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# Efficacy and safety of immunotherapies for Alzheimer's disease: A network meta-analysis

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**ADMINISTRATIVE INFORMATION**

**Support -** International Medical University.

**Review Stage at time of this submission -** Data analysis.

**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 June 2023 and was last updated on 18 June 2023.

## INTRODUCTION

**Review question / Objective** What are the therapeutic benefits of immunotherapies in the treatment of Alzheimer's disease? What are the potential harms of immunotherapies in the treatment of Alzheimer's disease?

**Rationale** Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the most common form of dementia affecting 58 million people with an enormous public health impact in 2021 and expected to be 88 million by 2050. Moreover, AD accounts for 60-70% of dementia cases. This disease is thought to begin even 20 years or more before symptoms arise. The total global cost of treatment for dementia was estimated to be $818 billion USD (2). The long duration of illness before death contributes significantly to the public health burden of the country as well as to the family and the patients' themselves.

Genetic factors play an important role in pathogenesis of AD (3). In addition to cerebral atrophy macroscopically, and senile plaques and neurofibrillary tangles can be found under histological examination. In addition to amyloid deposition in plaques, many different neurotransmitter abnormalities such as impairment of cholinergic transmission, noradrenaline, 5-HT, glutamate, and substance P have also been described.

The pathological hallmarks of AD are senile plaques which consists of amyloid fibrils which in turn composed of amyloid-beta (Aβ) peptide and neurofibrillary tangles consisting of hyperphosphorylated tau protein. The molecular and clinical events, including amyloid accumulation, neuroinflammation, tau accumulation, neural degeneration, cognitive decline, and occurrence of behavioral psychological symptoms, develop along with the disease progression. Moreover, the brains of patients with AD exhibited evidence of sustained inflammation.

Currently available treatments include anticholinesterase drugs which inhibits

cholinesterase enzyme such as donepezil, rivastigmine; N-methyl-D-aspartate (NMDA) receptor antagonist such as memantine. These drugs can only inhibit dementia symptoms for a limited period but cannot stop or reverse the disease progression.

**Condition being studied** Based on the amyloid hypothesis, the subsequent events of amyloid accumulation, neuroinflammation, tau accumulation, brain metabolism dysfunction, brain atrophy, cognitive decline can occur. Hence, a few approaches to reduce the amyloid burden have been developed and underwent clinical trials. Inhibition of gamma-secretase and beta-secretase enzyme which are responsible for synthesis of amyloid-beta (Aβ) peptide, targeting the depredating enzymes of Aβ and removing Aβ through immunotherapy are some of the therapeutic targets under anti-amyloid therapy of AD. Removal of amyloid by plasma exchange therapy, monoclonal antibodies, αβ aggregation inhibitors are some pharmacotherapies under anti-amyloid therapies.
Meanwhile, amyloid hypothesis has been challenged with some unfavourable results from completed and ongoing clinical trials, the interest has been shifted to non-antiamyloid therapies or possibility of agents with multiple targets to slow down the disease progression.
Active and passive immunotherapies targeting Aβ could reduce amyloid accumulation in preclinical mouse models of Aβ amyloid deposition. Multiple possible mechanisms for antibody mediated reductions and clearance of Aβ have been proposed and supported by various preclinical studies.
There was a published meta-analysis by Fernandez in 2021, where the cognitive improvement was analyzed from the 12 included studies compared between immunotherapies and placebo. This proposed study will differ from the published review in terms of methodology (pairwise meta-analysis versus network meta-analysis) as well as will be including newer interventions from the scope of immunotherapy in AD.
The aim of this study is to provide a reference on management of various immunotherapies in AD by performing a network meta-analysis. Network meta-analysis will permit the comparative effectiveness of interventions from direct comparisons as well as from indirect comparisons and hence this can allow the ranking of treatment. We do hope that this data will provide an assistance in clinical selection of pharmacotherapeutic interventions in the future management of AD.

## METHODS

**Search strategy** An extensive electronic search of the multiple databases will be done to identify relevant studies available from inception to Dec 2022.

**Participant or population** Alzheimer's disease, regardless of age, gender.

**Intervention** immunotherapies (Solanezumab, gantenerumab, crenezumab, lecanemab (Ban2401), intravenous polyclonal antibodies (immunoglobulins) (e.g., NewGam 10% IVIg, Albumin combined with immunoglobulin), umibecestat, atabecestat, bapineuzumab, aducanumab, active Ab vaccines (ACC-001, CAD106, and Affitope AD02) or ponezumab).

**Comparator** Alternative immunotherapies or placebo.

**Study designs to be included** Randomized controlled trial.

**Eligibility criteria** Studies published in English language only will be included. Studies must report at least one outcome related to changes in cognitive improvement.

**Information sources -** We will search the following databases to identify relevant RCTs:
1. Ovid MEDLINE
2. The Cochrane Library (CENTRAL)
3. PubMed
We will also search the following clinical trials registries:
1. ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- To do so, appropriate MeSH terms with suitable Boolean operators will be used. The following is an example of study search using key words and Boolean operators in PubMed.

**Main outcome(s)** Studies must report cognitive improvement with at least one of the outcomes: Alzheimer's Disease Assessment Scale (ADAS-cog) or Mini-Mental State-Exam (MMSE).

**Additional outcome(s)** Reported safety data will be recorded.

**Data management** Two investigators will independently screen the titles/abstracts of citations from the database search and retrieve full text of all potentially relevant articles. If studies have duplicated publications, maximum amount of data will be extracted from the available publications. Additionally, manual-search in the

references of the relevant reviews/ included studies. The two investigators then independently check the full-text articles for eligibility based on the inclusion criteria. Any discrepancy will be solved with the third investigator.

**Quality assessment / Risk of bias analysis** The methodological quality of the studies will be assessed using the Cochrane risk of bias tool, described elsewhere. Methodological quality assessment will be carried out by the two independent investigators (please add any two initials) and any discrepancy will be solved by discussion with the third investigator.

**Strategy of data synthesis** The clinical trialists or the investigators will be contacted to verify the key characteristics and any missing data in the published trials whenever possible. The efficacy of different therapeutic agents of immunotherapies therapies will be compared by pairwise meta-analysis. Relative risk and 95% confidence level will be measured for dichotomous outcomes and mean difference, or standard mean difference will be measure for continuous outcomes. Heterogeneity will be assessed using the $\chi^2$ test and the $I^2$ statistic. The I2 value of 25% will consider as low heterogeneity, 50% as the moderate heterogeneity, and more than 75% as a high heterogeneity. A two-tailed P value of less than 0.05 will be considered statistically significant. A funnel plot will be done to detect the publication bias.
A NMA and ranking of the various drugs will be done. An assessment of rank probabilities using surface under the cumulative ranking curves (SUCRA) plots will be done. Data extraction and analysis will be carried out independently by the two investigators. A consensus will be reached in case of discrepancy by discussing with the third investigator.
Data entry and analysis will be done with STATA 18 (Stata Corp, Txt), Review
Manager 5.4, and Covidence software.

**Subgroup analysis** Subgroup analysis will be done according to the drugs, time point, age, gender, disease severity, and/or comorbidities if data permits.

**Sensitivity analysis** Sensitivity analysis will be done either by excluding the studies with high risk of bias, high heterogeneity or by leave one out analysis method.

**Language restriction** English only.

**Country(ies) involved** Malaysia.

**Keywords** Alzheimer's Disease, cognition, meta-analysis, network meta-analysis, immunotherapies.

**Contributions of each author**

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