



Review Paper

Amyloid- β Peptide-targeting Immunotherapy in Alzheimer Disease: A Systematic Review of Clinical Studies



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ABSTRACT

Background: Amyloid- β (A β) peptide accumulation in the brain is a pathological hallmark of Alzheimer disease (AD). Because of the relationship between the A β plaque formation and AD progression, targeting A β has been advocated as a treatment strategy for this disease. Several studies have focused on immunotherapy methods, such as different vaccination approaches.

Materials & Methods: In this systematic review, we explored the main features of the vaccines used to date, including their efficiency in inducing anti-A β antibodies and removing A β plaques. We also summarized the reported clinical outcomes and mortality rates. A total of 29 articles written in English that describe human clinical trials using three different vaccines (AN1792, CAD106 and AADVax) were reviewed.

Results: Based on these studies, most of the patients who received one of these vaccines showed a significant anti-A β antibody response at some point during the trial. Several studies reported a decline in A β plaque load and an increase in A β phagocytosis in different brain regions. The

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time intervals between the initial vaccination and the booster doses vary among studies, but a 30-day interval has been suggested as the most appropriate by most studies. Meningoencephalitis, microhemorrhages, amyloid encephalopathy, allergic dermatitis and atrial fibrillation have been reported as the most common adverse effects in vaccinated patients.

Conclusion: Clinical investigations have shown improved functional and cognitive outcomes, such as the mini-mental state examination score (MMSE), for vaccinated patients compared to the control groups. However, more human clinical studies are needed for a more conclusive evaluation of the properties of different vaccines.

Keywords: Immunotherapy, Alzheimer disease, Amyloid- β peptide, Plaque, Amyloid, Cerebral amyloid angiopathy, Apolipoproteins E

Highlights

- Second-generation vaccines like CAD106 offer a good balance of efficacy and safety for research, making them potential candidates for further study.
- Amyloid- β (A β) peptide immunotherapy shows potential benefits, but its mechanisms and long-term impacts are unclear.
- Most patients receiving AN1792, CAD106, or AADVac1 show a significant anti-A β response.
- Further research is needed to document adverse effects better and optimize A β vaccines.

Introduction

Alzheimer disease (AD) is the most common form of dementia [1], with nearly 10 million new cases every year [2]. Cholinesterase inhibitors, N-methyl-D-aspartate receptor partial antagonists, and other medications used to treat secondary behavioral symptoms associated with AD are currently used to manage this disease [2]. However, no drug or other intervention can currently prevent, slow down, or stop AD progression [3]. Therefore, developing a clinically validated method to slow down the progression of AD is challenging but essential [4].

Although the exact mechanism of A β toxicity is still debated, interventions that prevent A β aggregation and deposition are among promising therapeutic strategies. In transgenic AD animal models, passive immunization with anti-A β antibodies and vaccination with A β 42 or other A β fragments have led to the elimination of A β deposits and improved behavioral deficits. These preclinical observations prompted clinical trials, one of which was abruptly stopped when several patients developed adverse neuroinflammatory reactions. Although the exact biological mechanisms of vaccination-induced A β

clearance from brain tissue have remained unclear, they may involve a combination of microglial Fc-receptor-mediated phagocytosis, the sequestration of A β in plasma with subsequent release of soluble A β from cerebrospinal fluid (CSF) into plasma, and antibody-mediated breakdown of A β fibrils [5]. In an AD animal model, antibody-induced A β clearance from brain parenchyma occurred within three days [6]. As a result, a multicenter trial was set up to test active immunization with a pre-aggregated synthetic A β 42 preparation (AN1792) in mild-to-moderate AD [5]. Due to the continuous production and maturation of therapeutic antibodies and the need for less frequent vaccine administration, active immunotherapy offers long-term advantages over passive immunotherapy. Furthermore, in phase III clinical trials in patients with mild-to-moderate AD, passive immunotherapies with monoclonal antibodies, including bapineuzumab and solanezumab, failed to meet their primary endpoint criteria, such as an improvement in cognition and activities of daily living index [7].

Active immunization with pre-aggregated human A β 42 effectively reduced the number of A β plaques in the transgenic mice [8-12] that expressed mutations associated with the dominantly inherited AD. Intriguingly, there was an inverse correlation between the levels of

remaining amyloid load in the brain and serum anti-A β antibody titers. The amyloid plaques that remain after vaccination are poorly identifiable, even though collapsed “moth-eaten” plaques have been documented.

The link between A β clearance and the status of neurofibrillary tangles, tau phosphorylation, and aggregation has not been fully described in AN1792-immunized patients. Nevertheless, post-mortem studies [1, 13] and in vivo amyloid imaging [14, 15] show the removal of A β following immunotherapy in patients living with AD [16, 17]. Although side effects of A β immunization have been observed in clinical trials [13, 17-19], the removal of A β is associated with potentially beneficial effects on the disease pathology, such as reduced tau phosphorylation in the brain [16] and diminished tau protein levels in the CSF [20]. A β immunization also alleviated disease-related deterioration of neuronal processes [21]. Notably, however, patients with mild-to-moderate cognitive impairment participating in the study by Serrano-Pozo et al. [22] developed persistent, progressive dementia and subsequently died of AD despite immunization.

Since the A β immunotherapy was successful in transgenic AD mice, a clinical trial was conducted in AD patients using aggregated A β 42 (AN1792) in an adjuvant formulated with QS-21. Aseptic meningoencephalitis occurred in a subset of patients (6%) in this study and the clinical trial was stopped. Instead of the six injections initially scheduled in this phase II study protocol, patients received only one to three injections of AN1792 [23]. Despite the interruption of this trial, modest but significant positive effects of immunization on select cognitive and functional outcome measures were documented. Further evaluation of the entire study cohort revealed limited cognitive benefits and “less worsening” of clinical outcome measures [23]. Similarly, the recently reported complications associated with bapineuzumab passive immunotherapy are attributed to the development of brain vasogenic edema in some participants carrying the apolipoprotein E ϵ 4 allele (*ApoE4*), which resulted in their exclusion from the study. Despite these adverse events, the pathology of abnormal neurites and tau levels/phosphorylation are reduced in AN-1792-immunized AD patients [24].

This review summarizes the effects of A β immunotherapy on AD pathological features and clinical outcomes. The evidence indicates that immunization with A β 42 has protective effects at the early stages of AD and significantly affects the pathogenesis of established AD. By clearing A β deposits in the brain, particularly in the

frontal cortex, A β immunotherapy slows the decline of cognitive and functional capacities of AD patients.

Materials and Methods

This systematic review was conducted according to the 2009 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline [25].

Search strategy

PubMed, Scopus, Web of Science, Google Scholar, and Embase were systematically searched using relevant search terms to identify pertinent articles published before 2023. Only articles written in English were considered in this review. Preclinical studies using animal models were excluded. The specific search terms used to identify AD immunotherapy studies are listed in Table 1.

This systematic review includes original, investigational, and follow-up studies undertaken to assess the potential effects of A β vaccination in AD patients. Only articles focusing on adult human populations were considered for this review. We included original research articles published from 2002 until 2023 written in English involving AD patients. Finally, we only included studies investigating the outcomes of vaccination trials in AD.

Inclusion and exclusion criteria

All relevant articles considering AD vaccines, including AADvac1, AN-1792 and CAD106, were screened before including them in the final analysis. Non-human studies, systematic reviews, meta-analyses, non-English language articles and duplicate publications were excluded.

Study selection methodology

The studies included in this review were chosen following a three-step process illustrated in Figure 1. All duplicate publications were eliminated first. Then, based on the inclusion and exclusion criteria stated above, the titles and abstracts of articles were independently assessed by two reviewers to create a shortlist of eligible publications. Subsequently, the same reviewers evaluated the full text of the publications. Finally, a third reviewer evaluated the quality and accuracy of the selected data. Disagreements among the three reviewers were resolved through discussions until a consensus was reached. The Newcastle-Ottawa scale (NOS) was used to assess the quality of each included study. The eight evaluation criteria of the Ottawa checklist were utilized

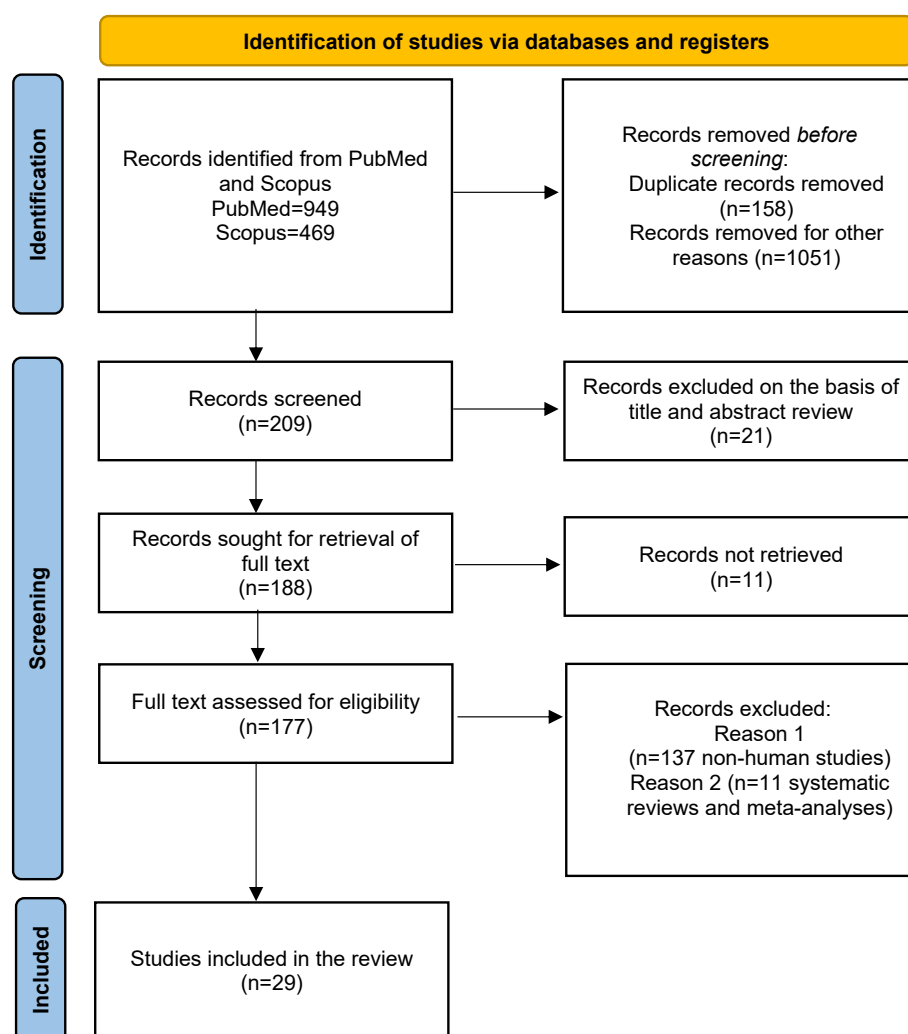


Figure 1. PRISMA 2020 flow diagram illustrating the search strategy for this systematic review

to assess the features of the studies, including selection, comparability and outcome. All studies were categorized into three groups based on their NOS scores: High quality (scores 7-9), moderate quality (scores 5-6) and low quality (scores 0-4).

Results

Demographic characteristics of the subjects

The review included 2725 AD patients in this review. The mean age of the patients was 75.69 years and 51% were female. The mean mini-mental state examination score (MMSE) score of AD patients was 21.24, while the control group had a mean MMSE score of 21.21.

Anti-A β immunization in AD

Most immunotherapies and vaccinations target A β to trigger a suitable immune response (anti-A β antibodies)

that removes the A β deposits and enhances cognitive and functional capacities. AN1792 was the first vaccine used for active immunotherapy in AD, and it was used in 26 out of 29 studies we reviewed. AN-1792 includes aggregated human A β 42 combined with a saponin-based adjuvant QS-21. The safety and tolerability of this vaccine were first demonstrated in a phase I study. Anti-A β 42 antibodies from AN1792 recipients could distinguish between A β plaques located extracellularly and those in brain blood vessels [5, 26].

AADvac1 is another vaccine comprising synthetic peptides resembling the misfolded tau protein, with aluminum hydroxide and keyhole limpet hemocyanin as adjuvants. AADvac1 attenuated neurofibrillary pathology and insoluble tau deposits in the brains of immunized AD patients. IgG antibodies against tau were produced in 29 out of 30 treated older individuals with mild-to-

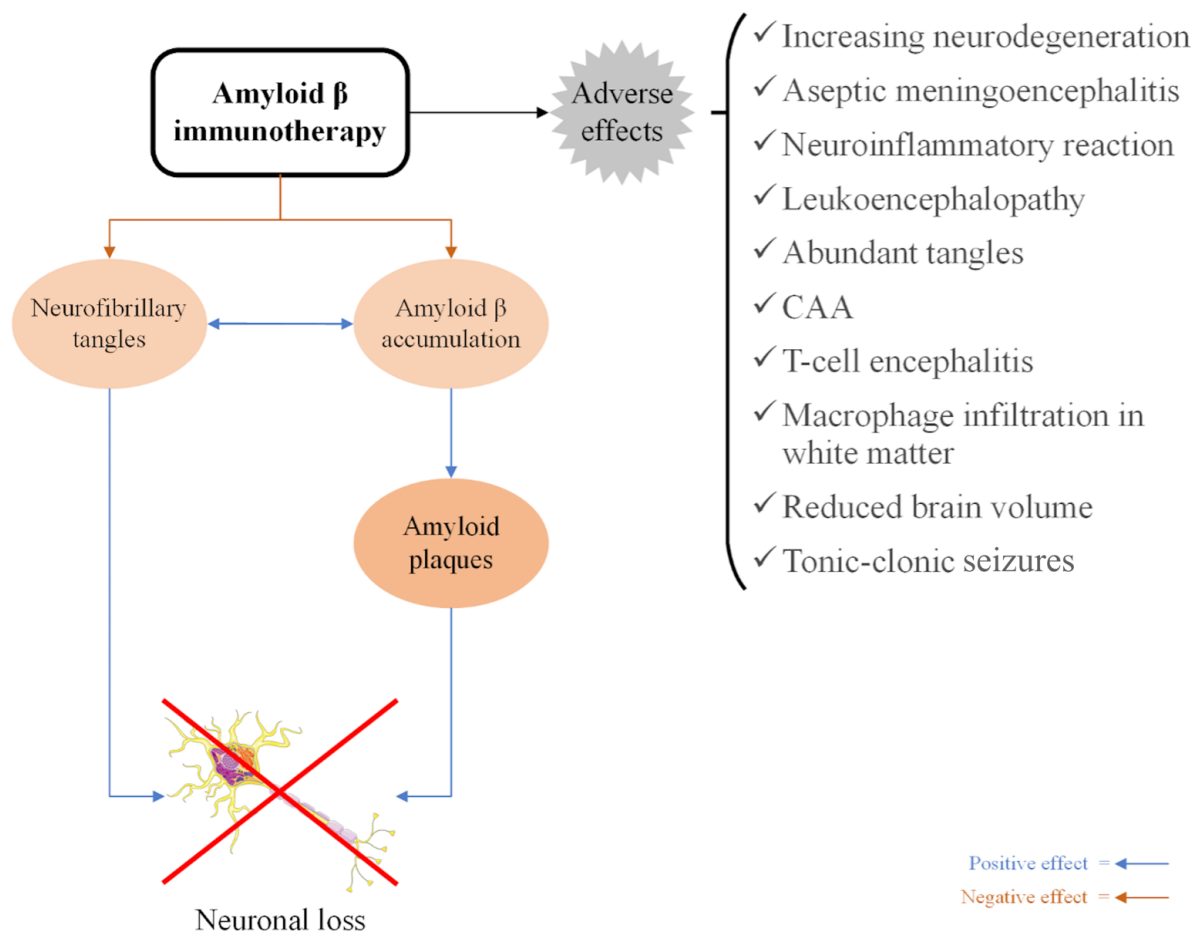


Figure 2. The mechanisms by which A β -targeting immunotherapy slow AD progression

moderate AD, demonstrating its strong immunogenicity in humans [27].

CAD106 is a second-generation vaccine for active A β immunotherapy that includes several copies of the A β 1-6 peptide attached to a carrier that consists of 180 copies of the bacteriophage Q coat protein. It successfully induces the production of anti-A β antibodies without causing an A β -specific T-cell response [28]. The first human study of CAD106 also shows a favorable safety profile and an encouraging antibody response when administered with adjuvants alum (50 μ g and 150 μ g) and MF59 (squalene-based oil-in-water emulsion, 125 μ L and 250 μ L) [28]. CAD106 administration without adjuvants at doses up to 150 μ g generates consistent anti-A β antibody responses in otherwise healthy AD patients without significant safety concerns. The combination of alum adjuvant and CAD106 (450 μ g) shows the optimum balance between tolerability and antibody response [7].

Survival time from the first immunization dose

The survival time of patients after injecting the first dose of AN1792 varies from 4 up to 184 months across different studies [29]. The longest and shortest survival times were observed in patients receiving AN1792 (225 μ g and 50 μ g, respectively) [30].

The time between the first dose of vaccine and booster

The time between the vaccine and the booster dose in the studies varied from 15 to 45 days. The most common choice was 30 days, as it was used in 7 out of 29 studies.

Adverse effects of vaccination

Cerebral microhemorrhage and vasogenic edema can be induced by passive and active A β immunization. Clinical trials have been suspended due to unfavorable outcomes such as meningoencephalitis [5], microhemorrhage in the brain, and cerebral amyloid angiopathy

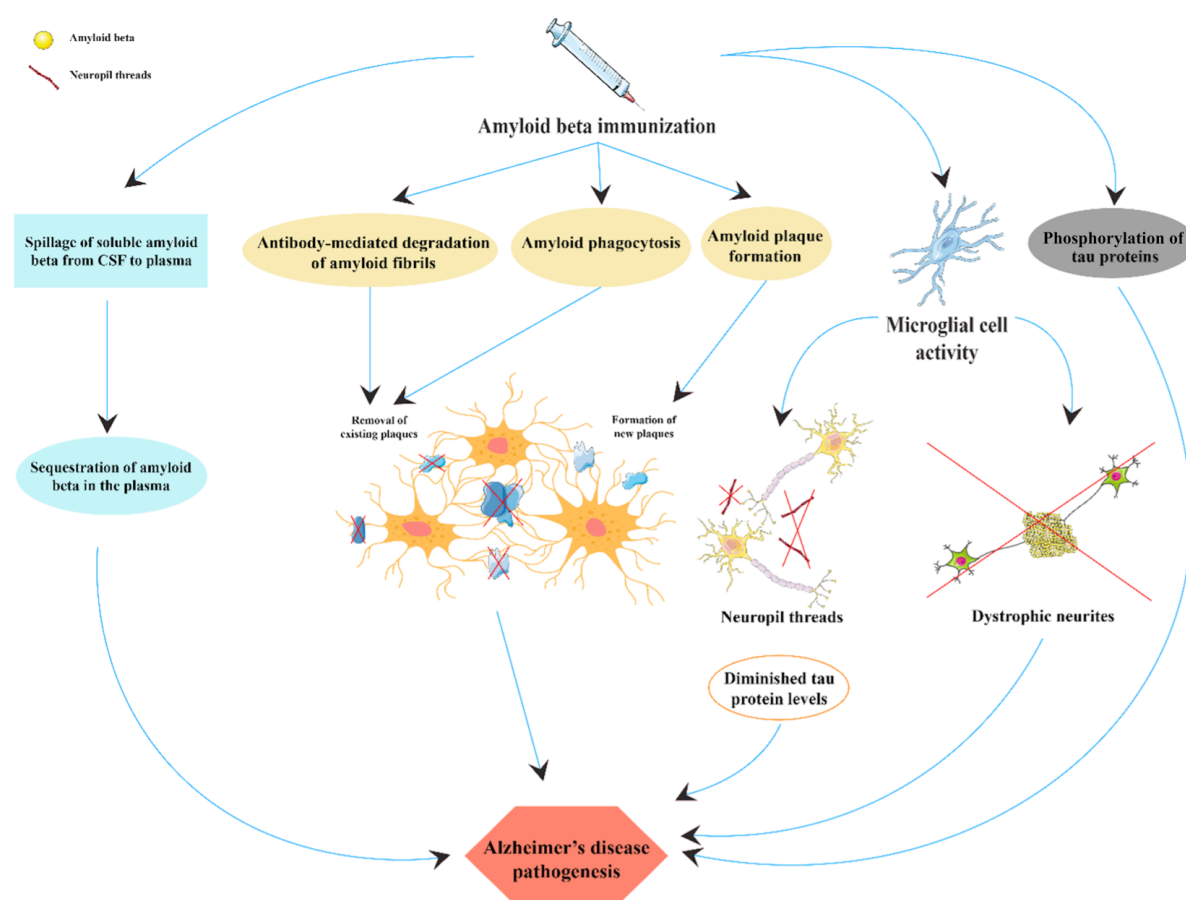


Figure 3. Graphical abstract

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Note: Amyloid-targeting immunotherapy has been advocated as a treatment strategy that can slow the progression of AD and reverse the disease symptoms. However, it has also been shown to cause several significant adverse effects in AD patients.

(CAA) [5, 31]. Thus, humoral antibody responses to AN1792 are restricted to the brain A β deposits, reducing the likelihood of post-vaccination aseptic meningoencephalitis in these patients.

In a study by Boche et al. [32], none of the patients receiving AN1792 experienced significant intracerebral hemorrhages caused by CAA. Still, they displayed a greater density of cortical microhemorrhages and microvascular deficits than the control group. Vaccination with AN1792 dissolves plaque deposits of A β 42, which departs the brain through the perivascular route, temporarily worsening CAA. Gilman et al. [33] permanently stopped the administration of AN1792 after the initial reports of meningoencephalitis and monitored patients closely for the next 9 months. The inflammatory response was speculated to be due to polysorbate 80 in the vaccine, which may have exposed more amino acids of the A β 42 peptide, escalating inflammatory T-cell responses. Orgogozo et al. [18] reported that 18 out of

298 AN1792 recipients experienced post-vaccination aseptic meningoencephalitis. Sakai et al. [31] evaluated the impact of ApoE, an A β transporter, on CAA and the formation of CAA-associated vasculopathy following A β immunotherapy with AN1792. They concluded that ApoE contributed to plaque clearance and A β delivery to the cerebral vasculature, with concentric splitting of the vessel wall being about three times more common in leptomeningeal arteries of immunized compared to non-immunized ones.

Unlike AN1792, no meningoencephalitis or vasogenic edema cases have been reported in patients receiving the AADvac1 vaccine. Among the studies using AADvac1, only one ApoE4 homozygote showed signs of new microhemorrhages [34]. Similar to AADvac1, no signs of central nervous system inflammation or clinical or subclinical cases of meningoencephalitis were observed in CAD106 studies [7, 28]. However, Vandenberghe et al. [7] reported amyloid-related imaging abnormali-

Table 1. Identified articles related to investigating the effects of immunotherapy on the pathophysiology and pathogenesis of Alzheimer's disease

Main Findings			Vaccinated AD patients generate antibodies that have a high degree of selectivity for the pathogenic target structures.	Following immunotherapy, ApoE assists with TAU Immunotherapy in the presence of ApoE can enhance the severity of the CAA.	Immunization leads to lowered TAU and is limited to neuronal processes (i.e. neuropil threads and dystrophic neurites).	Plaque is cleared as a consequence of immunotherapy. The developing neurodegeneration has not ceased following immunotherapy, however.		
Survival Time From 1 st Immunization Dose Mean (Months)							65.41	53.3
Time Between Vaccine and Booster (Months)								
ApoE4 Alleles (%)	Non-exposure							
	Exposure							
ApoE4 Carriers (%)	Non-exposure							
	Exposure							
ApoE4 Genotype (n)	Non-exposure							
	Exposure							
Mean±SD	Disease Duration (y)	Non-exposure						
		Exposure					9.83±2.97	9±2.44
		Total					3.6±2.3	
	MMSE Score	Non-exposure						
		Exposure						
		Total					21±3.2	
Age (y)	Non-exposure	77.82±6.62						
	Exposure	79.08±9.26					77.4±9.25	
	Total	72.1±7.2					78.2±7.4	
Non-exposure (n)			6	28	28	6		
Exposure (n)			24	12	10	20		
Male/Female (n)			21/9	20/20	20/18			
Sample Size			30	40	38	26		
Study Design (n)			RCT/double-blind	Cohort	Cohort	Cohort		
Disease Stage			Mild to moderate dementia	Moderate to severe arteriolosclerosis/AD	AD	AD		
Dose of Vaccine (µg)								
Authors			Hock et al. (2002) [5]	Sakai et al. (2014) [31]	Boche et al. (2010) [16]	Holmes et al. (2008) [45]		
Vaccine				AN1792 Vaccine				

Main Findings			Injured degenerating neurons are lost rapidly due to the Immunization of AD patients, which can be confirmed by a higher occurrence rate of cerebral atrophy in these cases.	Immunization leads to decreased plaque aggregation and removal of p-tau containing dystrophic neurites.	Immunization boosts Microglia phagocytic activity, although, after the plaque removal, the phagocytosis is lower in comparison with unimmunized AD.	Immunization leads to a decrease in plaque A β .
Survival Time From 1 st Immunization Dose Mean (Months)			58.54	58.5	48.77	91.87
Time Between Vaccine and Booster (Months)				p-tau		
ApoE4 Alleles (%)	Non-exposure					
	Exposure					
ApoE4 Carriers (%)	Non-exposure					
	Exposure					
ApoE4 Genotype (n)	Non-exposure		$\epsilon 4^+$ and $\epsilon 4^-$			
	Exposure		3.3, 3.4, 4.4		3.3, 3.4, 4.4	
Mean $\pm$ SD	Disease Duration (y)	Non-exposure				12
		Exposure	9.54 $\pm$ 2.94		8.66 $\pm$ 2.34	11.88 $\pm$ 4.32
		Total				
	MMSE Score	Non-exposure				
		Exposure	4.27 $\pm$ 7.4			
		Total				
	Age (y)	Non-exposure				
		Exposure	78.45 $\pm$ 9.44		78.6	
		Total				
	Non-exposure (n)		28	28	8	3
	Exposure (n)		11	11	9	15
	Male/Female (n)		20/19			
Sample Size		39	39	17	18	
Study Design (n)		Cohort	Cohort	Cohort	Cohort	
Disease Stage		AD	Severe AD		Moderate to severe AD	
Dose of Vaccine (μ g)					50-225	
Authors		Paquet et al. (2015) [21]	Amin et al. (2015) [53]	Zotova et al (2011) [52]	Nicoll et al. (2019) [29]	
Vaccine			AN1792 Vaccine			

Main Findings			Decrement of inflammatory-induced neuro-degeneration in immunized AD patient.	Immunization decreases hyper-phosphorylation of tau but does not clear all the plaques in the brain.	Immunization leads to a decrease in plaque Aβ and a temporary rise in the severity of CAA.	Pro-apoptotic protein expression is reduced by immunization in the brain of an AD patient	Antibody production influenced by Immunotherapy decelerates cognitive decline in AD patients.	Antibody production influenced by Immunotherapy decelerates cognitive decline in AD patients.	
Survival Time From 1 st Immunization Dose Mean (Months)			58.54	29.4	44.88	72.84			
Time Between Vaccine and Booster (Months)									
ApoE4 Alleles (%)	Non-exposure			50					
	Exposure			30					
ApoE4 Carriers (%)	Non-exposure			76.9					
	Exposure			60					
ApoE4 Genotype (n)	Non-exposure		ε4 ⁺ and ε4 ⁻			ε4 ⁺ and ε4 ⁻			
	Exposure		3.3, 3.4, 4.4			3.3, 3.4, 4.4			
Mean±SD	Disease Duration (y)	Non-exposure		10±4.5				3.4±2.2	
		Exposure	9.54	8.4±3.5	8.37±2.32	10.53±3.82		3.6±2.5	
		Total		9.55±4.27			3.6±2.3	3.43±2.25	
	MMSE Score	Non-exposure						19.2±2.5	
		Exposure						21.3±3.1	
		Total					21±3.2	19.56±2.61	
	Age (Y)	Non-exposure		77.4±7.3	78.54±7.43			68.8±7.2	
		Exposure	77.4	78.6±5.9	74.75±8.36	78.76±8.94		73.4±7.1	
		Total		77.73±6.97	76.94±7.82		72.1±7.2	69.60±7.18	
	Non-exposure (n)			28	13	11	28	6	9
	Exposure (n)			11	5	8	13	24	19
	Male/Female (n)			20/19	8/10	8/11	20/21	21/9	10/9
Sample Size			39	18	20	41	30	28	
Study Design (n)			Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	
Disease Stage			AD	AD	AD	AD	Mild to moderate AD	Mild to moderate AD	
Dose of Vaccine (μg)					50-225				
Authors			Zotova et al. (2013) [46]	Serrano-Pozo et al. (2010) [22]	Boche et al. (2008) [32]	Paquet et al. (2018) [54]	Hock et al. (2003) [51]	Hock et al. (2003) [51]	
Vaccine					AN1792 Vaccine				

Main Findings			Amyloid beta plaque is removed entirely as a result of Immunother- apy	There is no cor- relation between anti-A42 antibody titer level in serum and the occurrence of immunization meningoencepha- litis.	Amyloid plaque diminished fol- lowing immuniza- tion in the frontal cortex in along- side no clinical confirmatory sign of encephalitis.	Immunization (AN1792+QS-21) leads to a higher incidence of positive antibody response in AD patients.
Survival Time From 1 st Immuniza- tion Dose Mean (Months)			13		12	
Time Between Vaccine and Booster (Months)			1	1	1	1
ApoE4 Alleles (%)	Non-exposure					
	Exposure					
ApoE4 Carriers (%)	Non-exposure					
	Exposure					
ApoE4 Geno- type (n)	Non-exposure					
	Exposure				E3E4	
Mean±SD	Disease Duration (y)	Non-exposure				3.7
		Exposure			10	3.97
		Total				
	MMSE Score	Non-exposure				19.75
		Exposure	19±3.6	21.11±3.92	12	20.92
		Total				20.69
	Age (y)	Non-exposure				71.4
		Exposure		74.22±7.11	71	73.1
		Total				72.76
Non-exposure (n)			7	74	10	16
Exposure (n)			3	298	1	64
Male/Female (n)						51/29
Sample Size			10	372	11	80
Study Design (n)			Cohort	Cohort	Cohort	Cohort
Disease Stage			AD	Mild to moderate AD	AD	Mild to moderate AD
Dose of Vaccine (µg)			50-225	225	225	225-50
Authors			Nicoll et al. (2006) [1]	Orgogozo et al. (2003) [18]	Masliyah et al. (2005) [47]	Bayer et al. (2005) [26]
Vaccine			AN1792 Vaccine			

Main Findings			Antibody responders to immunization have a decline of tau level in CSF and a positive influence on memory function measured based on NTB in AD patients, indicating the usefulness of immunization.	Immunization-induced antibody responders display brain volume loss, probably due to decreased amyloid plaques and CSF shift.	Notable diminishing of cognition declines in immunized AD patients in comparison with non-immunized	Immunization may lead to clearance of plaque, although there is not a commensurate improvement in clinical symptoms of AD patients.
Survival Time From 1 st Immunization Dose Mean (Months)						
Time Between Vaccine and Booster (Months)			1			
ApoE4 Alleles (%)	Non-exposure		58.5	55.3		66.66
	Exposure		63.8	62.8		
ApoE4 Carriers (%)	Non-exposure				56.7	
	Exposure				80	
ApoE4 Genotype (n)	Non-exposure					
	Exposure					2.3, 3.3, 3.4, 4.4
Mean±SD	Disease Duration (y)	Non-exposure	3.9±1.9	3.9±1.8		n=6 9±3.84
		Exposure	3.7±1.9	3.7±2		7.77±2.48
		Total	3.73± 1.9	3.73± 1.96		8.44± 3.3
	MMSE Score	Non-exposure	20.2±3.5	20.2±3.5	19.8±2.8 Phase II	
		Exposure	20.4±3.3	20.5±3.3	21±3.3 Phase II	
		Total	20.36±3.33	20.44±3.34	20.4±3.05	
	Age (Y)	Non-exposure	71±8.3	70.7±8.2	73.7±8.65 Follow up	81.81±3.60
		Exposure	72.4±7.8	72.1±7.8	74.9±7.32 Follow up	80.66±4.84
		Total	72.12±7.89	71.82±7.87	74.9±7.32	81.29±4.19
Non-exposure (n)		16	57	Phase II= 72 Follow up= 30	11	
Exposure (n)		300	231	Phase II= 59 Follow up= 25	9	
Male/Female (n)		167/205	130 /158		11/9	
Sample Size		372	288	Phase II= 131 Follow up= 55	20	
Study Design (n)		Cohort	Cohort	Cohort	Cohort	
Disease Stage		Mild to moderate AD	AD	Mild to moderate AD	AD	
Dose of Vaccine (µg)		225	225	225	50-225	
Authors		Gilman et al. (2005) [33]	Fox et al. (2005) [4]	Vellas et al. (2009) [30]	Maarouf et al. (2010) [24]	
Vaccine		AN1792 Vaccine				

Main Findings			The first study proving that the rate of amyloid deposition in AD patients is reduced by immunotherapy	evocation of Aβ –specific immune response following immunization alongside clinical safety and tolerability of usage	Immunization elicited satisfactory antibody response, furthermore demonstrating safety in clinical usage.	Immunization elicited satisfactory antibody response, furthermore demonstrating safety in clinical usage.				
Survival Time From 1 st Immunization Dose Mean (Months)										
Time Between Vaccine and Booster (Months)							1.5	1.5	1.5	0.5
ApoE4 Alleles (%)	Non-exposure									
	Exposure									
ApoE4 Carriers (%)	Non-exposure							60	57	20
	Exposure								92	77
ApoE4 Genotype (n)	Non-exposure									
	Exposure									
Mean±SD	Disease Duration (y)	Non-exposure						1.9±2.8	31±19.9	25±23.5
		Exposure		1.6±1.5	25.3±15.9	25.2±24				
		Total		1.63±1.7	26.58±16.8	25.16 ±23.92				
	MMSE Score	Non-exposure	29.4±0.8	22.9±1.9	21.1±3.3	23.4±2.5				
		Exposure	29.1±1.1	22.19±2.16	21.1±3.6	21.3±2.6				
		Total	29.20±1	22.19±2.16	21.1±3.5	21.68±2.5				
	Age (y)	Non-exposure	66.1±4.8	68±8.4	70.6±7.6	67±9.5				
		Exposure	64.9±3.7	67.2±9.1	68.9±8	68.2±7.8				
		Total	65.32±4.11	67.29±9	69.28±7.91	67.97±8				
	Non-exposure (n)		23	15	7	5				
	Exposure (n)		42	106	24	22				
	Male/Female (n)		21/44	57/64	19/12	11/16				
Sample Size		65	121	31	27					
Study Design (n)		Cohort	Cohort	Cohort	Cohort					
Disease Stage		Mild AD	Mild AD	Mild to moderate AD	Mild to moderate AD					
Dose of Vaccine (µg)		450	150-450	50	150					
Authors			Riviere et al. (2021) [55]	Vandenberghe et al. (2016) [7]	Winblad et al. (2012) [28]	Winblad et al. (2012) [28]				
Vaccine			CAD106 Vaccine							

Main Findings			Immunization may be a valuable therapeutic option in AD patient Considering raising Aβ1—40 levels in serum and antibody response against Aβ.	First, human studies manifest profitable safety and remarkable active immune therapy (vaccine) immunogenicity.	Reduction in deterioration of cognition level accompanied by the existence of a trend for slower brain atrophy in MRI in patients with high AADvac1IgG titers indicate efficacy of immunization.		
Survival Time From 1 st Immunization Dose Mean (Months)							
Time Between Vaccine and Booster (Months)						1	1
ApoE4 Alleles (%)	Non-exposure						
	Exposure						
ApoE4 Carriers (%)	Non-exposure						
	Exposure						
ApoE4 Genotype (n)	Non-exposure						
	Exposure						
Mean±SD	Disease Duration (y)	Non-exposure	1.8±1.3	2±0.9			
		Exposure	1.6±1.5	1.9±1.5			
		Total	1.63±1.46	1.92±1.41			
	MMSE Score	Non-exposure	22.8±2.3	20.3±4.5			
		Exposure	22.5±2.1	20.7±3.9			
		Total	22.55±2.13	20.62±4	20.7±4.1		
	Age (y)	Non-exposure	66.3±6.9	68.5±12.4			
		Exposure	68.2±8.2	67.7±6.5			
		Total	67.83±7.98	67.86±7.88	67.1±8.1		
	Non-exposure (n)		11	6			
	Exposure (n)		47	24			
	Male/Female (n)		35/23	17/13	16/10		
Sample Size		58	30	26			
Study Design (n)		A randomized placebo-controlled, double-blind trial	A randomized placebo-controlled, double-blind trial	Open-label, single-arm interventional follow-up trial			
Disease Stage		Mild AD	Mild to moderate AD	Mild to moderate AD			
Dose of Vaccine (μg)		150					
Authors		Farlow et al. (2015) [2]	Novak et al. (2016) [50]	Novak et al. (2018) [34]			
Vaccine		CAD106 Vaccine	AADVac1 Vaccine				



Abbreviations: MMSE: Mini-mental state exam; ApoE4: Apolipoprotein E; AD: Alzheimer disease; Aβ: Amyloid β; tau: Tubulin associated unit; p-tau: Phosphorylated tubulin associated unit; CSF: Cerebrospinal fluid; NTB: Neuropsychological test battery; RCT: Randomized controlled clinical trials.

Note: Search terms used to identify articles describing studies on the effects of immunotherapy on the pathophysiology and pathogenesis of AD

ties (ARIAs) in 6 out of 120 patients, all of whom had a robust serological response to CAD106. None of those ARIA patients displayed neurological symptoms. However, this study recorded several severe adverse events (SAEs) reported in a single patient, including allergic dermatitis (immediately following the fourth injection), atrial fibrillation (6 weeks following the first injection), and acute psychosis (14 weeks following the seventh injection) were 3 of the 26 SAEs in the entire study group of 58 patients. The researchers thought that these SAEs might be linked to CAD106 injection. Nasopharyngitis and injection site erythema were the most common adverse events associated with the CAD106 vaccine [28].

ApoE4

ApoE4 was the most significant genetic risk factor for sporadic AD and severe CAA development in A β -immunized AD patients [35, 36]. AD patients carrying the ϵ 4 allele are up to 15 times more likely to develop AD than ϵ 3. Moreover, they experience more severe and frequent CAA comorbidity compared to carriers of other ApoE alleles or ApoE-negative AD patients [37]. The ApoE4 has been linked to tonic-clonic seizures independent of AD and A β . The complex mechanisms underlying the association between ApoE4 and AD are believed to involve tau phosphorylation, A β peptide clearance, and neuronal death [38]. Several mechanisms have been proposed for A β removal from the brain parenchyma without immunotherapy. First, ApoE influences A β uptake by cells since the A β and ApoE complex is endocytosed and digested enzymatically [39]. Second, ApoE facilitates the A β transport across the blood-brain barrier (BBB) [40] via the very low-density lipoprotein receptor and low-density lipoprotein receptor-related protein 1 [41]. Moreover, a perivascular drainage channel has been suggested as an essential A β elimination mechanism. Failure of this channel due to age-related mechanisms plays a significant role in the development of CAA [42-44]. Sakai et al. [31] reported that ApoE mediates the amyloid plaque clearance. A β delivery to the brain microvasculature is consistent with ApoE's significant role in removing A β from the brain after A β immunotherapy. Thus, ARIAs associated with A β immunotherapy may reflect a severe age-related vascular alteration in some AD patients, particularly in ApoE4 carriers, who display rapid plaque disaggregation. According to preclinical data, CAD106 can decrease the buildup of A β in the brain by triggering antibodies that prevent amyloid deposition. Notably, CAD106 was shown to be safe and effective in a patient population with a higher proportion of ApoE4 carriers (>60%) than the general population (>23%), supporting this association [2].

Clinical outcomes and immunological findings

Although the precise biological mechanisms underlying vaccination-induced clearance of A β from brain tissue are still unknown, they possibly involve a combination of phagocytosis by microglial Fc-receptors, sequestration of A β in plasma that leads to the release of soluble A β from CSF into plasma, and the breakdown of A β fibrils by antibodies (Figure 2).

Most AD patients immunized with aggregated A β 42 (AN1792) show a favorable immune response by generating antibodies with a high selectivity towards A β plaques, which identify amyloid plaques, diffuse A β deposits, and vascular amyloid in subarachnoid and perforating cerebral blood vessels. However, while A β immunization leads to the removal of A β from the brain, the cognitive decline persists, probably because of the continued presence of phospho-tau in the brain. For instance, Boche et al. [16] showed that the reduction of A β in neuronal processes such as neuropil threads and dystrophic neurites was observed in AD patients actively immunized with AN1792. In contrast, the development of neurofibrillary tangles due to phospho-tau buildup in the neuronal cell bodies remained unaffected. In another study, Holmes et al. (Long-term effects of A β 42) [45] performed a post-mortem assessment of AD patients immunized with AN1792 (50 μ g or 225 μ g). They demonstrated that 7 out of 8 patients with complete plaque removal experienced severe end-stage dementia before death. This finding indicates that plaque clearance did not correlate with the AN1792 dosage or improved clinical outcomes. The study found no significant difference in survival rates (hazard ratio 0.93; 95% CI, 0.43-3.11; $P=0.86$) or delay in dementia progression (1.18; 95% CI, 0.45-3.11; $P=0.73$) between the AN1792 and placebo group.

Elevation in the levels of neurodegeneration-associated protein, eukaryotic initiation factor 2 α and neurotic curvature indicate neuronal health. Despite the apparent improvement in the health of remaining neurons, there was a more significant loss of neurons, suggesting that only damaged neurons may be removed following vaccination. This discrepancy between the decrease in brain volume and improved cognitive performance was also noted in other studies [4, 21]. Zotova et al. reported that levels of the activated macrophage and microglia marker CD68 in both white and gray matter were higher in the immunized Alzheimer's disease (iAD) group compared to non-immunized control Alzheimer's disease (cAD) cases. Moreover, the A β 42 load was lower ($P=0.036$) in the brains of iAD compared to cAD patients.

Additionally, in the iAD group, the CD68 levels are inversely associated with A β 42 load, suggesting that A β immunization enhances microglial reactivity and phagocytic activity in the presence of plaques. Interestingly, in long-surviving iAD patients, CD68 expression is lower despite complete plaque clearance, indicating a reduction in phagocytic activity post-plaque removal. The assessment of major histocompatibility complex (MHC) class II cell surface receptor HLA-DR, another microglia activation marker, on the cells that clustered around amyloid plaques reveals no significant differences between iAD and cAD groups, indicating that this microglia activation marker may have been exclusively connected to their phagocytic activity specifically when plaques are present.

The similarity of CD68 and HLA-DR loading in the pons of both groups raises the possibility that AD-associated pathology caused the observed variations in microglial activation in the cortex. It has been proposed that phagocytic activity initially increases after immunization with A β 42 microglial. Still, it may decrease once the plaques are cleared, returning to levels similar to those observed in unimmunized AD patients at the same disease stage [46]. A β vaccination may also minimize tau phosphorylation and improve tau pathology in the hippocampus. According to some review studies, AN1792 immunization significantly reduces plaque load and increases amyloid phagocytosis in the frontal cortex and, to a lesser extent, in the temporal lobe [1, 47]. AN1792 vaccination reduced amyloid plaques, attenuated hippocampal neurite abnormalities, and potentially minimized tau phosphorylation. Some studies noted that despite these reductions, there are fewer and smaller remaining dense-core amyloid plaques; however, they might still be harmful [22]. This issue raises concerns that plaque clearance alone might not be sufficient to prevent disease progression.

The long-term outcome of AN1792 immunization was further examined by Vellas et al. [30], who showed low but detectable and persistent anti-A β antibody titers in responders from a phase II vaccine trial. Moreover, the same study also reported a significantly slower functional decline in immunized compared to placebo-treated patients over approximately 4.6 years following vaccination. Despite no significant difference in brain volume reduction between the two groups after 3.6 years, no new encephalitis was reported in immunized individuals. These results highlight the potential of A β immunotherapy in improving long-term functional outcomes in AD [30]. Notably, as reported, AD patients who were

actively immunized with A β (AN1792) could remain virtually plaque-free for up to 14 years [29].

CAD106 is the first active immunotherapy shown to reduce amyloid depositions in AD patients. Winblad et al. [28] reported robust anti-A β antibody responses in CAD106-treated patients, with 67% and 82% in the first and second cohorts, respectively, meeting the expected criteria for antibody response [48]. These findings imply that CAD106 induces a better antibody response over 7 injections, consistent with the conclusions of an earlier phase I study. Notably, CAD106 also had a favorable safety profile, with no serious adverse effects reported in AD patients. The good safety profile, combined with the immunogenicity of CAD106, supports its potential as a viable therapeutic option for managing AD. The neuropsychological test battery (NTB) appears to be a valid and sensitive assessment of changes in cognitive functions in individuals with mild and moderate AD. The psychometric characteristics of the NTB denote its potential value in assessing treatment efficacy in clinical trials that include participants with moderate AD [28, 49]. In the clinical trials by Novak et al. [34, 50],

AADvac1 shows an acceptable safety profile, with booster doses leading to sustained IgG titers throughout immunization-free intervals. According to MRI evaluations, patients with higher anti-A β antibody titers exhibit slower deterioration in cognitive function and reduced brain atrophy, suggesting the vaccine's efficacy in slowing down the disease progression. Although AADvac1 is still relatively new compared to AN1792, the evidence thus far indicates promising results, particularly regarding safety and cognitive benefits. The long-term impact of AADvac1 is still under investigation, but the early data suggest that it could be a valuable addition to the arsenal of AD treatments.

Discussion

Our review demonstrates sufficient published data to conclude that the A β vaccination significantly impacts the pathogenesis of AD. Placebo-controlled randomized trials discussed in this review show that A β vaccination can slow cognitive decline in AD patients [51]. Several other studies have demonstrated that A β immunotherapy reduces amyloid plaque burden and promotes amyloid phagocytosis in the frontal cortex and, to a lesser extent, in the temporal lobe. AD patients who experience a significant reduction in amyloid load can remain plaque-free for nearly 14 years [29]. This efficacy period prevents repeated accumulations of neurodegeneration-associated proteins, including A β . Notably, immunization of AD

patients with A β 42 induces the production of antibodies with a great degree of selectivity for the pathogenic amyloid structures. For example, they do not cross-react with denatured or native full-length amyloid precursor protein or its physiological derivatives, such as soluble A β 42 monomers, dimers, and trimers. However, one of the most concerning side effects of A β immunotherapy is CAA-associated vasculopathy, which can develop after A β plaque removal. It has been proposed that ApoE may induce structural abnormalities in the blood vessel walls after transporting A β out of the brain [31]. In addition to amyloid clearance, A β immunotherapy has significantly reduced in AD brains. This reduction likely reflects the clearance of the tau-containing dystrophic neurite component of plaques. Immunization effectively reduces tau aggregation and decreases tau hyperphosphorylation, critical factors in AD progression. Furthermore, active immunization could effectively improve or reverse memory deficits [22]. Interestingly, while A β immunotherapy has been shown to improve microglial phagocytic activity, after the clearance of A β plaques, microglia phagocytic activity decreases to levels similar to those in unimmunized AD cases [29, 52].

However, while A β immunization is pivotal in preventing plaque formation and removing existing plaques, it does not necessarily stop the progression of neurodegeneration. Nearly all immunized individuals who died because of the AD neurodegenerative processes during the follow-up phase of the A β immunization trial had the highest anti-A β antibody titers, and their brains were free from amyloid plaques. A longer time interval does not lower the effect of the immunization, and there was no significant correlation between the amount of plaque removal and survival time since the first immunization dose. These findings suggest substantial plaque removal does not benefit survival [29]. This finding implies that despite the clearance of plaques, progressive neurodegeneration can continue in AD brains. An *in vivo* imaging demonstrates an increased rate of cerebral atrophy in A β -immunized AD patients, possibly indicating accelerated loss of damaged and degenerating neurons [21]. One of the most significant adverse effects of A β vaccination was observed by Orgogozo et al. [18]. They found that some AD patients developed signs and symptoms related to aseptic meningoencephalitis during the A β immunization process. The potential mechanism responsible for the induction of mild-to-severe meningoencephalitis includes T-cell and microglial activation, which must be considered carefully when developing safer A β immunotherapy for AD patients. However, the exact relationship between post-vaccination meningoencephalitis and serum anti-A β 42 antibody titer has

remained unclear. Many studies have documented the dramatic adverse effects of A β immunotherapy, such as neuroinflammatory reactions, meningoencephalitis, and leukoencephalopathy [47]. Other phenomena, including CAA, T-cell encephalitis, and macrophage infiltration in the white matter, were observed in the preclinical studies by Masliah et al. [47]. The MRI imaging of AD patients immunized with AN1792/QS-21 demonstrates reduced brain volume in antibody responders. The decrease in brain volume did not worsen cognitive performance. Although the reason for this decline is still unclear, it may be due to amyloid removal and the associated CSF shifts [4]. This review identifies cerebral micro hemorrhage, vasogenic edema, meningoencephalitis, and CAA as the most common adverse effects that have led to the postponement of AN1792 immunization trials.

In contrast, second-generation active immunotherapies, including CAD106, have offered a significant safety profile. They have avoided the T-cell response by using fragmented A β peptides or peptide mimetics of the A β N-terminus, which are recognized by B-cells only. Recent studies show that CAD106 is the first active A β immunotherapy that slows amyloid deposition in AD patients. Using CAD106 with an alum adjuvant leads to one of the best balances between antibody response and tolerability recorded thus far. The acceptable antibody response and the favorable safety profile of CAD106 indicate its potential as a valuable therapeutic option for treating AD patients [28]. Additionally, AD patients who respond to AADvac1 vaccination with high titers of anti-tau antibodies exhibit slower brain atrophy in MRI evaluation and a slower decline in cognitive assessment scores than those with low antibody titers. Notably, AN1792, AADvac1, and CAD106 vaccinations did not cause microhemorrhage inflammation in the central nervous system. However, there are a few reports of minor side effects, such as ARIAs, in patients receiving CAD106 injections. Other minor adverse effects associated with CAD106 vaccination include allergic dermatitis, atrial fibrillation, acute psychosis, nasopharyngitis, and erythema at the injection site [21, 53] (Figure 3).

Conclusion

This systematic review evaluated the effects of A β immunotherapy on AD pathogenesis and the progression of the disease processes. A β immunotherapy has been shown to prevent the formation of new A β plaques and even reduce the pre-existing plaques. The inhibitory effect of A β vaccination on amyloid plaque formation appears relatively specific and is not associated with general disturbances of the physiological processes. Most

studies report improved cognitive performance and memory in vaccinated AD patients compared to unvaccinated ones. Despite the positive overall results observed with three different types of vaccines, there are remaining uncertainties about the exact mechanisms of their action, particularly concerning the effects of immunization on the progression of neurodegeneration and brain atrophy in AD patients. This review also highlighted the main adverse effects associated with the use of different A β vaccines in AD. Given the development of these side effects has led to the suspension of some clinical trials, more immunization studies need to be performed to document the adverse effects caused by vaccinations more comprehensively and decipher the causes of these complications. Moreover, future studies should also focus on optimizing vaccine strategies, combining these immunotherapies with other treatments, and extending follow-up durations to thoroughly understand the long-term impacts on AD progression.

Ethical Considerations

Compliance with ethical guidelines

The current study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1399.960).

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Authors contributions

Conceptualization and study design: Haideh Mosleh and Hani Ghayyem; Supervising: Mohammadreza Kossari; Writing—original draft, review & editing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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