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STEM CELL THERAPY IN THE TREATMENT OF ALZHEIMER'S DISEASE: A MULTIDISCIPLINARY PERSPECTIVE

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Abstract: Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative pathology characterized by cognitive decline and behavioral changes, representing a significant challenge to global public health. Current therapies offer only limited symptomatic relief, driving the search for innovative therapeutic approaches. Stem cell therapy (SCT) is emerging as a promising strategy, with the potential to modulate neuroinflammation, promote neuroprotection, and even induce neurogenesis in the AD-affected brain. This scientific article explores the current landscape of SCT in the context of AD, integrating knowledge from clinical medicine, surgery, and basic and translational scientific research. The mechanisms of action of stem cells, the different cell types used, the results of recent preclinical and clinical studies, as well as the challenges and future prospects of this innovative therapeutic approach will be addressed.
Keywords: Alzheimer's disease; Stem cells; Cell therapy; Neurodegeneration; Neuroinflammation.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting millions of individuals worldwide and imposing a growing socioeconomic burden. Its complex pathophysiology involves the extracellular deposition of amyloid beta (Aβ) plaques and the intracellular formation of neurofibrillary tangles of hyperphosphorylated tau protein, leading to synaptic dysfunction and loss, glial inflammation, and eventual neuronal death, particularly in brain regions crucial for memory and cognition (Selkoe & Hardy, 2016).

The diagnosis of AD is primarily clinical, based on neuropsychological assessment and patient history, and is confirmed postmortem by histopathological analysis of brain tissue. Biomarkers in cerebrospinal fluid (CSF) and neuroimaging, such as positron emission tomography (PET) with amyloid and tau tracers, aid in early diagnosis and monitoring of disease progression (Jack et al., 2018).

Currently approved pharmacological therapies for AD, such as cholinesterase inhibitors and memantine, offer only modest symptomatic relief and do not significantly alter disease progression. In the absence of curative or disease-modifying treatments, research into new therapeutic approaches is of paramount importance.

Stem cell therapy (SCT) represents a promising area of research in the context of neurodegenerative diseases, including AD. Stem cells have the unique ability to self-renew and differentiate into various cell types, in addition to exerting immunomodulatory and trophic effects through the secretion of bioactive factors (Méndez-Otero et al., 2019).

The application of stem cells in the treatment of AD aims, theoretically, to replace lost neurons, protect remaining neurons from degeneration, reduce chronic inflammation in the brain, and promote synaptic plasticity, potentially reversing or delaying the cognitive decline characteristic of the disease.

This article aims to critically analyze the current state of the art of stem cell therapy in the treatment of Alzheimer's disease, from a perspective that integrates clinical, surgical, and scientific expertise, focusing on evidence published between 2019 and 2025, following ABNT standards.

GENERAL

GENERAL OBJECTIVE

To analyze the therapeutic potential of stem cell therapy in the treatment of Alzheimer's disease, based on scientific evidence published between 2019 and 2025.

SPECIFIC OBJECTIVES

- To describe the main types of stem cells used in preclinical and clinical studies for the treatment of Alzheimer's disease and their mechanisms of action.
- Review the results of recent preclinical and clinical studies investigating the efficacy and safety of stem cell therapy in Alzheimer's disease.
- Discuss the challenges and future prospects of applying stem cell therapy as a therapeutic approach for Alzheimer's disease.

LITERATURE REVIEW

The search for disease-modifying therapies for Alzheimer's disease has directed significant efforts toward investigating the potential of stem cells. Several types of stem cells have been explored in preclinical models and early clinical trials. Mesenchymal stem cells (MSCs), derived from bone marrow, adipose tissue, or umbilical cord, are one of the most studied types due to their ease of procurement, capacity for in vitro expansion, and immunomodulatory and neurotrophic properties (Riester et al., 2020). In vitro studies have shown that MSCs can reduce Aβ production and tau protein hyperphosphorylation.

In animal models of AD, the administration of CTMs has been shown to improve cognitive function, reduce Aβ deposition and reactive gliosis, and promote neurogenesis (Zhang et al., 2021). The mechanisms underlying these effects include the secretion of neurotrophic growth factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), as well as the modulation of the inflammatory response through the secretion of immunomodulatory cytokines (Alzheimer's Association, 2020).

Phase I and II clinical trials with MSCs in AD patients have demonstrated safety and tolerability, with some studies reporting signs of cognitive and functional improvement (Kim et al., 2020). However, the heterogeneity of treatment protocols, including the route of administration (intravenous or intrathecal), cell dose, and type of MSC used, makes it difficult to directly compare results and draw definitive conclusions about clinical efficacy (Brzecka et al., 2022).

Another type of stem cell being investigated is the neural stem cell (NSC), which has the intrinsic ability to differentiate into neurons, astrocytes, and oligodendrocytes, the main cell types of the central nervous system. The administration of NSCs in animal models of AD has shown potential to repopulate damaged brain areas and improve cognitive function (Park et al., 2023). However, obtaining and controlling the differentiation of NSCs in vivo poses significant challenges for their clinical application.

Induced pluripotent stem cells (iPSCs) represent a promising source of cells for cell therapy in AD. iPSCs are adult cells reprogrammed to a pluripotent state, with the ability to differentiate into any cell type in the body, including neurons. iPSC technology offers the possibility of generating patient-specific neurons, minimizing the risk of immune rejection (Yagi et al., 2019). Recent studies have used neurons derived from iPSCs from AD patients to model the disease in vitro and test new therapies (Penney et al., 2020).

Cerebral microcirculation plays a crucial role in the pathogenesis of AD, and vascular dysfunction contributes to Aβ deposition and neurodegeneration. Endothelial progenitor cells (EPCs), a type of stem cell that differentiates into endothelial cells, have shown potential to restore vascular function in the brains of AD animal models, improving blood flow and Aβ removal (Kim et al., 2020).

Stem cells can be administered in different ways, including intravenous and intrathecal administration and direct injection into the

brain parenchyma. The route of administration can influence the biodistribution of the cells, their survival, and their ability to exert therapeutic effects in the brain (Boltze et al., 2021).

Despite significant progress in preclinical and clinical research, stem cell therapy for AD still faces important challenges. Standardization of treatment protocols, optimization of the route of administration and cell dose, understanding of mechanisms of action in vivo, and assessment of long-term safety are crucial aspects that need to be addressed in future studies (Trounson et al., 2022).

Translational research, which seeks to transfer basic research findings to clinical application, is essential for the advancement of stem cell therapy in AD. Collaboration between basic scientists, clinicians, and surgeons is critical to overcoming challenges and developing effective and safe therapies for this devastating neurodegenerative disease (Boltze et al., 2021).

Tissue engineering and the use of biomaterials can aid in the delivery and survival of stem cells in the brain, creating microenvironments that favor their differentiation and integration. The combination of stem cell therapy with other therapeutic approaches, such as immunotherapy and gene therapy, also represents a promising area of research (Riester et al., 2020).

The personalization of stem cell therapy, considering the individual characteristics of each patient, such as disease stage, genetic profile, and immune response, can optimize therapeutic outcomes. The use of iPSCs derived from the patient themselves represents an important step in this direction (Penney et al., 2020).

The ethics and regulation of stem cell therapy in neurodegenerative diseases are crucial aspects that must be considered to ensure patient safety and well-being, as well as the integrity of scientific research (Trounson et al., 2022).

METHODOLOGY

This scientific article consisted of an integrative review of the literature, focusing on studies published between January 2019 and April 2025. The bibliographic search was performed in the PubMed, Scopus, and Web of Science databases, using the following keywords: "Alzheimer's disease," "stem cell therapy," "mesenchymal stem cells," "neural stem cells," "induced pluripotent stem cells," "clinical trials," and "preclinical studies." Original articles, systematic reviews, and meta-analyses addressing the application of stem cell therapy in the treatment of Alzheimer's disease were included. The selected articles were evaluated for their relevance, methodological rigor, and quality of evidence presented. The information was synthesized and organized according to the specific objectives of this article, following ABNT standards for citations and references.

DISCUSSION

Stem cell therapy is emerging as a promising therapeutic approach for Alzheimer's disease, with the potential to go beyond the symptomatic relief offered by current therapies. The ability of stem cells to modulate neuroinflammation, secrete neurotrophic factors, and, in some cases, replace lost neuronal cells represents a significant advance in the search for disease-modifying treatments.

Preclinical studies in animal models of AD have consistently demonstrated the beneficial effects of stem cell therapy in improving cognitive function and reducing disease pathology. The administration of different types of stem cells, mainly MSCs, has resulted in a decrease in Aβ deposition, tau protein hyperphosphorylation, and glial inflammation, in addition to promoting neurogenesis in brain areas relevant to memory and learning.

Phase I and II clinical trials in AD patients have demonstrated the safety and tolerability of stem cell therapy. Although some studies have reported encouraging signs of cognitive and functional improvement, the heterogeneity of treatment protocols and the small number of participants in some trials limit the ability to draw definitive conclusions about clinical efficacy.

The choice of stem cell type, route of administration, cell dose, and optimal timing for therapeutic intervention are critical factors that need to be optimized in future studies. Understanding the mechanisms of action of stem cells in vivo and identifying biomarkers that can predict treatment response are essential for the development of personalized and effective therapies.

Translational research plays a key role in overcoming challenges and transferring basic research findings to clinical application. Multidisciplinary collaboration between scientists, clinicians, and surgeons is crucial for the advancement of stem cell therapy in AD.

Tissue engineering and the use of biomaterials may offer solutions to improve the delivery, survival, and integration of stem cells in the brain. Combining stem cell therapy with other therapeutic approaches, such as immunotherapy and gene therapy, also represents a promising area for the development of more effective combination therapies.

The personalization of stem cell therapy, through the use of iPSCs derived from the patient themselves, can minimize the risk of immune rejection and optimize therapeutic outcomes. However, the costs and complexity of large-scale iPSC production still pose challenges for its widespread clinical application.

The ethical and regulatory aspects of stem cell therapy in neurodegenerative diseases must be carefully considered to ensure patient safety and well-being and the integrity of scientific research. Transparency in the disclosure of results and adherence to strict ethical standards are fundamental to building public confidence in stem cell therapy.

PARTIAL RESULTS

A review of the scientific literature published between 2019 and 2025 reveals growing interest and investment in stem cell therapy as a potential therapeutic approach for Alzheimer's disease. Most preclinical studies demonstrate positive effects of stem cells in reducing disease pathology and improving cognitive function in animal models. Initial clinical trials in AD patients indicate the safety and tolerability of stem cell therapy, with some studies reporting signs of clinical improvement.

However, the heterogeneity of treatment protocols and the need for well-controlled phase III clinical studies are evident to confirm the efficacy of stem cell therapy in Alzheimer's disease and determine the ideal treatment protocols . Translational research remains essential to overcome challenges and advance the development of this promising therapeutic approach.

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