REVIEW ARTICLE

Spotlight on the Clinical Development, Inventions, and Prospects of the Alzheimer's Disease Vaccines

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Abstract

Alzheimer's disease (AD) is a degenerative neurological illness. AD causes severe morbidity and expensive healthcare. Although medicines are intended to control symptoms, there is currently no cure for AD or way to stop its development. The conception of vaccines is becoming recognized as a possible tactic. The objective of this review article is to highlight the vaccines under development for AD and inventions related to AD vaccines. The literature for this article was searched on PubMed, reliable websites (United States Food and Drug Administration, innovator companies, clinicaltrial.gov), and patent databases utilizing various keywords belonging to AD vaccines. The literature reveals that many vaccines (ACI-24.060, ACI-35.030_JNJ-2056. ALZN-002, AV-1959D, GV1001, and UB-311) are under development for AD. These vaccines act on different targets (Amyloid-β, Tau protein, DNA-based antigens, and telomerase reverse transcriptase). The patent search is suggestive for various foreseeable inventions (personalized vaccine; Tau and Amyloid co-targeting; combination therapies; hybrid vaccines, and patient-compliant vaccine delivery methods). The development of AD vaccines represents a promising frontier in addressing one of the most challenging neurodegenerative disorders. As research progresses, AD vaccines could play a crucial role in transforming treatment paradigms, offering new avenues for prevention, and potentially moving us closer to a cure.

Key words: Alzheimer's disease, clinical development, patent, prospects, vaccine

INTRODUCTION

Alzheimer's disease (AD) is a gradual, degenerative neurologic ailment that causes memory loss, behavioral issues, and inability to perform daily tasks. AD is the most frequent cause of dementia and ageing-related morbidity and mortality.[1,2] The World Health Organization estimates that 55 million individuals worldwide have dementia, with 60–70% of cases being AD.[3] The condition progresses from preclinical to mild cognitive impairment to dementia. Patients may not notice changes early in the disease, but they develop minor memory and cognitive issues, which lead to memory, language, and problem-solving issues that impair daily activities.[4] AD causes increasing memory loss, behavioral issues, and loss of independence owing to the inability to do everyday tasks.[1,2,5] High direct medical costs and unpaid family care for AD patients

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make it a major burden. Although survival rates vary, the average is 4–8 years after diagnosis.[6,7] Maintaining the quality of life, treating cognitive symptoms, and managing behavioral and psychosocial dementia symptoms are current treatment aims.[1,2,8] No AD treatments cure or prevent it completely.[8] Therefore, AD remains an unmet medical need [Table 1].[1-10]

Vaccine is an active immunotherapy method, that aims to stimulate the body to generate an immune response to a specific substance to form an immune memory, and then when the substance appears in the body, the body can spontaneously generate an immune response to quickly remove the substance, block the disease process, and achieve disease prevention and treatment.[11] Vaccination-induced immune memory can last for decades or even a lifetime. Vaccination is a public health triumph. Vaccination immunity allowed smallpox to be eradicated and polio, measles, tetanus, and other diseases to be limited.[12] Vaccines are generally more robust and effective than administered antibodies in preventing practically any spread associated with a pathogen. They are also much cheaper to manufacture and maintain.[13] Many vaccines have been developed for infectious diseases as well as non-infectious diseases.[12,13]

The AD treatment is based on signs and symptoms, but there is no cure for AD.[1,2,8] Developing vaccines against AD seems to be a useful strategy to combat AD.[14] The objective of this review article is to highlight the vaccines under development for AD and inventions related to AD vaccines. This review will be useful for scientists involved in developing preventive and curative therapies for AD. The literature for this article was searched on PubMed, reliable websites (United States Food and Drug Administration, innovator companies, clinicaltrial.gov), and patent database (https://worldwide.espacenet.com/patent/) utilizing various keywords belonging to AD vaccines.

Table 1: General information about Alzheimer's disease[1-10]

Risk factors	Aging; genetics; environmental factors; medical factors
Stages	Pre-symptomatic stage; early stage; moderate stage; severe stage
Neuropathology	Senile plaques; neurofibrillary tangles; synaptic loss
Hypotheses/ pathways	Amyloid-β; Tau protein; Cholinergic system; Inflammation
Symptoms	Memory loss; misplacing items; asking questions repetitively; decreased or poor judgment; withdrawal from work or social activities; changes in mood and personality; new problems with words in speaking or writing; trouble understanding visual images and spatial relations
Diagnosis	Mental status testing; neuropsychological tests; interviews with friends and family; Vitamin B-12 in the body; cerebrospinal fluid test; magnetic resonance imaging; computerized tomography; positron emission tomography
Treatments	Cholinesterase inhibitors like donepezil, rivastigmine, and galantamine; N-methyl d-aspartate antagonists like memantine; antibodies such as aducanumab, lecanemab, and donanemab-azbt
Challenges	Delayed diagnosis; lack of biomarkers; no cure; limited treatment options; individual variability; complex disease mechanisms; clinical trial challenges; need for specialized care; rising prevalence; economic costs; social stigma; lack of awareness

VACCINES IN CLINICAL TRIAL

ALZN002

ALZN002, a disease-modifying biologics and active immunotherapy product, combats the amyloid-beta (Aβ) proteins associated with AD. ALZN002 intravenous vaccine stimulates the immune system to create anti-amyloid antibodies that neutralize Aβs and prevent plaque buildup. The development of Aβ plaques within the brain is a hallmark of AD. The Aβ peptides, especially Aβ42, that make up these plaques clump together and interfere with cell communication, causing neurons to die off and cognitive abilities to deteriorate. According to Alzamend Neuro (the developer of ALZN002), ALZN002 boosts the patient's immune system to fight AD. Alzamend Neuro and bioRASI are conducting Phase II of the clinical trial on ALZN002 [NCT05834296, Table 2].[15,16]

GV1001 (tertomotide)

GV1001 (originally developed for cancer) is a 16-amino-acid peptide from the catalytic site of human telomerase reverse transcriptase. The cellular machinery and lifespan are regulated by telomerase reverse transcriptase. Aging and neurodegeneration are linked to its dysregulation. The subcutaneous injection of the GV1001 vaccine is repurposed for AD, wherein it protects brain cells against reactive oxygen specie, neurotoxicity, and apoptosis caused by Aβ and oxidative stress. GemVax has conducted Phase II clinical trials on GV1001 [NCT03184467, Table 2], whereas Samsung Pharma is conducting Phase III clinical trials on GV1001 [NCT05303701, Table 2].[17]

ACI-35.030/JNJ-2056

ACI-35.030 is under development for AD by AC immune SA and Janssen Research and development. The vaccine

Table 2: Clinical trial data of the Alzheimer's disease vaccines[15-35]

CT Data	NCT05834296 (ALZN002)	NCT05303701 (GV1001)	NCT04445831 (ACI-35.030)	NCT05642429 (AV-1959D)	NCT05462106 (ACI-24.060)	NCT02551809 (UB-311)	NCT02579252 (AADvac1)	NCT03461276 (ABvac40)	NCT01227564 (ACC-001)
Acronym	None	None	None	None	None	None	ADAMANT	None	None
Other IDs	ALZN002-01	GV1001-AD-CL3-S002	ACI-35-1802 2018-004573-27	IMM-AV1959D-101 R01AG074983	ACI-24-AD-DS-2102 2021-006195-17 2022-500069-29-00	V203-AD	AC-AD-003 2015-000630-30	AB1601	B2571010 B2571010 3134K1-2208
Primary purpose	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment
Allocation	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized	Randomized
Intervention	ALZN002 versus placebo	GV1001 versus placebo	ACI-35.030 versus placebo	AV-1959D versus placebo	ACI-24.060 versus placebo	UB-311 versus placebo	AADvac1 versus placebo	ABvac40 versus placebo	ACC-001+QS-21 versus placebo
Phase	1/2a	3	1/2a	1	1b/2	2a	2	2	2
Status	Active, not recruiting	Not yet recruiting	Completed	Recruiting	Recruiting	Completed	Completed	Completed	Completed
Objective	To find an effective dose for the phase 2b efficacy study	To assess the safety and effectiveness of subcutaneous GV1001	To assess safety, tolerability, and immunogenicity	To find safety and tolerability	To assess safety, tolerability, immunogenicity and pharmacokinetics	To find safety and efficacy	To find safety and efficacy	To find safety and tolerability	To find safety, tolerability, and efficacy
Enrollment (Sex/Age)	30 (All/60–85 years)	750 (All/55–85 years)	57 (All/50–75 years)	48 (All/60–85 years)	140 (All/35–85 years)	43 (All/60–90 years)	208 (All/50–85 years)	134 (All/55–80 years)	63 (All/50–80 years)
Sponsor	Alzamend Neuro	Samsung Pharmaceutical	AC Immune	Institute for Molecular Medicine	AC Immune	United Neuroscience	Axon Neuroscience	Araclon Biotech	Pfizer
Collaborators	bioRASI	None	Janssen Research and development	National Institute on Aging; Clinartis	Worldwide Clinical Trials	None	None	None	Janssen Alzheimer immunotherapy research and development
Locations	United States	South Korea	Finland, Netherlands, Sweden, UK	United States	United States; Spain; UK	Taiwan	Austria, Czechia, Germany, Poland, Romania, Slovakia, Slovenia, and Sweden	France, Italy, Spain, and Sweden	United states
Study start	2023-07-05	2024-06	2019-07-31	2023-02-27	2022-06-21	2015-10	2016-03	2017-12-13	2011-02
Study completion	2028-03-03	2028-06	2023-09-05	2026-11-07	2026-06	2018-08	2019-06	2023-03-23	2014-02
Last update posted	2024-07-30	2024-09-23	2024-07-16	2024-10-01	2024-05-31	2020-03-17	2019-11-14	2023-09-25	2016-02-25
Other related CT	None	NCT03184467 (Phase 2; GemVax and Kael)	None	None	None	NCT03531710 (Phase 2a; Terminated)	NCT01850238/ NCT02031198 (Both Phase I studies)	NCT03113812 (Phase I)	NCT01284387 (Phase 2 by Janssen)

comprises 16 synthetic tau fragments phosphorylated at the protein's pathogenic phosphorylation sites S396 and S404 and bound in a lipid bilayer. In AD, neurofibrillary tangles are formed when the Tau protein, which typically helps to stabilize neuronal microtubules, gets hyperphosphorylated. Neuronal dysfunction and degeneration are both exacerbated by these tangles. The vaccine addresses AD tauopathy by activating an immune response to pathological phosphorylated tau conformers while preventing autoimmune B and T cell responses to normal versions of this ubiquitous intracellular protein. AC immune has completed phase 1/2 clinical trial on ACI-35.030 [NCT04445831, Table 2].[18-20]

AV-1959D

AV-1959D is a DNA-based intradermal vaccine that induces antibodies to Aβ peptides without activating or damaging autoreactive T cells. Vaccines derived from DNA or RNA direct cells in the body to create antigenic proteins, such as tau or Aβ, which stimulate an immune response. The vaccine combines three copies of Aβ1-11 with 12 T-cell-activating epitopes. They contain a synthetic pan-T cell antigen, tetanus toxin, hepatitis B, and influenza viral antigens. Foreign antigens activate memory and helper T cells to increase antibody responses. The Phase I clinical trial for AV-1959D is being done by the Institute for Molecular Medicine [NCT05642429, Table 2].[21,22]

ACI-24.060

AC immune is developing ACI-24.060, a liposome vaccine of ACI-24 for AD. ACI-24 contains a sequence of 15 amino acids with complete identity with the human sequence 1–15 of Aβ. This peptide antigen is linked to a liposomal carrier to stimulate antibodies against Aβ while avoiding meningoencephalitis and hemorrhage. ACI-24.060 is under Phase II of the clinical trial [NCT05462106, Table 2].[23,24]

UB-311

UB-311, a synthetic Aβ protein inhibitor-based intramuscular vaccine, targets the Aβ peptide's N-terminal amino acids (1–14) and is considered a long-term immunogenic and effective management for mild to moderate AD. United Neuroscience has completed the Phase II clinical trial for UB-311 [NCT02551809, Table 2].[25-27]

AADvac1

AADvac1, a synthetic peptide obtained from amino acids 294–305 of the tau sequence, is a tau protein aggregation inhibitor. This active vaccine (aluminum hydroxide-based suspension in phosphate buffer for subcutaneous administration) is designed to stimulate an immune reaction against pathologically altered types of tau protein. Axon Neuroscience has completed a Phase II clinical trial for AADvac1 [NCT02579252, Table 2].[28-30]

ABvac40

ABvac40 vaccine targets the C-terminus of Aβ40 peptide. ABvac40 composition includes several repeats of a synthetic peptide that corresponds to amino acids 33–40 of Aβ40. ABvac40 subcutaneous vaccine is composed of a conjugate of Aβx-40 with a protein carrier (keyhole limpet hemocyanin), formulated in a phosphate buffer including 0.35% aluminum hydroxide as the adjuvant. Araclon biotech has completed the Phase II clinical trial for ABvac40 [NCT03461276, Table 2].[31]

ACC-001 (Vanutide cridificar)

ACC-001 is the conjugate comprising several short Aβ fragments connected to a carrier derived from deactivated diphtheria toxin. The Aβ fragments utilized in vanutide cridificar comprise amino acids 1–7. This immunotherapeutic intramuscular vaccine lowers brain Aβ deposits in patients with AD (AD). Pfizer has completed the Phase II clinical trial for ACC-001 [NCT01227564, Table 2].[32-34]

We searched the clinicaltrial.gov database on September 13, 2024, employing the NCT number and name for each vaccine mentioned above.[35] The important data for each clinical study are provided in Table 2 [Figure 1].

INVENTIONS ON AD VACCINES

We searched the Espacenet patent database for patents related to AD vaccines utilizing keywords (Alzheimer + vaccine) in the title/abstract section of the Espacenet database on September 2, 2024.[36] This search provided 103 hits, which are difficult to discuss in this article. Accordingly, we list below some granted patents and other important published patent applications related to the AD vaccine [Table 3].

The development of vaccines for AD is necessitated by the increasing global prevalence of the condition and the absence of effective curative therapies.[1-3] The development of AD vaccines presents several key advantages over other treatment options, including prophylactic potential, early action in asymptomatic stages, long-term and durable immunity, reduced need for chronic medication, lower risk of treatment-related side effects, reduced long-term care costs, improved quality of life, the potential to be combined with other therapies, convenience, accessibility, and disease-modifying potential.[1,2,8,14] Many companies are actively involved in developing AD vaccines, including Alzamend Neuro, AC Immune, Samsung Pharmaceutical, Institute for Molecular Medicine, United Neuroscience, Axon Neuroscience, Araclon

Table 3: Inventions related to Alzheimer's disease vaccines

Serial number	Patent/application number (applicant; Status)	Summary
1	US2023338535A1 (Janssen pharmaceuticals; under review)	This publication provides a method of inducing at least 20 weeks of an immune response against a phosphorylated Tau protein (pTau) in a human with a liposome formulation of ACI-35.030. This publication also provides an overview of the study design for cohort 1 (ACI-35.030 or placebo) in a Phase 1b/2a study (NCT04445831).[20]
2	WO2024156912A1 (AC Immune; No national phase entry)	This publication claims a liposomal vaccine composition of ACI-24.060 for AD. This publication also provides preparation of liposomal vaccine composition ACI-24.060 and information about its Phase 1 b/2 AD trial.[23]
3	US2022023401A1 (United Biomedical; Under Review)	This application describes a pharmaceutical composition of UB-311 for AD. This publication also provides preparation of UBI-311 vaccine formulation, its pre-clinical studies, and clinical studies (safety, tolerability, and efficacy).[26]
4	US9102752B2 (United Biomedical; Patented case)	This patent claims a pharmaceutical composition comprising a combination of Aβ peptide immunogen constructs having specified amino acid sequences for immunotherapy and prevention of AD. This patent also discusses the pharmacological aspects of UB-311 which is discussed above.[27]
5	US11945849B2 (Othair prothena; patented case)	This patent relates to AD vaccine composition capable of causing an immune response to the Aβ and Tau present in patients. The claimed composition comprises a polypeptide having a specified amino acid sequence and at least one pharmaceutically acceptable diluent.[37]
6	US9173928B2 (Matsumoto Yoh; Patented case)	This patent discloses a DNA vaccine (YM3711) for AD.[38]
7	US8912145B2 (Hokko chemistry industry; patented case)	This patent discloses A1aB1bM1 (a fusion protein with a specified amino acid sequence) composition, which significantly decreased the number of amyloid plaques in mice as compared to the controls. This patent also mentions the preparation and pharmacological parameters of A1aB1bM1.[39]
8	US8409581B2 (Affiris; Patented case)	This patent claims many isolated peptides (for example MV002) with specific amino acid sequences capable of binding to an antibody that is specific for an epitope of the Aβ. This patent also claims their formulations (mimotope vaccine) to treat AD.[40]
9	US9345753B2 (Yeda research and development; patented case)	This patent unveils a vaccine composition (for example Aβ1-15-p458 vaccine) for a neurological disorder associated with Aβ plaque accumulation comprising a covalent conjugate Aβ1-15 peptide and an HSP60 peptide (p458h or p458) and a pharmaceutically acceptable carrier, excipient or diluent.[41]
10	US7279165B2 (Cytos biotechnology; patented case)	This patent claims a method of reducing amyloid plaques in AD using a composition comprising a virus-like particle of an RNA-bacteriophage having a specified amino acid sequence and at least one a A (beta) 1–6 peptide.[42]
11	US2023364210A1(Othair Prothena; Under Review)	This publication describes β-amyloid vaccine compositions for the treatment of AD comprising one or more peptides encompassing 3–10 amino acids from residues 1–10 or residues 12–25 of specified amino acid sequence.[43]
12	US2023302127A1 (Othair Prothena; Under Review)	This publication provides Tau vaccine composition for AD comprising peptides encompassing 3–13 amino acids from residues 244–400 of specified amino acid sequence.[44]
13	EP2412811B1 (Matsumoto Yoh; Patented case)	This patent covers a DNA vaccine (anti-Aβ antibody inducer) for AD comprising a recombinant vector, which comprises repeats of DNA encoding Aβ1-42, a DNA encoding an immunoglobulin Fc sequence, and a DNA encoding interleukin-4.[45]
14	KR102530956B1 (ALZ Dementia Korea; Patented case)	This patent discloses a vaccine composition for amyloid-β accumulation-related diseases, comprising the peptide of a specified amino acid sequence or the fusion protein of a specified amino acid sequence as an active ingredient.[46]
15	KR101802251B1 (Kyunghee University Industry-Academic Cooperation Foundation; Patented case)	This patent discloses a vaccine composition for preventing or treating AD or dementia containing Aβ peptide and bvPLA2 (bee venom phospholipase A2) as active ingredients.[47]

Aβ: Amyloid-beta-peptide, AD: Alzheimer's disease

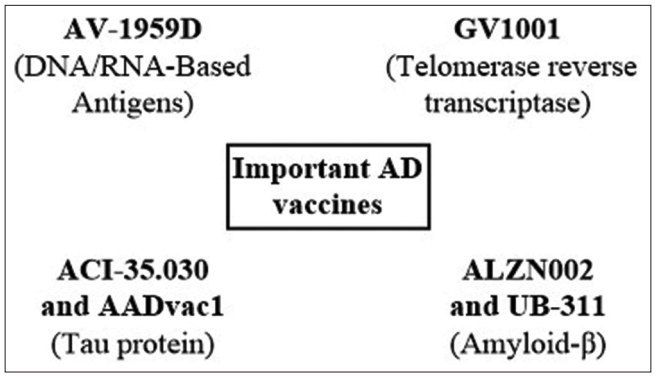

Figure 1: Important Alzheimer's disease vaccines in computed tomography and their targets

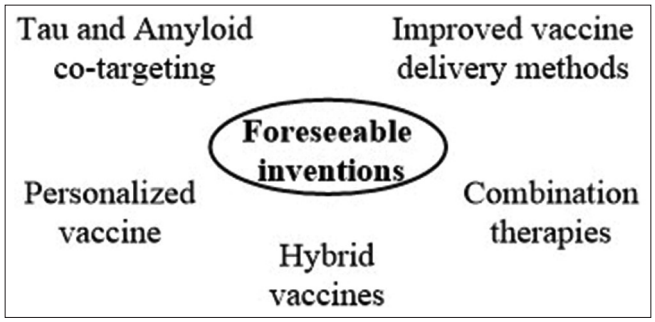

Figure 2: Foreseeable inventions in Alzheimer's disease vaccines

Biotech, bioRASI, Janssen Research and Development, National Institute on Aging, Clinartis and Pfizer [Table 2]. These companies have targeted the key pathological hallmarks of AD. The primary targets for AD vaccines include Aβ peptides (ALZN002 and UB-311), Tau Protein (ACI-35.030 and AADvac1), DNA/RNA-based antigens (AV-1959D) and telomerase reverse transcriptase (GV1001).

Despite the involvement of many companies in developing AD vaccines, there exist some challenges, including the complexity of AD pathology (multiple disease mechanisms and heterogeneity), target selection, targeting the right patient population, difficulty in inducing an appropriate immune response (autoimmune reactions, balancing Inflammation, and weakened immune system of old patients), limited clinical trial success (failure of AN1792 due to encephalitis and long trials), safety concerns (adverse reactions and off-target effects), the timing of intervention, ethical considerations in at-risk populations, and high development costs.[1,2,8,14]

Many pharmaceutical inventions are patentable.[48-50] A lot of inventions have been made on AD vaccines [Table 3]. However, all of them have not been reduced to practice. There remains a scope in developing more AD vaccines (personalized vaccine; vaccines targeting multiple pathways of AD-like Tau and amyloid co-targeting; combination with monoclonal antibodies; combination with anti-inflammatory and neuroprotective agents; hybrid vaccines), patient-compliant pharmaceutical compositions (novel vaccine delivery methods and oral dosage forms). Inventions related to improved immunogenicity of AD vaccines are also foreseeable [Figure 2].

CONCLUSION

The development of AD vaccines represents a promising frontier in addressing one of the most challenging neurodegenerative disorders. Many promising vaccine candidates are under development for combating AD. Future directions include personalized vaccines tailored to individual genetic profiles, combination therapies integrating vaccines with other treatments, and targeting multiple pathological pathways beyond Aβ and tau. Advances in vaccine delivery methods and preventive strategies could significantly alter disease management, potentially enabling earlier intervention in high-risk populations. As research progresses, AD vaccines could play a crucial role in transforming treatment paradigms, offering new avenues for prevention, and potentially moving us closer to a cure.

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ETHICAL DISCLOSURE

None required.

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