ORIGINAL RESEARCH PAPER

Neurology

A LITERATURE REVIEW OF ACTIVE Aβ-IMMUNOTHERAPY WITH CAD106 FOR ALZHEIMER'S DISEASE

KEY WORDS: Alzheimer, Aβ-amyloid, CAD106, Immunotherapy, Novel-therapies, Vaccine

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ABSTRACT

Background: CAD106 is a second generation immunotherapeutic agent developed for the treatment of Alzheimer's disease. It induces an antibody response against Aβ-peptides in the brains of Alzheimer patients and has been found to be safer than the former vaccine formulations in animal models. The review assesses the safety, tolerability and immunogenicity of CAD106 in the treatment of Alzheimer's disease. Materials and methods: An electronic search was done on 'PubMed' using the keywords "CAD106", "Alzheimer's disease", "immunotherapy AND Alzheimer's disease". Three randomized placebo-controlled trials were studied for the review. Results: The three trials reported mild to moderate adverse events with the use of CAD106. The vaccine induced an acceptable serologic response without evoking an autoimmune response or causing T-cell activation. It reduced the brain-amyloid load in strong serologic responders. However, no treatment-related benefits were seen. Conclusion: CAD106 is safe, tolerable and immunogenic with uncertain treatment-related benefits.

INTRODUCTION

Alzheimer's disease (AD) is a degenerative disease of the brain characterized by an insidious onset of dementia leading to global loss of cognitive abilities.[1] The illness progresses gradually from preclinical, mild and moderate to severe stages with a shortened life expectancy.[2]

The key factor in the pathogenesis of Alzheimer's disease is amyloid-β (Aβ) peptides[3] which are formed by the proteolytic cleavage of Amyloid Precursor Protein (APP) by β and γ secretases.[4]

The current treatment for AD comprises cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists which are aimed at modifying the neurotransmitter-imbalance due to the disease. However, they have no impact on amyloid plaques in the brain. [5]

Immunotherapy is a novel approach that targets Aβ peptides in the brain[6]. It involves either direct administration of antibodies such as bapineuzumab or vaccinating against Aβ peptides.[7] The former vaccine formulations such as AN1792 induced a variable immune response and caused autoimmune meningoencephalitis due to T-cell activation.[7] However, the animal experiments with the second generation vaccine, CAD106, showed promising results.[8] The vaccine did not activate Aβ-specific T-cells, reduced the brain amyloid accumulation and induced efficacious Aβ antibody titers in APP transgenic mice. CAD106 is now being studied extensively in clinical trials for the treatment of Alzheimer's disease.[9] However, studies reviewing the results of these trials are lacking. Hence we felt the need to review the literature regarding the safety, tolerability, and immunogenicity of the CAD106 vaccine in the treatment of Alzheimer's disease. This has implications for the treatment of Alzheimer's disease, training of mental-health professionals and further research.

MATERIALS & METHODS

We did an electronic search on 'PubMed' using the keywords "CAD106", "Alzheimer's disease", "immunotherapy AND Alzheimer's disease" etc. Articles from 2010 onwards were included; animal studies, postmortem studies, review articles, theory-based studies and studies in languages other than English were excluded. Three randomized controlled trials were finalized for the review. The data were extracted under the following headings: study title, author names, year of publication, type of the study, duration of the study, sample size, purpose of study, diagnostic criteria of Alzheimer's disease, Mini-Mental Status Examination scores of AD patients, neuropsychiatric tests for clinical assessment of patients, investigations, defining serological response, dosage, duration and mode of administration, incidence of non-serious adverse events, most common non-serious adverse events, serious adverse events, incidence of serious adverse events, most common serious adverse events, Amyloid-Related Imaging Abnormalities (ARIA), CNS inflammation, immunogenic response, T-cell response, neuroimaging results, CSF biomarkers, treatment-related benefits, study highlights and limitations. The findings were tabulated and analyzed.

RESULTS

Three drug trials were evaluated to study the safety, tolerability, and immunogenicity of CAD106 vaccine in the treatment of Alzheimer's disease.

Year Of Publication:

The first article was published in 2012[10], the second in 2015[11] and the third in 2017.[12]

Type of study:

All the studies were randomized, double-blind, placebo-controlled trials. The first was a phase I[10], the second phase IIa[11] and the third phase IIb[12] trial. The second trial comprised of a placebo-controlled core study followed by an open-label extension study.[11]

Duration of study:

The duration of the first trial was 52 weeks.[10] The second trial comprised of a 52 weeks core study followed by a 66 weeks extension study[11] while the third trial was conducted for 90 weeks.[12]

Sample size:

The first trial enrolled 58 patients.[10] The second trial enrolled 58 patients in the core and 45 patients in the extension study[11] whereas the third trial included 121 patients.[12]

Purpose of study:

All the trials were conducted to assess the safety, tolerability, and immunogenicity of CAD106 vaccine in the treatment of Alzheimer's disease.[10,11,12]

Diagnostic-criteria for AD:

All the trials used the Diagnostic and Statistical Manual of Mental Disorders (4th Edition) for the diagnosis of Alzheimer's disease.[10,11,12] The second and the third trial also used the guidelines given by the National Institute of Neurological and Communicative Disorders and Stroke; and the Alzheimer's disease and Related Disorders Association.[10,11,12] The three trials enrolled AD patients with mild to moderate cognitive impairment with their MMSE scores ranging from 16 to 26 in the first trial[10] and 20 to 26 in the second and the third trial.[11,12]

Neuropsychiatric tests for clinical assessment of patients:

A battery of different neuropsychiatric tests was used to assess the clinical progression of all the patients. A detailed enlisting of these tests is given in table 1.[10,11,12]

Investigations:
In all the trials, the patients were evaluated using the following investigations: Serum Aβ-IgG titers, plasma $A\beta_{1-40,}$ characterization of Aβ and Qβ specific T cell response in Peripheral Blood Mononuclear Cells (PBMC), disease-related biomarkers in CSF and volumetric MRI brain.[10,11,12] The third trial also employed amyloid PET sub-study with ^{18}F-florbetapir to assess the amyloid load in the brains of AD patients.[12]

Defining serologic response:
The serologic response was defined as Aβ-IgG titers above the threshold. In the first trial, the threshold was set at 16 units.[10] In the second and the third trial it was set at 16 units between the second and the third injections and 26.8 units after the third injection.[11,12] In the third trial, the Aβ-IgG titer above 35.7 units after 2 or more injections (not necessarily consecutive) starting from the second injection onwards, was defined as a strong serologic response whereas those not meeting the criteria for serologic response were called non-responders.[12]

Dosage, Schedule, and Mode of administration:
In the first trial, CAD106 was administered at a dose of 50 µg at 0, 6 and 18 weeks in cohort 1 and 150 µg at 0, 2 and 6 weeks in cohort 2 subcutaneously.[10] In the second trial, CAD106 was administered at a dose of 150 µg. During the core study, it was given at 0, 6 and 12 weeks subcutaneously in cohort 1 and at 0, 2 and 6 weeks subcutaneously or intramuscularly in cohort 2. During the extension study, 4 injections were given at 12 weeks interval, subcutaneously in cohort 1 and intramuscularly in cohort 2.[11] In the third trial, cohort 1 received 50 µg of the vaccine with either alum or MF59 as an adjuvant and cohort 2 received 450 µg of the vaccine with or without 450 µg of alum; at 0, 6, 12, 24, 36, 48, and 60 weeks intramuscularly.[12]

Non-serious adverse events:
In the first trial, 97.83% of CAD106-treated patients and 91.67% of placebo-treated patients reported non-serious adverse events. The most common adverse events in CAD106-treated patients were nasopharyngitis, fatigue, and headache in cohort 1 and injection site erythema, chills, fatigue, injection site pain, fever, and headache in cohort 2.[10] In the second trial, 74.5% of CAD106-treated patients and 63.6% of placebo-treated patients experienced non-serious adverse events such as headaches, administration site reactions and fever.[11] Similarly, the third trial reported mild to moderate adverse events like headache, hypertension and fever in 83% of CAD106-treated and 80% of placebo-treated patients.[12]

Serious adverse events:
The first trial did not report any serious adverse events.[10] The second trial reported cardiovascular adverse events in CAD106-treated patients, 12.8% in the core study and 13.3% in the extension study. These included myocardial ischemia, complete atrioventricular block, rhythm disturbances (bradycardia, tachycardia, ventricular extrasystoles), and left ventricular hypertrophy. A single case of small sulcal subarachnoid hemorrhage was reported during the core study.[11] The third trial reported serious adverse events in 24.5% of CAD106-treated and 6.7% of placebo-treated patients. The investigators attributed allergic dermatitis, atrial fibrillation, and acute psychosis to the study drug.[12]

Amyloid-Related Imaging Abnormalities (ARIA):
ARIAs are the abnormal changes seen in the brain on neuroimaging studies associated with amyloid-modifying therapies in the treatment of Alzheimer's disease. ARIAs consist of cerebral hemorrhage (ARAI-H) and parenchymal edema (ARAI-E).[13]

The first trial did not report any ARIAs.[10] The second trial reported ARIAs in 6.90% of total patients. 75% of them occurred in CAD106-treated patients who were carriers of ApoE4 allele whereas 25% occurred in placebo-treated non-carrier patients. 75% of these ARIAs were micro-hemorrhages while 25% were subarachnoid hemorrhages. All the patients remained asymptomatic.[11] The third trial reported ARIAs in 5.66% of CAD106-treated patients. 83.33% of these were ARIA-H and 16.67% were ARIA-E. All the patients were asymptomatic and were strong serologic responders. The ARIA-E resolved spontaneously and the treatment schedule was resumed whereas the ARIA-H cases led to treatment discontinuation.[12]

CNS inflammation:
None of the three trials reported any evidence of central nervous system inflammation on clinical examination, neuroimaging or CSF examination associated with the use of CAD106.[10,11,12]

Immune response:
In the first trial, the serologic response was obtained in 67% of patients in cohort 1 and in 82% of patients in cohort 2. The Aβ IgG titers peaked around 8 weeks following the first dose that persisted for up to 20 weeks above the threshold.[10] In the second trial, 63.8% of patients developed a serologic response during the core study. 50% of these maintained Aβ-IgG titers above the threshold at the end of the extension study.[11] In the third trial, the serologic response was detected in 62.3% of patients in cohort 1 and in 89.2% of patients in cohort 2. Also, a strong serologic response was recorded in 55.1% of patients in cohort 1 whereas in 81.1% of patients in cohort 2.[12]

T-cell response:
The three trials assessed the IFN-γ levels in peripheral blood mononuclear cells as a marker of T-cell activation against $A\beta_{1-6}$ and $A\beta_{1-42}$ peptides and reported that CAD106 did not cause T-cell activation.[10,11,12]

Neuro-imaging:
The neuroimaging findings in the first and the second trial were consistent with the natural progression of the disease and showed no treatment-related changes. However, in the third trial, amyloid PET sub-study with ^{18}F-florbetapir reported a significant negative correlation between the percentage change in the amyloid PET and the area under the curve (AUC) of the serum Aβ-IgG titers in CAD106 treated patients ($r=-0.84$, $p=0.0004$). Also, a decrease of amyloid load in 30% of strong serologic responders with a high AUC was observed. However, the strong-serologic responders had a larger percentage decrease in the cortical grey-matter volume from baseline to week 78 as compared to the placebo-treated patients as found in the volumetric MRI studies.[10,11]

Treatment-related benefits:
None of the three trials reported a significant treatment-related benefit in CAD106-treated patients as compared to the placebo-treated patients.[10,11,12] Surprisingly, the third trial reported a numerically higher decline in the MMSE scores of CAD106-treated strong serologic responders as compared to the placebo-treated patients over 78 weeks.[12]

Limitations
The limitations of the three trials were a small sample size, short duration, complicated study design and interruptions during the trials.[10,11,12]

DISCUSSION
We reviewed three randomized placebo-controlled double-blind trials assessing the safety, tolerability and immunogenicity of CAD106 vaccine in the treatment of mild to moderate Alzheimer's disease. The trials confirmed that CAD106 induces an acceptable serologic response without evoking an autoimmune response or causing T-cell activation. Although serious adverse events like allergic dermatitis, acute psychosis and some cardiovascular events along with Amyloid-Related Imaging Abnormalities have been reported in some of the patients, their association with the use of CAD106 is not confirmed. Overall, CAD106 appears to have a favourable safety and tolerability profile with good immunogenic potential. The trials have reported a reduction in the amyloid load in the brains of strong serologic responders. However, the reduction in the cortical grey-matter volumes and the MMSE scores over time was more pronounced in strong serologic responders as compared to the placebo group. Also, none of the

trials reported any significant treatment-related benefits in the CAD106-treated patients. Hence, the clinical efficacy of CAD106 needs to be investigated in future studies. Our study has implications for the treatment of Alzheimer's disease, training of mental-health professionals and research.

Conclusion

CAD106 is a safe, tolerable and immunogenic vaccine with the potential to reduce the brain-amyloid load in patients of Alzheimer's disease with uncertain treatment-related benefits.

TABLE 1: Comparison of Three Randomized Placebo-Controlled Trials of CAD106 Vaccine in Patients with Alzheimer's disease

	TRIAL 1	TRIAL 2	TRIAL 3
Author	Winblad B et al	Farlow MR et al	Vandenberghe R et al
Year of publication	2012	2015	2017
Type of study	Randomized, double-blind, placebo-controlled, phase I trial	Multicenter, randomized, double-blind, placebo-controlled core study followed by open label-extension study, phase IIa trial	Randomized, double-blind, placebo-controlled, phase IIb trial
Duration of study	52-week	52 weeks phase core study, 66 weeks extension study	90 weeks
Sample size	58 patients	58 patients in core study; 45 patients in extension	121 patients
Purpose of study	To assess the safety and tolerability of CAD106 for patients with Alzheimer's disease.	To investigate the long-term safety, tolerability and antibody response after repeated CAD106 injections.	To assess safety, tolerability, and immunogenicity of CAD106 with/without adjuvant in patients with Alzheimer's disease.
Diagnostic criteria for AD	DSM-IV	DSM-IV; NINDS; ADRDA	DSM-IV; NINDS; ADRDA
MMSE scores of AD patients	16-26	20-26	20-26
Neuro-psychiatric tests for clinical assessment of patients	Neuropsychological Test Battery (NTB), MMSE, Clinical Dementia Rating (CDR) outcome, Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCSADL) scale	MMSE, Global Deterioration Scale, Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog; 11 items), Trail Making Test Part A, Category fluency test, Alzheimer's Disease Cooperative Study–Activities of Daily Living, Neuropsychiatric Inventory Questionnaire	Alzheimer's Disease Assessment Scale-Cognitive Subscale, Alzheimer's disease Cooperative Study–Activities of Daily Living, Clinical Dementia Rating scale, MMSE, Neuropsychiatric Inventory Questionnaire, Category Fluency Test–animals, Controlled Oral Word Association Test–letters, Computerized tests (CogState)
Investigations	Serum Aβ-IgG titers, plasma $Aβ_{1-40,}$ IFN-γ levels in PBMC, Disease-related biomarkers in CSF, Volumetric MRI brain	Serum Aβ-IgG titers, Plasma $Aβ_{1-40}$, IFN-γ levels in PBMC, Disease-related biomarkers in CSF, Volumetric MRI brain	Serum Aβ-IgG titers, Plasma $Aβ_{1-40}$, IFN-γ levels in PBMC, Disease-related biomarkers in CSF, Volumetric MRI brain, Amyloid PET sub-study with ^{18}F-florbetapir
Defining serologic response	SR: Aβ-IgG titers >16U	SR: Aβ-IgG titers >16U between 2nd & 3rd injections and >26.8 U after 3rd injection.	SR: Aβ-IgG titers >16U between 2nd & 3rd injections and >26.8 U after 3rd injection. SSR: Aβ-IgG titers >35.7 units after ≥2 different injections from 2nd injection onwards. NR: Aβ-IgG titers below threshold.
Dosage	Cohort 1: 50 µg; Cohort 2: 150 µg	150 µg	Cohort 1: 150 µg with alum or MF59; Cohort 2: 450 µg with or without alum 450 µg.
Schedule and mode of administration	Cohort 1: weeks 0, 6, 18 Cohort 2: weeks 0, 2, 6 s.c.	Core study cohort 1: Weeks 0, 6, 12 s.c. Core study cohort 2: Weeks 0, 2, 6 s.c. or i.m. Extension study: 4 injections at 12 weeks interval s.c. in cohort 1 & i.m. in cohort 2	Up to 7 injections at weeks 0, 6, 12, 24, 36, 48, 60 i.m.
Incidence of Non-serious adverse events	97% in all AD patients	74.5% in CAD106-treated & 63.6% in placebo-treated AD patients	83% in CAD106-treated & 80% in placebo-treated AD patients
Most common Non-serious adverse events	Nasopharyngitis, fatigue, headache, injection site conditions, chills, fatigue & fever	Headache, administration site conditions & fever	Headache, hypertension & fever
Incidence of Serious adverse events	CAD106 group: Cohort 1: 17%, Cohort 2: 18% Placebo group: Cohort 1: 14%, Cohort 2: 0%	CAD106 group: Core study: 12.8% , Extension study: 15.6%	CAD106 group: 24.5%. Placebo group: 6.7%

Serious adverse events	No SAEs were related to study drug	Myocardial ischemia, complete atrioventricular block, rhythm disturbances, left ventricular hypertrophy, sulcal subarachnoid hemorrhage	Allergic dermatitis, atrial fibrillation, acute psychosis
Incidence of Amyloid-Related Imaging Abnormality	0%	6.90% in all AD patients: 75% were CAD106-treated & 25% were placebo-treated.	5.66% of CAD106-treated patients
Amyloid-Related Imaging Abnormality	None	Microhemorrhages (75%), subarachnoid hemorrhages (25%)	ARIA-H (83.33%), ARIA-E (16.67%)
CNS inflammation	None	None	None
Percentage of AD patients showing serologic response	Cohort 1: 67%, Cohort 2: 82% Peak mean Aβ IgG titers were recorded in 8 weeks persisting for up to 20 weeks.	Core study: 63% Extension study: 50%	Cohort 1: NRs: 37.7% SRs: 62.3% SSRs: 55.1% Cohort 2: NRs: 10.8% SRs: 89.2% SSRs: 81.1%
T-cell response	None	None	None
Neuroimaging	Changes consistent with natural disease progression	Changes consistent with natural disease progression	A significant negative correlation between percentage change in amyloid PET and AUC of serum Aβ-IgG titers was found in CAD106 treated patients. A decrease of amyloid load was seen in 30% of SSRs. Volumetric MRI found a larger decrease in cortical grey-matter volume in SSRs than in others.
Treatment-related benefits	No treatment-related benefits	No treatment-related benefits	No treatment-related benefits, Decline in MMSE scores was more in SSRs than in placebo-treated patients.
Study highlights	CAD106 was safe, tolerable & immunogenic, Did not evoke autoimmune response, Did not cause T-cell activation.	CAD106 was safe, tolerable and immunogenic, Did not induce T-cell response.	CAD106 was safe, tolerable
Limitations	Small sample size, Small duration of study	Not mentioned	Small sample size, Complicated study design, Temporary interruptions

*DSM-IV, Diagnostic and Statistical Manual of Mental Disorders version IV;

NINDS, National Institute of Neurological and Communicative Disorders and Stroke;

ADRDA, Alzheimer's Disease and Related Disorders Association;

PBMC, Peripheral Blood Mononuclear Cells;

S.C., Subcutaneous; I.M., Intramuscular;

SR, serologic responder; SSR, strong serologic responder; NR, non-responder;

ARIA-H, amyloid-related imaging abnormality-hemorrhage; ARIA-E, amyloid related imaging abnormality-edema; AUC, Area Under Curve

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