

REVIEW ARTICLE

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Alzheimer's disease and immunotherapy

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Abstract

Alzheimer's disease (AD) is the leading cause of dementia, characterized by neuropathological features such as amyloid- β (A β) plaques, neurofibrillary tau tangles, and neurodegeneration. Immunotherapy offers a promising potentially disease-modifying treatment for AD. We review recent advances in AD immunotherapy, specifically focusing on A β , tau, and neuroinflammation-targeted approaches, and gain insights from randomized controlled trials to propose disease-modifying directions.

Keywords Alzheimer's disease, Immunotherapy, Amyloid-beta, Tau, Neuroinflammation

1 Introduction

Alzheimer's disease (AD) is a severe neurodegenerative disorder characterized by progressive cognitive function deficits, ultimately impairing daily quality of life. The deposition of amyloid- β (A β) peptides into senile plaques outside neurons and the presence of neurofibrillary tangles (NFT) composed of hyperphosphorylated tau (pTau) protein inside neurons are the predominant histopathological features of AD (Long and Holtzman 2019). In addition, there is growing evidence that neuroinflammation plays a significant role in the early stages of AD progression (Smirnov and Galasko 2022).

Immunotherapy has gained attention as a promising approach to modify the course of AD (Høiland-Carlson

et al. 2023). This therapy encompasses two fundamental approaches: stimulating the immune system to generate its antibodies through vaccines (active immunization) or administering foreign antibodies directly (passive immunization). The recent accelerated approval of two anti-A β antibodies, aducanumab and lecanemab, by the US Food and Drug Administration (FDA) was considered to be a significant advancement in "disease-modifying therapy for AD." However, it has sparked controversy (Zhang et al. 2023).

This review aims to provide context for recent advances in immunotherapies targeting A β , tau, and neuroinflammation, elucidating their mechanisms in AD. The literature review on AD immunotherapy spans from inception to October 2023, incorporating sources such as PubMed, meeting abstracts, and Alzforum.org. The search focused on English-language publications. Clinical trials related to AD immunotherapy are identified through a search on ClinicalTrials.gov using the keywords "Alzheimer's disease immunotherapy," with exclusion criteria for "terminated" trials and "completed" trials with negative results. We will also explore the pros and cons of each therapeutic approach. Additionally, we will highlight the most recent developments and offer insights into the future of AD immunotherapy.

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2 Immunotherapy targeting A β

Extensive genetic studies have supported the causative role of A β accumulation in AD pathogenesis. Consequently, anti-A β immunotherapies gained much attention in the AD research community. Currently, active immunity vaccines targeting A β , namely ABvac 40, ACI-24, and UB-311 (Table 1), have advanced to Phase 2 clinical trials. And passive immunotherapies targeting A β immunity are in development and have progressed to late-stage clinical trials involving antibodies: ABBV-916, aducanumab, donanemab, Gantenerumab, lecanemab, remternetug, solanezumab (Table 1). Among them, both aducanumab and lecanemab have received FDA approval.

2.1 ABvac40

ABvac40 is the first active vaccine targeting the C terminus of A β 40 peptide, which comprises multiple replicates of the short C-terminal fragments of A β 40 (A β 33-40). Terminal A β -directed antibodies at the C-terminus generated by ABvac40 can provide protection against N-terminus truncated and/or modified A β peptides, such as pyroglutamate-3 A β , which is described as highly toxic and readily aggregate (Lacosta et al. 2018).

2.2 ACI-24

ACI-24 is a liposome vaccine designed to elicit an antibody response against aggregated A β peptides without concomitant pro-inflammatory T cell activation, which was based on the truncated A β -15 serial sandwiched between palmitoylated lysine at either end and anchored into the surface of liposomes. Preclinical studies have shown that subcutaneous injection of ACI-24 into double-transgenic mice with APPxPS1 reduces amyloid and improves memory, and produces high-titer antibodies against A β IgG1 and IgG2b (Muhs, Hickman et al. 2007). In a Phase 2 clinical study, ACI-24 produced a significant IgM antibody response but a low IgG titer. Cerebrospinal fluid (CSF) levels of A β 40 and A β 42 were elevated from baseline, indicating target binding, but amyloid Positron Emission Computed Tomography (PET) was not altered.

2.3 Aducanumab

Aducanumab (Aduhelm, BIIB037) is a fully human IgG1 monoclonal antibody that exhibits high affinity against a conformational epitope found on A β . It specifically binds to aggregated forms of A β rather than monomer. In the brain, BIIB037 preferentially binds to parenchymal amyloid over vascular amyloid (Soderberg et al. 2023).

In 2021 aducanumab received accelerated approval from the US FDA (Sevigny et al. 2016; Knopman et al.

2021). However, FDA approval is controversial because of the therapeutic effects on cognitive ability that barely meet the clinical endpoint and are limited to specific subsets of patients. Of note, the FDA's approval of aducanumab was based on the drug's ability to reduce amyloid plaques detected through PET scans, under the assumption that this intervention would be "reasonably likely to predict a clinical benefit to patients". In particular, the 2 identically designed phase 3 trials of aducanumab [EMERGE (NCT02484547) and ENGAGE (NCT02477800)] were terminated prematurely, with subsequent analyses on a larger data set producing contradictory results (Budd Haeberlein et al. 2022). Data from the EMERGE trial demonstrated a statistically significant change across all four primary and secondary clinical endpoints. In contrast, the ENGAGE trial failed to meet both its primary and secondary endpoints. A dose and time-dependent reduction in pathophysiological markers of AD was observed in both trials (Budd Haeberlein et al. 2022). A meta-analysis of clinical trials has shown that there is no statistically significant effect of A β removal on cognition, even with the use of aducanumab (Ackley et al. 2021). FDA required the company to verify clinical benefits through a post-approval (phase 4) trial.

2.4 Donanemab

Donanemab, also known as N3pG, is a humanized IgG1 monoclonal antibody developed from mouse mE8-IgG2a. Donanemab recognizes pyroglutamate, which forms aggregates in amyloid plaques, and removes it from the brain. Early results from phase 1 and phase 2 clinical studies provide some compelling evidence that donanemab can reduce the burden of amyloid and tau proteins (Zhang and Song 2017).

A phase 3 TRAILBLAZER-ALZ 2 study (NCT04437511) enrolled 1736 participants with early symptomatic AD [Mild Cognitive Impairment (MCI)/mild dementia] with amyloid and low/medium or high tau pathology based on PET imaging. Treatment with donanemab significantly decelerated cognitive and functional decline in individuals with early symptomatic AD when compared to the placebo group (Lowe et al. 2021, Sims et al. 2023). Among individuals with low to medium tau levels, donanemab demonstrated a 36.0% slowing of clinical progression as measured by Clinical Dementia Rating scale sum of boxes (CDR-SB), and 35.1% slowing as measured by integrated Alzheimer Disease Rating Scale (Sims et al. 2023). The TRAILBLAZER-ALZ-3 trial is testing donanemab in asymptomatic individuals between 65 and 80 years old who have evidence of elevated brain A β . The study will run for 3 years, with a clinical primary outcome of time to clinical progression

Table 1 Summary of large-scale clinical trials of Aβ-targeting immunotherapy

Target Type	Agent name	Immune type	Mechanism of action	Administration	Clinical Trial Identifier(phase)	Sponsor	Clinical outcome	Reference
Aβ	ABvac 40	active	An investigational vaccine targeting the C terminus of Aβ40 to generate an immune response	subcutaneous injection (SI)	NCT03113812 (Phase 1) NCT03461276 (Phase 2)	Araclon Biotech S.L	Phase 1 study showed safety and tolerability profile while eliciting a consistent and specific immune response. An ongoing phase II clinical trial is unpublished.	PMID: 29378651 ALZFORUM
	ACI-24	active	A liposome vaccine designed to elicit an antibody response against aggregated Aβ peptides	Subcutaneous injection (SI)	NCT05462106 (Phase 1 and 2)	AC Immune SA	Safe, well tolerated, and immunogenic in people with mild AD, but no change on amyloid-PET.	ALZFORUM
	Aducanumab (Approved)	passive	A high-affinity, fully human IgG1 monoclonal antibody to deposited amyloid plaques	Intravenous infusion (IV)	NCT02477800 (Phase 3) NCT02484547 (Phase 3)	Biogen	Safe, well tolerated, Most of the associated symptoms in adverse events were headache	PMID: 34807243
	Donanemab	passive	A humanized IgG1 monoclonal antibody recognizing Aβ(p3-42) to deposited amyloid plaques	Intravenous infusion (IV)	NCT04437511 (Phase 3)	Eli Lilly & Co	Treatment significantly slowed decline on the primary outcome of iADRS by 40 percent, and improved all secondary clinical endpoints.	ALZFORUM
	Lecanemab(Approved)	passive	A humanized IgG1 version binding to large, soluble Aβ protofibrils to deposited amyloid plaques	Intravenous infusion (IV)	NCT03887455 (Phase 3)	Eisai Inc	Safe, well tolerated and PET-amyloid negative at 18 months	ALZFORUM
	UB-311	active	A synthetic peptide vaccine aims to stimulate a T-helper type 2 regulatory immune response over a T-helper type 1 proinflammatory response, and to avoid cross-reactivity with similar endogenous antigens	Intramuscular injection	NCT02551809 (Phase 2)	United Biomedical	Safe, well-tolerated, and generated a robust immune response.	PMID: 37392597

Table 1 (continued)

Target Type	Agent name	Immune type	Mechanism of action	Administration	Clinical Trial Identifier(phase)	Sponsor	Clinical outcome	Reference
	ABBV-916	passive	Monoclonal antibody targeting the N-terminal truncated Aβ modified with pyroglutamate at position 3 (N3) to remove amyloid plaques	Intravenous injection (IV)	NCT05291234 (Phase 2)	AbbVie	Unpublished	ALZFORUM
	Gantenerumab	passive	A fully human IgG1 antibody binding to the N-terminal and central amino acids of the conformational epitope on the Aβ fibrils with sub-nanomolar affinity to break down and degrade amyloid plaques by recruiting microglia and activating phagocytosis	Subcutaneous injection (SI)	NCT01760005 (Phase 2/3)	Hoffmann-La Roche	Participants with AD had increased levels of Aβ in the cerebrospinal fluid and decreased total tau values, but did not improve cognition (with symptoms) or prevent cognitive decline (without symptoms). A phase 2/3 study called the Dominelli Hereditary Alzheimer's Disease Network Trial Unit (DIAN-TU) are ongoing.	PMID: 37386015
	Remternetug	passive	An N3pG-Aβ mAb against pyroglutamate Aβ	Intravenous infusion or subcutaneous injection	NCT03720548 (Phase 1) NCT05463731 (Phase 3)	Eli Lilly and Company	When Received 2,800 mg monthly, every participant dropped below the amyloid positivity threshold within three months in Phase 1; The result of Phase 3 is unpublished.	ALZFORUM

Table 1 (continued)

Target Type	Agent name	Immune type	Mechanism of action	Administration	Clinical Trial Identifier(phase)	Sponsor	Clinical outcome	Reference
	Solanezumab	passive	A humanized monoclonal IgG1 antibody directed against the mid-domain of the Aβ peptide	Intravenous infusion (IV)	NCT01760005 (Phase 2/3)	Eli Lilly and Company	In patients with mild to moderate AD and patients with pre-clinical AD, solanezumab did not slow cognitive decline. A phase 2/3 study called the Dominelli Hereditary Alzheimer's Disease Network Trial Unit (DIAN-TU) are ongoing.	PMID: 37386015

as measured by clinical dementia rating scale global score (CDR-GS) (NCT05026866).

2.5 Lecanemab

Lecanemab (Lecanemab-irmb, BAN2401, mAb158) is the humanized IgG1 antibody derived from the mouse monoclonal antibody mAb158, which selectively binds to soluble A β aggregates (oligomers and protofibrils) (Soderberg et al. 2023). Soluble A β has been demonstrated to be more neurotoxic than monomers or insoluble fibrils. Lecanemab is believed to target the most toxic pathological amyloid species (Dyck et al. 2023).

In the phase 3 clinical trial (NCT03887455) of 1795 participants with 1:1 ratio assigned to receive lecanemab or placebo, lecanemab slowed CDR-SB decline by 27% at 18 months compared to placebo, suggesting that treatment with lecanemab over 18 months resulted in a slowdown in cognitive and functional decline, equivalent to delaying disease-related clinical progression by 4–5 months over the course of 1.5 years (Dyck et al. 2023). In addition to meeting all primary and secondary outcomes of cognition and function, lecanemab treatment also yielded differences in AD biomarkers, including CSF, plasma, and PET measures of tau, indicating a downstream pathophysiologic effect of A β plaque removal. In fact, two-thirds of people in the treatment group were negative for amyloid PET at 18 months. Tau PET showed a significant slowdown in tangle accumulation in the medial temporal lobe, and trend level slowdown in other brain regions. The astrocytosis biomarker glial fibrillary acidic protein (GFAP) decreased after treatment, and the A β 42/40 ratio increased in CSF and plasma A β 42/40, especially in CSF, and p-tau181 decreased in both. Safety concern was raised especially in APOE ϵ 4 homozygote carriers, with amyloid-related imaging abnormalities (ARIA) with edema or effusions detected in 32.6% of treated participants compared with 3.8% in the placebo group. About a quarter of the participants developed symptoms, which were usually mild and transient (Dyck et al. 2023). A large ongoing immunotherapy trial, AHEAD (NCT04468659) is testing lecanemab in participants with preclinical AD as well as in individuals with an intermediate level of A β accumulation (Rafii et al. 2023).

On January 6, 2023, lecanemab received approval via the Accelerated Approval pathway by the FDA, based on evidence of its effect on the surrogate endpoint of amyloid removal in the phase 3 trial (Larkin 2023). On July 19, the FDA announced that lecanemab had transitioned to traditional approval.

2.6 UB-311

UB-311 is a synthetic peptide vaccine that binds helper T cell epitopes to A β 1-14 sequence, packaged in a proprietary vaccine delivery system. This approach is designed to stimulate T-helper type 2 modulation of immune responses rather than T-adductor type 1 pro-inflammatory responses and to avoid autoimmune responses. UB-311 was safe, well tolerated and produced a robust immune response. In the phase 2 study, in the UB-311 group, an antibody response rate of 97% was observed and continued to be 93% at the end of the study (Yu et al. 2023). In May 2022, the US FDA granted fast-channel status to UB-311 for the treatment of AD, facilitating accelerated development and review.

2.7 Others

ABBV-916 is a monoclonal antibody to A β . It recognizes N-terminal truncated A β modified with pyroglutamate at position 3 (N3), a form that is aggregated in amyloid plaques (Zhang et al. 2023). Its specificity is similar to donanemab and remternetug. The aim of these antibodies is to remove amyloid plaques quickly and completely.

Gantenerumab is a fully human IgG1 antibody and binds to the N-terminal and central amino acids of the conformational epitope on the A β fibrils. It works intensively to break down and degrade amyloid plaques by recruiting microglia and activating phagocytosis. Two phase 3 trials, GRADUATE I and II, with subcutaneous gantenerumab in subjects with MCI and mild AD, did not meet the primary endpoint of slowing the clinical decline in cognitive impairment (Yadollahikholes and Rojas 2023). Solanezumab and Gantenerumab are being evaluated by the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) in a Phase 2/3 trial aimed at preventing dementia in 210 people (Zhang et al. 2023).

Remternetug (LY3372993, N3pG-A β mAb) is an in-development monoclonal antibody, which recognizes the pyroglutamate form of A β in amyloid plaques. Remternetug induced a high clearance of amyloid load (Zhang et al. 2023).

Solanezumab is a humanized monoclonal IgG1 antibody directed against the mid-domain of the A β peptide. It recognizes soluble monomeric, not fibrillary A β . The therapeutic rationale is that it may provide benefit by sequestering A β , shifting equilibria between different species of A β , and removing small soluble species of A β that are directly toxic to synaptic function. In patients with mild to moderate AD, solanezumab failed to significantly slow the rate of cognitive decline and brain atrophy (Doody et al. 2014; Honig, Vellas et al., 2018). In a Phase 3 trial involving patients with preclinical AD, solanezumab

did not slow cognitive decline over 240 weeks compared to placebo (Sperling, Donohue et al. 2023).

2.8 Advantages and limitations

In the last 20 years, based on the identification of A β plaques as the hallmark pathology of AD (Zhang and Song 2017) and the amyloid cascade hypothesis (Hardy and Higgins 1992), targeting-A β strategies have been the main therapeutic strategies for AD treatment (Song et al. 2022). These approaches include active immunization against A β using specific antigens and passive immunization by direct administration of A β -specific antibodies (Sun et al. 2021). Aducanumab and lecanemab, the first effective disease-modifying therapies for AD, were recently approved by the US FDA through an accelerated approval pathway. It's an important milestone for AD research.

How was this milestone achieved? Identifying the correct targets was crucial. The success is also attributable to advances in AD biomarkers. It's important to use PET or CSF measures to select patients and measure biological effects. The use of PET or CSF measures of A β and tau as primary inclusion criteria ensures that AD is the cause of patients' clinical syndrome. Amyloid PET has proven to be a valuable biomarker for assessing treatment response, enabling the identification of clinically relevant effects of anti-A β therapies. Recent phase 3 trials of lecanemab and donanemab have clearly demonstrated this relationship. The hypothesis that removing amyloid would reasonably predict clinical benefit underpinned the FDA's controversial accelerated approval of aducanumab and less controversial accelerated approval of lecanemab for early AD. Selecting the appropriate population at the right stage of disease is also important. The lecanemab trial participants were generally at an earlier disease stage, as per enrollment criteria mandating less severe short-term memory impairments.

Although aducanumab and lecanemab have received traditional regulatory approval, several challenges remain in the clinical translation of anti-amyloid agents. Firstly, which A β species should be targeted? First-generation agent bapineuzumab targeted the N-terminus of aggregated A β , while second-generation agents like crenezumab, gantenerumab, and solanezumab were developed to target non-plaque A β species. Third-generation agents, such as lecanemab (high-affinity antibodies against soluble A β oligomers and protofibrils) and aducanumab/donanemab (targeting plaque A β), were also developed (Yadollahikholes and Rojas 2023). The first and second-generation agents did not demonstrate significant changes in cognition (Doody et al. 2014; Ostrowitzki et al. 2022). The trials of lecanemab, aducanumab and donanemab demonstrated clinical efficacy, indicating

oligomers, protofibrils and plaques might be the ideal targets. However, during the disease continuum, there is possibly a mixed format of A β , even at the early stage, thus targeting a single format of A β might not be the best choice.

Secondly, how can the safety of A β immunotherapy be modified? ARIAs are defined as a spectrum of image abnormalities detected on different MRI sequences, which are serious side-effect of A β immunotherapy. ARIAs include focal cerebral edema/effusion (ARIA-E) and hemosiderin accumulation (ARIA-H, a marker of previous microbleeds). The third-generation agents also prompted safety concerns (Alhazmi and Albratty 2022). Data from EMERGE, TRAILBLAZER-ALZ, and Clarity AD trials showed that the incidence of ARIA was 41.3%, 38.9%, and 26.6% in patients treated with the most effective dose of aducanumab, donanemab, and lecanemab, respectively (Yadollahikholes and Rojas 2023). ARIA is especially a safety concern for APOE ϵ 4 homozygote carriers, thus testing APOE status is helpful at the beginning of these trials. Three deaths were reported in lecanemab-treated patients who developed intracerebral hemorrhage after the primary trial was completed (Reish et al. 2023). Further understanding of the A β -mediated AD pathophysiology and more specific anti-A β antibodies are needed (Zhang et al. 2023). However, a substantial gap remains between experimental and clinical studies, highlighting the need for greater emphasis on toxicology and safety.

Thirdly, how can we enhance the effectiveness of A β immunotherapy? The blood-brain barrier (BBB) presents a formidable challenge for peripherally administered antibodies engaging targets within the central nervous system (CNS) (Wang et al. 2018). Studies estimated that the BBB excludes 99.9% of the dose of peripherally administered antibodies (Nisbet et al. 2017). Researchers developed nanoparticles (Mulvihill et al. 2020), adeno-associated virus vector (Selles et al. 2023) and low-intensity ultrasound (Leinenga et al. 2021, Chen et al. 2022) to enhance the delivery of antibodies through BBB. Studies reported that the use of these vectors with A β antibodies could enhance the selectivity and permeability of antibodies in the CNS at lower dose (Mulvihill et al. 2020), but also decrease amyloid deposits and attenuate cognitive function deficits (Liu et al. 2020, Xie et al. 2020, Kong et al. 2022, Jung et al. 2023, Selles et al. 2023).

Fourthly, when should the intervention begin? Recently, a consensus has emerged in favor of early intervention, prompting a shift in the focus of AD clinical trials from secondary to primary prevention (Zhang et al. 2023). However, the ideal timing for administering anti-A β therapeutics remains uncertain. Conducting trials in AD is challenging due to the long time required to observe

the transition from preclinical to clinical stages of AD. To illustrate, recent trials in secondary prevention for autosomal dominant AD, assessing the efficacy of anti-amyloid agents such as solanezumab and gantenerumab, did not succeed in slowing cognitive decline. This could be attributed to the inadequacy of the treatment period or variations in A β pathogenesis between sporadic AD and familial AD (Salloway et al. 2021). The optimal duration of therapy is still unclear (Ramanan and Day 2023). In addition, numerous concerns exist regarding the most appropriate trial design for evaluating preventive treatments in healthy, asymptomatic individuals. This is particularly pertinent given the potential for unforeseen financial burdens and the consideration of antibodies that could cause ARIA (Joseph-Mathurin et al. 2022).

3 Immunotherapy targeting tau

Tau is a microtubule associated protein involved in the polymerization and assembly of microtubules. The aggregated and hyperphosphorylated tau protein is one of the main drivers of neurodegeneration in AD. The emergence of insoluble tau pathology coincides with the onset of clinical symptoms of AD and strongly predicts patterns of clinical decline (Sanchez et al. 2021, Samudra et al. 2023). Tau is another theoretically important AD therapeutic target. But to date no disease-modifying therapies targeting tau are approved by the US FDA for the treatment of AD. Currently there are a number of tau-directed trials underway at various phases (Table 2).

3.1 AADvac1

The first anti-tau vaccine, AADvac1, uses a peptide containing one of the epitopes of the DC8E8 antibody, 294KDNKHPVGGGS305, conjugated to keyhole limpet hemocyanin (KLH) along with aluminum hydroxide as an adjuvant (Zheng et al. 2016; Plotkin and Cashman 2020). This approach seeks to generate antibodies that block aberrant tau-tau interactions. Studies in transgenic rat models showed that AADvac1 resulted in decreases in abnormally phosphorylated tau, tau oligomers and cerebral neurofibrillary pathology (Yanamandra et al. 2013).

AADvac1 was tested in phase 1 clinical trials (NCT01850238) and its follow-up open-label trial (NCT02031198), which showed acceptable safety and effective immunogenicity (Novak et al. 2017, 2018; Novak et al. 2019). Then it advanced to a Phase 2 study (NCT02579252). The preliminary findings of Phase 2 study showed positive immunogenicity (98.2% of patients produced specific anti-tau antibodies) (Novak et al. 2021). Tau biomarkers and neurofilament light chain (NfL) biomarkers indicate significant slowing of neurodegenerative progression (Vaz and Silvestre 2020). The

excellent results of Phase 2 study may lead its progression to Phase 3.

3.2 Bepranemab

Bepranemab (UCB0107, UCB 0107, antibody D) is a humanized monoclonal IgG4 antibody. It targets the mid-region of tau (aa 235–246), before the microtubule binding region (MTBR). It will more effectively impede the cell-to-cell spread of pathogenic, aggregated tau compared to N-terminally targeted anti-tau antibodies. In vivo, bepranemab may inhibit tau aggregation and the spread of tau pathology (Roberts et al. 2020).

A Phase 1 randomized controlled trial (RCT) (NCT03464227) showed no drug-related adverse events or changes in safety results. In June 2021, a Phase 2 RCT (NCT04867616) to evaluate the efficacy, safety, and tolerability of bepranemab in patients with MCI or mild AD began recruitment. The study will run until November 2025.

3.3 E2814

E2814 is a humanized monoclonal IgG1 antibody targeting the MTBR of tau, which is the main NFT component (Roberts et al. 2020). This antibody binds to extracellular tau, thereby preventing the intercellular spread of pathological tau aggregates and mediating the clearance of microglia.

A Phase 1 RCT of E2814 was completed in August 2020. The most frequent side effects were headache, nausea, and vomiting. In June 2021, a Phase 1/2 trial (NCT04971733) began to assess safety and target engagement in people with dominantly inherited AD. In November 2021, amendments were made to the study design of Dominantly Inherited Alzheimer Network Trial Unit, which incorporated the usage of the anti-A β antibody lecanemab. This Phase 1/2 RCT (NCT05269394) will enroll 168 participants with normal cognition, MCI, or mild dementia. The potential benefits of the anti-tau antibody E2814 will be tested while an anti-amyloid antibody lecanemab is given as a background therapy. The study will run through 2027.

3.4 JNJ-63733657

JNJ-63733657 is a humanized IgG1 monoclonal antibody which recognizes the MTBR of tau. It has high affinity for tau phosphorylated at residue 217 and more potently interferes with propagation of pathogenic aggregated tau between cells. JNJ-63733657 was reported to eliminate pathogenic tau "seeds" in a cell-based assay and inhibit the spread of tau pathology in a mouse model (news from AAT-AD/PD Focus Meeting 2018).

Two Phase 1 RCTs evaluating the safety and tolerability of JNJ-63733657 observed no safety concerns, and the

Table 2 Summary of large-scale clinical trials of tau-targeting immunotherapy

Target Type	Agent name	Immune type	Mechanism of action	Administration	Clinical Trial Identifier (phase)	Sponsor	Clinical outcome	Reference
Tau	AADvac1	active	blocks aberrant tau-tau interactions	subcutaneous injection (SI)	NCT01850238 (Phase 1) NCT02579252 (Phase 2)	Axon Neuroscience SE	phase I: favorable safety profile in moderate AD patients Phase 2: Positive immunogenicity can significantly slow down neurodegeneration	PMID:27955995
	ACI-35	active	targets the pathological conformers of hyperphosphorylated tau	subcutaneous injection (SI)	NCT04445831 (Phase 1, 2)	AC Immune SA	Unpublish	ALZFORUM
	APNmAb005	passive	recognizes conformational epitopes in tau oligomers, binds to and clear tau oligomers from synapses	Intravenous infusion (IV)	NCT05344989 (Phase 1)	APRINOIA Therapeutics	Unpublish	ALZFORUM
	Bepranemab	passive	targets the intermediate region of tau (aa 235–246) and interferes with the intercellular proliferation of pathogenic aggregated tau	Intravenous infusion (IV)	NCT03464227 (Phase 1) NCT04867616 (Phase 2)	UCB Pharma	The drug is safe and tolerated	PMID:37389302
	E2814	passive	binds extracellular tau, thereby preventing the intercellular spread of pathological tau aggregates and mediating the clearance of microglia	Intravenous infusion (IV)	NCT04971733 (Phase 1, 2)	Eisai Inc	Phase 1: Side effects of headache, nausea and vomiting	ALZFORUM
	JNJ-63733657	passive	recognizes the microtubule binding region of tau, and eliminate pathogenic tau "seeds"	Intravenous infusion (IV)	NCT03375697 (Phase 1) NCT04619420 (Phase 2)	Janssen Research & Development, LLC	No safety issues were noted, with the most frequent complaints being back pain and headache	PMID:34107398
	Lu AF87908	passive	binds to highly phosphorylated tau aggregates and reduces brain-derived tau aggregation	Intravenous infusion (IV)	NCT0414986 (Phase 1)	H. Lundbeck	Unpublish	ALZFORUM
	MK-2214	passive	identify pathological tau proteins in the AD brain	Intravenous infusion (IV)	NCT05466422 (Phase 1)	Teijin Pharma	Unpublish	ALZFORUM

Table 2 (continued)

Target Type	Agent name	Immune type	Mechanism of action	Administration	Clinical Trial Identifier (phase)	Sponsor	Clinical outcome	Reference
	Semorinemab	passive	binds the N-terminus of both monomeric and oligomeric Tau	Intravenous infusion (IV) subcutaneous injection(SI)	NCT02820896 (Phase 1) NCT03828747 (Phase 2)	Genentech, Inc	CSF total tau and phosphorylated tau decreased in all treated groups, but downstream markers of neurodegeneration and inflammation did not change	PMID:37643887
	PNT001	passive	identify phosphoThr231 in MTBR and block tau aggregation	Intravenous infusion (IV)	NCT04096287 (Phase 1)	Pinteon Therapeutics, Inc	adverse events and abnormalities on clinical and laboratory measures	ALZFORUM
	PRX005	passive	inhibition of tau protein binding to heparin sulfate proteoglycan protects rat cortical neurons from tau toxicity	-	Preclinical stage	Prothena	-	-

most prevalent complaints included back pain and headaches. In January 2021, a Phase 2 trial (NCT04619420) started on 420 individuals with early AD symptoms and a positive tau PET scan. The trial will run until 2025.

3.5 Semorinemab

Semorinemab (RO7105705, MTAU9937A, RG6100) is a humanized IgG4 monoclonal antibody that binds to the N-terminus of both monomeric and oligomeric tau. Treatment with the antibody reduced brain pathology in P301L mice in a dose dependent manner (Ayalon et al. 2021).

Phase 1 study of semorinemab in 74 volunteers showed no serious adverse events (Ayalon et al. 2021). In 2017, a Phase 2 study TAURIEL in 457 people with prodromal or probable AD showed that Semorinemab did not meet the primary or secondary endpoints (Teng et al. 2022). In February 2019, another Phase 2 trial AURIET (NCT03828747) in 272 people with moderate AD, confirmed by amyloid positivity on PET or CSF testing, and moderate dementia. In 2021, it was announced that semorinemab showed a 43.6% slowing of decline on the ADAS-Cog11 co-primary endpoint, but there were no other positive cognitive or functional outcomes. In November, the company reported at the Clinical Trials on AD (CTAD) that the treatment did not change tangle accumulation measured by GTP1 PET. A decision on a Phase 3 RCT will depend on additional data from LAURIET's ongoing long-term extension study and biomarker measurements.

3.6 Others

ACI-35 is another active immunotherapy vaccine targeted the pathological conformers of hyperphosphorylated tau. The vaccine contains 16 copies of a synthetic tau recognizing the pathological phosphorylation residues S396 and S404 of tau. APNmAb005 is a humanized monoclonal anti-tau IgG antibody that reacts with tau aggregates in early AD cases, but not with tangles and neurofilaments that form later in the disease (Tai et al. 2022). Lu AF87908 is a humanized murine IgG1 monoclonal antibody against tau protein phosphorylated at serine 396 and 404. Humanized antibodies bind to phosphorylated tau in the brains of patients with AD and primary tau after death, blocking the aggregation of brain extracts (Helboe et al. 2022). MK-2214 is an anti-pSer413 tau monoclonal antibody. It could reduce hyperphosphorylated tau proteins, tau oligomers, tangle formation, and synaptic loss (Umeda et al. 2015). PNT001 is a monoclonal antibody directed against tau cis-isomers phosphorylated by threonine 231 (Galas et al. 2006; Hamdane et al. 2006). PRX005 is an anti-tau IgG1 humanized antibody that binds with high affinity to the R1, R2, and R3 repeats

within MTBR. It could inhibit the binding of tau protein to heparin sulfate proteoglycan and protect rat cortical neurons from tau toxicity (Katsinelos et al. 2018). They are underway at clinical trial Phase 1.

3.7 Advantages and limitations

Up to now, 2 tau vaccines and 9 anti-tau antibodies have entered RCT for the treatment of AD. And none of the 11 drugs reached a phase 3 RCT.

Although the development of anti-tau antibodies is not as advanced as the anti-A β , the following points can help improve the results of future attempts. Questions need to be answered, regarding the choice of the immunogen, the site of action of anti-tau antibodies (intracellular or extracellular) and the epitope of tau protein to be targeted, as well as mechanism of action and safety (Panza et al. 2023). First, therapeutic targets related to tau should be chosen with greater precision to mitigate potential adverse events and should be tailored to the disease's stage and subtype. It is possible to achieve more clinical effects by designing different aspects of multi-targeted therapy strategies for different forms of intracellular and extracellular tau proteins. Second, the pathogenesis of AD encompasses amyloid and tau pathology, so combinations of antibodies could potentially be used to slow AD progression. Studies suggest that a multi-target approach is likely to be more central and effective in controlling disease progression, offering superior efficacy, safety, and specificity (Dujardin et al. 2022, Jung et al. 2023, Zhang et al. 2023). In one trial (NCT05269394), the potential benefits of an anti-tau antibody (E2814) will be tested while an anti-amyloid antibody (lecanemab) is given as a background therapy.

4 Immunotherapy targeting neuroinflammation

In addition to tau and A β pathologies, neuroinflammation plays a crucial role in exacerbating AD progression (Leng and Edison 2021). Microglia is thought to play an important role in neuro-immune response and inflammation in the CNS. A β and phosphorylated tau protein could be recognized by receptors such as Toll-like receptor 4 (TLR-4) on the surface of microglia, promoting the release of inflammatory factors in AD brains. The inflammatory factors, in turn, increase the formation of A β deposits and NFT, thus creating a vicious cycle that exacerbates the disease process. A number of disease-modifying therapeutics in current AD clinical trials is attempting to target neuroinflammation (Cummings et al. 2022) (Table 3).

4.1 AL002

AL002 is a humanized monoclonal IgG1 antibody which binds the microglial receptor triggering receptor

Table 3 Summary of large-scale clinical trials of neuroinflammation-targeting immunotherapy

Target Type	Agent name	Immune type	Mechanism of action	Administration	Clinical Trial Identifier (phase)	Sponsor	Clinical outcome	Reference
Neuroinflammation	AL002	passive	monoclonal antibody which binds the microglial receptor TREM2 and induce microglia proliferation	Intravenous infusion (IV)	NCT04592874 (Phase 2)	AbbVie, Alector	Completion in the end of 2023	ALZFORUM
	AL044	passive	antibody targeting MS4A on microglia		Phase 1	Alector	-	ALZFORUM
	CpG 1018®	active	oligodeoxynucleotides mimic bacterial DNA to activate innate immunity	subcutaneous injection	NCT05606341 (Phase 1)	Dynavax Technologies	Completion in November 2024	ALZFORUM
	Gamunex	passive	one of several IVIg products	Intravenous infusion (IV)	NCT01561053 (Phase 2/3)	Grifols Biologicals Inc	fewer deleterious changes in subcortical structures and less metabolic decline	PMID: 35867135
	IBC-Ab002	passive	monoclonal antibody inhibits the immune checkpoint protein aka PD-L1	Intravenous infusion (IV)	NCT05551741 (Phase 1)	ImmunoBrain Checkpoint	Completion in late 2024	ALZFORUM
	Pepinemab	passive	monoclonal antibody neutralizes semaphorin 4D	Intravenous infusion (IV)	NCT04381468 (Phase 1/2)	Vaccinex, Inc	Completion in February 2024	ALZFORUM
	TB006	passive	monoclonal antibody against Galectin-3	Intravenous infusion (IV)	NCT05074498 (phase 1b/2a) NCT05476783 (phase 2)	TrueBinding, Inc	safe and well tolerated	ALZFORUM

expressed on myeloid cells 2 (TREM2) and induces microglia proliferation. In APP/PS1 mice or 5XFAD mice, AL002 injection was able to recognize mouse TREM2 and double the number of CD11b-positive microglia, which expressed more pro-inflammatory and repair genes, halving nearby amyloid deposits and improving cognitive performance (Wang et al. 2020).

The Phase 1 trial showed the antibody was well tolerated and no serious adverse events were noted. In January 2021, the Phase 2 INVOKE-2 study (NCT04592874) started enrolling 265 people with early AD. Because some serious adverse events were found in people with two copies of the ApoE4 allele, the company amended

the protocol to exclude them. No additional related serious adverse events were subsequently reported (Jan 2023 company presentation). The trial will run through the end of 2023.

4.2 Gamunex

This immunoglobulin preparation (Intravenous Immunoglobulin (IVIg), Human Albumin Combined with Flebogamma) is used in obstetric indications to prevent and treat blood conditions related to rhesus factor incompatibility. It is one of several IVIg products being tested clinically as an AD treatment following Phase 1 and 2 results for Baxter Healthcare’s IVIg product, Gammagard™.

A multicenter Phase 2/3 trial (NCT01561053) compared three doses of 5% human albumin plus 5% immunoglobulin to placebo delivered intravenously in 350 people with mild to moderate AD. The results showed that albumin with IVIg was associated with less deleterious changes in subcortical structures and less metabolic decline compared to the typical progression of AD. This effect was more marked in the group treated with high albumin + IVIg (Cuberas-Borros et al. 2022).

4.3 Pepinemab

Pepinemab is a humanized IgG4 monoclonal antibody which neutralizes semaphorin 4D (sema4D). Sema4D binds to receptors on glia and activates inflammatory cytokine release, thereby inhibits axon extension and oligodendrocyte migration, and disrupts the BBB (Luque et al. 2018). According to data presented at the 2020 AAT-AD/PD conference, Sema4D was elevated in human postmortem brain of Huntington's disease (HD) and AD. In preclinical work, pepinemab slowed brain atrophy and improved some behaviors in the HD mouse model (Southwell et al. 2015).

Pepinemab has both Orphan Drug and Fast-Track designation for HD from the FDA. In May 2020, Vaccinex registered a Phase 1/2 trial of this drug (NCT04381468) in early AD. It will run through February 2024.

4.4 Others

Four anti-neuroinflammation antibodies are still in phase 1 RCT. CpG 1018 is a proprietary immune adjuvant made up of short, unmethylated cytosine-phosphate-guanine oligodeoxynucleotides (CpG ODNs). Its components mimic bacterial DNA to activate innate immunity through binding to the toll-like receptor 9 (TLR9), which is an important regulator of microglia. Studies showed that CpG oligodeoxynucleotides treatment activated microglia, and then stimulated clearance of amyloid pathology and improved performances on cognitive tests in mouse and monkey models (Scholtzova et al. 2009; 2014; 2017; Patel et al. 2021).

The humanized IgG1 antibody IBC-Ab002 inhibits an immune checkpoint protein called programmed death ligand, aka PD-L1, stimulating the immune system. In preclinical efficacy studies, a single antibody dose improved cognitive performance one month later in 5xFAD, DM-HTau (K257T/P301S), and PS19 (p301S Tau) mice (AAIC poster).

TB006 is a humanized monoclonal antibody against Galectin-3, which involved in microglia activation and A β aggregation (Boza-Serrano et al. 2019). In preclinical evaluation TB006 has been shown to significantly reduce A β /Tau protein aggregation and neuroinflammation by inhibiting Galectin-3 (Tao et al. 2020).

AL044 is an antibody targeting MS4A, a brain immune checkpoint molecule and a genetic risk factor for late-onset AD (Ma et al. 2019). Some MSA4 family members could regulate TREM2 receptor activity, suggesting a role for these proteins in the microglia response to AD pathology (Deming et al. 2019).

4.5 Advantages and limitations

The neuroinflammation molecular targets are challenging because they have a dynamic role in relation to AD development and progression. They can have both detrimental and beneficial roles (Dujardin et al. 2022). In addition, the complicated communication between multiple cell types coordinates both innate and adaptive immune responses (Zhou et al. 2020, Zeng et al. 2023). For example, the activation of TREM2 may be an effective treatment strategy during the early stages of AD that are defined by amyloid pathology, but it is not clear if it will work at the symptomatic stage of AD when tau pathology is present. Clinical trials with TREM2 agonist antibodies have entered phase 2 (NCT04592874) in early AD, so more data will emerge soon.

Another possible therapeutic target that influences microglial responses to AD pathologies is APOE. APOE expression influences cross-talk between microglia and astrocyte to coordinate innate immune responses to AD pathologies (McAlpine et al. 2021). Therapeutic reduction of APOE4 protein significantly protected against tau pathology and associated neurodegeneration, decreased neuroinflammation, and preserved synaptic density (Litvinchuk et al. 2021, Wang et al. 2021, Koutsodendris et al. 2023). Thus, therapeutic strategies that aim to reduce APOE expression may be most effective in modulating neuroinflammatory responses that contribute to amyloid and tau-mediated neurodegeneration.

Fully unravelling the interplay between the various facets of the immune system and AD pathology at different disease stages is crucial for developing potent immunotherapies for AD.

5 Conclusion

The recent success of phase 3 clinical trials involving the anti-A β monoclonal antibodies lecanemab and donanemab marks a significant milestone in AD research. Ongoing progress in understanding the cellular and molecular factors impacting AD pathogenesis will result in the discovery of new effective targets for AD treatment (Srivastava et al. 2019, Rai et al. 2020). More accurate disease models such as brain organoids are also required to test the preclinical effects of candidate drugs (Cazzaniga, et al. 2022), which could bridge the gap between basic research and the clinical practice (Chen et al. 2022; Zhang et al. 2023). Accurate

biomarkers are essential to identify individuals in the pre-clinical stage of AD, enabling early intervention to prevent or slow down disease progression (Self and Holtzman 2023). And the development of innovative drug delivery systems that integrate multiple therapeutic targets in pre-clinical stages would be more potent and cost-effective. In particular, the therapeutic targets should be more specific to avoid possible AEs and should address the disease stage and subtype (Tijms et al. 2024). These solutions could facilitate the exploration and development of a more refined immunotherapy for AD.

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Authors' contributions

Jianping Jia and Wei Qin conceived the idea and framework of the manuscript. Wei Qin, Yana Pang, Shuya Nie wrote the first draft of the manuscript; Wei Qin, Meina Quan and Jianping Jia reviewed and revised the manuscript; Jianping Jia supervised the review; All authors read and approved the final manuscript.

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Availability of data and materials

The data are available on request from the corresponding author.

Declarations

Consent for publication

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