapy have shown promising results (Table 1). Research and clinical trials have revealed the mechanism at work and the effects of specific antibodies in reducing the spread of tau in the brain.

Table 1 Passive and active tau immunotherapy for AD.

	Reference	Antibodies	Targets	Outcomes
Passive immunotherapy	[6]	PHF6 and PHF13	Transgenic mice	Decrease p-tau levels in the brain and CSF
	[11]	RO6926496 antibody anti-tau/pS422 (RG7345)	Transgenic mice	Reduced the accumulation of tau disorder
	[12]		Healthy young volunteers	Phase I: Completed Study results have not been submitted
	[14]	BIIB092 (BMS-986168)	Animal models	Reduced levels of tau in the interstitial space and soluble Aβ1-40 in the brain
	[14]		Patients with MCI/mild AD	Phase II: Terminated The study (NCT03352557) was terminated due to lack of efficacy following the placebo-controlled period readout
	[10]	C2N-8E12 (ABBV-8E12)	Transgenic model	Decreased p-tau level and aggregation
	[15]		Patients with early AD	Phase II: Terminated Discontinued because of lack of efficacy in the parent study (Study M15-566; NCT02880956)
	[16, 17]	● RO 7105705 (MTAU9937A and RG6100) ● LY3303560	Healthy volunteers and Patients with Mild-to Moderate AD	Phase I: Completed
	[18]	● BIIB076 (NI-105 and 6C5 hulgG1/I)	Healthy volunteers and AD patients	Decrease in total CSF and free tau levels Phase I: Completed
	[19, 20]	● JNJ-63733657 ● UCB0107)		Phase II: Ongoing

Active immunotherapy	[24]	● AADvac1 is an	AD patients	Decreased NFT formation and inhibited tau aggregation with significant behavioral improvement Phase II: Completed
	[25, 26]	● ACI-35	Animals vaccinated Patients with mild to moderate AD	Significant reduction in a specific soluble p-tau Ser396 and improved longevity devoid of any significant off-target inflammatory response Phase 1b: Ongoing

However, secondary effects and the risk associated with repeated immunizations can hinder the progress of trials, prompting researchers to favor passive immunization, which presents fewer risks.

As tau is an intracellular protein, the action of antibodies remains complex as its passage through the blood–the blood-brain barrier and the neuronal membranes remain complex. Some studies have demonstrated a reduction in tau protein aggregation in animal models, which explains why these antibodies target the spread of tau protein in the extracellular space. The exact mechanism of these antibodies has not been fully elucidated, and risks and adverse effects are expected. In this method, unlike with innate proteins, the antibodies carry the risk of adverse immune responses. The impact of immunotherapy on tau species requires further investigation.

5. Conclusion

Tau-targeted therapy is relevant through active and passive immunotherapy strategies and has demonstrated safety and efficacy in animal models and human clinical trials. Progress in this area is needed to develop new effective antibodies that will prevent the progression of AD. Improved monitoring of patients receiving such therapy is also required. Continued investigation into this area of study will provide proof to the effectiveness of this approach while also deciphering the mechanism of tau protein action.

Author Contributions

NEK, drafted and revised the manuscript.

Funding

No funding was provided for this study.

Competing Interests

The author has declared that no competing interests exist.

References

1. Posner H, Curiel R, Edgar C, Hendrix S, Liu E, Loewenstein DA, et al. Outcomes assessment in clinical trials of Alzheimer's disease and its precursors: Readying for short-term and long-term clinical trial needs. Innov Clin Neurosci. 2017; 14: 22.

2. Bakota L, Brandt R. Tau biology and tau-directed therapies for Alzheimer's disease. Drugs. 2016; 76: 301-313.
3. Leuzy A, Chiotis K, Lemoine L, Gillberg PG, Almkvist O, Rodriguez-Vieitez E, et al. Tau PET imaging in neurodegenerative tauopathies—still a challenge. Mol Psychiatry. 2019; 24: 1112-1134.
4. Jadhav S, Avila J, Schöll M, Kovacs GG, Kövari E, Skrabana R, et al. A walk through tau therapeutic strategies. Acta Neuropathol Commun. 2019; 7: 22.
5. Boutajangout A, Ingadottir J, Davies P, Sigurdsson EM. Passive immunization targeting pathological phospho-tau protein in a mouse model reduces functional decline and clears tau aggregates from the brain. J Neurochem. 2011; 118: 658-667.
6. Sankaranarayanan S, Barten DM, Vana L, Devidze N, Yang L, Cadelina G, et al. Passive immunization with phospho-tau antibodies reduces tau pathology and functional deficits in two distinct mouse tauopathy models. PloS One. 2015; 10: e0125614.
7. Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, et al. cis p-tau: Early driver of brain injury and tauopathy blocked by antibody. Nature. 2015; 523: 431-436.
8. Lee SH, Le Pichon CE, Adolfsson O, Gafner V, Pihlgren M, Lin H, et al. Antibody-mediated targeting of tau in vivo does not require effector function and microglial engagement. Cell Rep. 2016; 16: 1690-1700.
9. Gu J, Congdon EE, Sigurdsson EM. Two novel Tau antibodies targeting the 396/404 region are primarily taken up by neurons and reduce Tau protein pathology. J Biol Chem. 2013; 288: 33081-33095.
10. Yanamandra K, Kfoury N, Jiang H, Mahan TE, Ma S, Maloney SE, et al. Anti-tau antibodies that block tau aggregate seeding in vitro markedly decrease pathology and improve cognition in vivo. Neuron. 2013; 80: 402-414.
11. Collin L, Bohrmann B, Göpfert U, Oroszlan-Szovik K, Ozmen L, Grüninger F. Neuronal uptake of tau/pS422 antibody and reduced progression of tau pathology in a mouse model of Alzheimer's disease. Brain. 2014; 137: 2834-2846.
12. Hoffmann-La Roche. A single-center, randomized, investigator/subject blind, single ascending dose, placebo controlled, parallel study to investigate the safety, tolerability and pharmacokinetics of RO6926496 following intravenous infusion in healthy subjects [Internet]. Bethesda, MD: Clinicaltrials.gov; 2016 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/nct02281786.
13. Bright J, Hussain S, Dang V, Wright S, Cooper B, Byun T, et al. Human secreted tau increases amyloid-beta production. Neurobiol Aging. 2015; 36: 693-709.
14. Biogen. Randomized, double-blind, placebo-controlled, parallel-group study to assess the safety, tolerability, and efficacy of BIIB092 in subjects with mild cognitive impairment due to Alzheimer's disease or with mild Alzheimer's disease [Internet]. Bethesda, MD: Clinicaltrials.gov; 2021 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03352557.
15. AbbVie. A phase 2 multiple dose, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ABBV-8E12 in subjects with early Alzheimer's disease [Internet]. Bethesda, MD: Clinicaltrials.gov; 2021 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT02880956.
16. Eli Lilly and Company. Multiple-dose, dose-escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of LY3303560 in patients with mild cognitive impairment due to Alzheimer's disease or mild to moderate Alzheimer's disease [Internet].

Bethesda, MD: Clinicaltrials.gov; 2019 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03019536.
17. Genentech, Inc. A Phase 1, randomized, placebo-controlled, double-blind, single and multiple ascending dose study to assess the safety, tolerability, and pharmacokinetics of intravenous and subcutaneous RO7105705 administered in healthy volunteers and patients with mild-to-moderate Alzheimer's disease [Internet]. Bethesda, MD: Clinicaltrials.gov; 2017 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT02820896.
18. Biogen. A phase 1, randomized, blinded, placebo-controlled, single-ascending-dose study to evaluate the safety, tolerability, and pharmacokinetics of BIIB076 in healthy volunteers and subjects with Alzheimer's disease [Internet]. Bethesda, MD: Clinicaltrials.gov; 2020 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03056729.
19. Janssen Research & Development, LLC. A 2-part randomized, placebo-controlled, double-blind, single and multiple ascending dose study to investigate safety and tolerability, pharmacokinetics and pharmacodynamics of JNJ-63733657 in healthy subjects and subjects with Alzheimer's disease [Internet]. Bethesda, MD: Clinicaltrials.gov; 2020 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03375697.
20. UCB Biopharma S.P.R.L. A subject-blind, investigator-blind, randomized, placebo-controlled, first-in-human study to evaluate safety and tolerability, pharmacokinetics, and pharmacodynamics of single ascending intravenous doses of UCB0107 in healthy male subjects [Internet]. Bethesda, MD: Clinicaltrials.gov; 2018 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03464227.
21. Sigurdsson EM. Tau immunotherapies for Alzheimer's disease and related tauopathies: Progress and potential pitfalls. J Alzheimers Dis. 2018; 64: S555-S565.
22. Theunis C, Adolfsson O, Crespo-Biel N, Piorkowska K, Pihlgren M, Hickman DT, et al. Novel Phospho-tau monoclonal antibody generated using a liposomal vaccine, with enhanced recognition of a conformational Tauopathy epitope. J Alzheimers Dis. 2017; 56: 585-599.
23. Rozenstein-Tsalkovich L, Grigoriadis N, Lourbopoulos A, Nousiopoulou E, Kassis I, Abramsky O, et al. Repeated immunization of mice with phosphorylated-tau peptides causes neuroinflammation. Exp Neurol. 2013; 248: 451-456.
24. Axon Neuroscience SE. A 24 months randomised, placebo-controlled, parallel group, double blinded, multi centre, phase 2 study to assess safety and efficacy of AADvac1 applied to patients with mild Alzheimer's disease [Internet]. Bethesda, MD: Clinicaltrials.gov; 2019 [cited date 2021 December 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT02579252.
25. Hung SY, Fu WM. Drug candidates in clinical trials for Alzheimer's disease. J Biomed Sci. 2017; 24: 47.
26. Theunis C, Crespo-Biel N, Gafner V, Pihlgren M, Lopez-Deber MP, Reis P, et al. Efficacy and safety of a liposome-based vaccine against protein Tau, assessed in tau. P301L mice that model tauopathy. PloS One. 2013; 8: e72301.