ISSN: 2641-2020
DOI: 10.33552/APPR.2025.04.000595
Archives of
Pharmacy & Pharmacology Research
Iris Publishers

Opinion

Challenges of Anti-Amyloid Immunotherapy for the Treatment of Alzheimer's Disease

Gustavo Alves Andrade Dos Santos*

Faculdade São Leopoldo Mandic de Araras, Medical School, Araras, Brazil

University of São Paulo (USP), School of Medicine of Ribeirão Preto, Brazil

Department of Food and Nutrition, School of Food Engineering, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

***Corresponding author:** Gustavo Alves Andrade Dos Santos, Faculdade São Leopoldo Mandic de Araras, Medical School, Araras, Brazil
University of São Paulo (USP), School of Medicine of Ribeirão Preto, Brazil
Department of Food and Nutrition, School of Food Engineering, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil
Email: gusfarma@hotmail.com

Received Date: December 14, 2024

Published Date: January 03, 2025

Abstract

In this paper, I present the broad possibilities generated by new treatments for Alzheimer's disease (AD), with increasingly specific targets, representing a huge advance when compared to initial therapies, but on the other hand I emphasize the risks associated with these new therapies, which need to be removed in the search for more effectiveness and less toxicity for patients with AD.

Keywords: Monoclonal Antibodies; Alzheimer Disease; Immunotherapy; Amyloid Beta-Peptides; Tau Protein

Introduction

Alzheimer's disease involves brain changes, including excessive accumulation of beta-amyloid protein fragments and an abnormal form of tau protein, as well as damage and neurodegeneration. Alzheimer's disease involves brain changes that contribute to the progression of dementia [1]. Extracellular amyloid-β (Aβ) plaques and neurofibrillary tangles containing intracellular tau in the brain represent a kind of signature of Alzheimer's disease (AD). For a long time, it was considered that the pathophysiology of AD involved alterations in amyloid beta (Aβ) as precipitating factors of the disease and from there, a deleterious cascade involving tau pathology and neurodegeneration. In addition to this aspect of functioning as a "triggering factor", it is believed that Aβ and tau act independently and in the absence of specific interaction. However, very recently, evidence suggests the opposite and affirms that both pathologies have synergistic effects. These findings help to explain the negative results of anti-Aβ clinical trials and suggest that trials carried out specifically with TAU need to be revised [2].

The accumulation of Aβ, the most important peptide in senile plaques in Alzheimer's disease, is considered the molecular "trigger" of the pathophysiology and progression of Alzheimer's dementia. Thus, Aβ has been the main target for the development of AD therapy. However, repeated failures of clinical trials involving

anti-Aβ therapy have cast considerable doubt on the amyloid cascade hypothesis and whether the strategy for a drug capable of reversing AD is on the right track. On the other hand, the more recent satisfactory results of Aβ-targeted trials have reduced these doubts [3]. The accumulation and aggregation of Aβ is considered an essential trigger in the pathogenesis of AD, which in its evolution gives rise to neurofibrillary tangles (NFTs), neurodegeneration and dementia. The progression of AD presents tau and Aβ with incorrect "breaks" and the formation of aggregates in a region of the brain, respectively. This process disseminates in some regions of the brain, causing gradual morphological and functional deterioration. The extracellular accumulation of amyloid-β peptides (Aβ) generated by the cleavage of the amyloid precursor protein (APP) and the hyperphosphorylated Tau protein chains accumulating inside neurons are typical markers of AD [4].

Strategies for treating AD have advanced significantly since the beginning, although some of the drugs that were initially used successfully are no longer as effective. Tacrine was the first anticholinesterase drug to be used in the treatment of Alzheimer's disease, but it had to be withdrawn shortly after it was marketed due to its hepatotoxicity. Other anticholinesterase drugs such as rivastigmine, donepezil and galantamine represented important advances. Next came memantine, a glutamate inhibitor, with robust results, especially in advanced stages of the disease. The cholinergic hypothesis, on which the use of current drugs for the treatment of AD is based, has been an important therapeutic resource, but with a better understanding of the tau protein and beta-amyloid, other molecules have been researched. The formation of senile plaques due to the incorrect degradation of beta amyloid and the hyperphosphorylation of tau are targets for the creation of new drugs [5].

New molecules related to the pathophysiology of Alzheimer's disease (AD) have been investigated in randomized clinical trials, and some have received considerable attention for presenting important statistical results in clinical outcomes compared to placebo [6]. Monoclonal antibodies targeting amyloid-β (Aβ) protein were the first group of drugs considered suitable for clinical use in AD; they bind to different species of the protein aggregation chain. This is the "amyloid cascade hypothesis", which is based on the triggering of a cascade of pathophysiological events, with synaptic dysfunction, inflammation, aggregation and spreading of phosphorylated tau (p-tau) tangles. Spreading of p-tau is associated with synaptic loss and neurodegeneration, with outcomes such as cognitive decline and dementia. When monoclonal antibodies bind to Aβ aggregates, they facilitate the clearance of Aβ from the brain, greatly reducing the deleterious effects of Aβ deposition and, therefore, delaying cognitive and functional decline [7].

In the US, the approval of aducanumab as "the first disease-modifying drug for Alzheimer's disease" was greeted with great euphoria as a breakthrough by many. However, in response to the controversial decision, three members of the Food and Drug Administration's (FDA) independent expert advisory committee, who voted almost unanimously against approval, resigned, describing it as the worst decision ever made to approve a drug in the US [8]. Aducanumab is a monoclonal antibody used to treat Alzheimer's disease and mild dementia. Its mechanism of action is to remove amyloid plaques in the brain, which are associated with disease [9]. Lecanemab is a monoclonal antibody that binds with high affinity to soluble Aβ protofibrils, which have been shown to be more toxic to neurons than insoluble monomers or fibrils. It is FDA-approved and indicated for the treatment of early AD and has been shown to be well tolerated in several clinical trials, although risks include an increased rate of amyloid-related imaging abnormalities (ARIA) [10]. Donanemab is directed against the modified, insoluble, N-terminally truncated form of β-amyloid present only in brain amyloid plaques, termed as an immunoglobulin G1 monoclonal antibody. The drug acts by binding to the N-terminally truncated form of β-amyloid and aids in the clearance of plaques through microglia-mediated phagocytosis. It has important adverse events, such as amyloid-related imaging abnormalities and infusion-related reactions [11].

Discussion

Immunotherapies have emerged as a possible solution for reducing the damage caused by AD. Many drugs have been developed, some approved and others have not even gone beyond the initial stages of clinical research. Although very promising, these molecules present very worrying adverse reactions that have a direct impact on patient survival. Yes, we can think of drugs that present benefits, but which include very undesirable events. Another issue is the fact that, even if they work successfully, new and promising drugs may have limited therapeutic effects depending on the phase (evolution) in which the disease presents itself. For example, if we think of the TAU protein, we can imagine a stage beyond the initial one, since the formation of neurofibrillary tangles comprises stages from the mild phase of AD.

Considering the Continuum process in AD, mild cognitive decline and subjective cognitive decline, we can think that the ideal would be a drug that acts as early as possible, that is, before the formation of plaques, in phases prior to the hyperphosphorylation of the TAU protein. However, the new drugs, called "disease-modifying drugs for Alzheimer's disease" are still unable to act between phases 1 and 2 of the Continuum.

The Continuum phases are Phase 1 -Cognitively normal or Preclinical; Phase 2 - Mild Cognitive Impairment; Phase 3 - Dementia [12]. So, the question remains: is it worth using anti-amyloid immunotherapies or not?

Immunotherapy has shown promise as a treatment for Alzheimer's disease and may be the first treatment to modify the disease itself:

Preclinical results: Immunotherapy has shown promising results in animal models, reducing amyloid buildup and preventing further disease.

Clinical trials: Some clinical trials have shown positive results, such as reducing brain atrophy and cognitive decline in patients with mild to moderate Alzheimer's.

FDA-approved drugs: Aducanumab was approved by the FDA in 2022, and Lecanemab was approved in 2023. These drugs target the progression of the underlying Alzheimer's disease, rather than just treating the symptoms.

Immunotherapy for Alzheimer's works by teaching the immune system to ignore potentially harmful proteins as "self" antigens. This may help reduce the buildup of amyloid proteins in the brain, which can cause damage that leads to symptoms of dementia. Future research may focus on developing safer and more effective antibodies and targeting molecules other than beta-amyloid, such as tau protein. However, there are negative reports of the use of immunotherapies, with an emphasis on ARIA (Amyloid-related imaging abnormalities), which are abnormal changes that can be observed in MRI scans of the brains of patients with Alzheimer's.

Conclusion

There is a gold rush in search of solutions for the treatment of AD, whether in preventive form or even in therapeutic use, as a cure. After the cholinergic hypothesis, the Amyloid hypothesis emerged, and the advances in the understanding of this disease are unquestionable, but the progress has also shown weaknesses for the "disease-modifying drugs for Alzheimer's disease", and from this significant advance, it is expected that there will be an improvement of these molecules in search of effective solutions with a lower risk of toxicity for patients.

Acknowledgement

I declare that this discipline was one of my main favorite researches without having sponsorship or funding from any association.

Conflict of Interest

No conflict of interest.

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