A Systematic Approach to Treatment-Associated Mesenchymal Stem Cells in Alzheimer's Disease

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Abstract: Human neurological disorders such as Alzheimer's disease (AD), are caused by neuron loss in the central nervous system, affecting memory, learning, and is the most common cause of dementia in the elderly. Currently, the use of mesenchymal stem cell (MSC)-based technologies and therapies have become the focus of research and investigations to treat AD, due to the diverse benefits on various cellular mechanisms such as neural cell replacement and cell modulations performed in clinical trials on animal subjects, thus MSC cell therapy becomes a promising and efficient alternative therapy for the development of a reliable therapeutic tool for AD in humans. We describe through review the potential use of mesenchymal stem cells for AD treatment. This is a review, following PRISMA rules for systematic reviews. MSCs therapy has been presented as a strategy for the replacement or regeneration of neural cells for AD patients. The pre-clinical results observed are recent in MSC-based therapies, therefore, few human clinical trials are in progress, recommending more clinical human trials with MSCs for the discovery and revolution of AD, since, there is still no cure and the number of people with AD has increased in recent years.

Keywords: Mesenchymal Stem Cells, Alzheimer Disease, Clinical Trials, Infusion, Dementia.

1. INTRODUCTION

Alzheimer's is an incurable neurodegenerative disease; over time, it exhibits slow and progressive cognitive deterioration and synaptic damage, leading to deteriorated mental function. It affects mainly the elderly, with dementia in 50 to 70% of cases [1]. Due to the disease's significant impact on the elderly, this pathology has been one of the biggest health problems in medical practice [2].

Alzheimer's disease (AD) clinical manifestations are impaired learning, language, cognition, short-term memory, progressing to forgetfulness of past events, confusion, behavioral disorders, and body function deterioration [3]. It is noted that the early damage of AD occurs primarily in the entorhinal cortex, hippocampus, basal prosencephalon, and especially the cholinergic neuron degeneration [4].

Studies evidence that the main responsible for AD in the Central Nervous System (CNS) are accumulation and aggregation of β-amyloid plaques composed of peptides and neurofibrillary tangles (NFTs), leading to neuronal loss, vascular damage, and dementia [5]. NFTs are intraneural filament deposits composed mainly of hyper phosphorylated Tau protein, a microtubule-stabilizing protein that maintains neuronal cell structure and axonal transport. The disruption of neuronal circuitry and synaptic loss in the human cortex and hippocampus contribute to the decline of cognitive development in AD [6].

Regarding the treatment, it is observed several clinical trials, research, immunotherapies and drugs used for treatment, but they could not find a cure [7,8]. However, discovered symptomatic treatments currently used, such as cholinesterase and N-Methyl-D-aspartate (NMDA) receptor antagonists [9]. Noteworthy is memantine, an antagonist used in dementia in the moderate to severe stages of AD. The drug is a non-competitive voltage-dependent NMDA receptor antagonist that acts by reducing glutaminergic excitotoxicity [10]. It is worth mentioning memantine's adverse reactions in phase 2 studies by Jarvis and Figgitt [11]. The authors report side effects in patients with diarrhea, dizziness, headache, insomnia,

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restlessness and fatigue. For Zemek [12], memantine use combined with acetylcholinesterase inhibitors is an excellent prognostic for slowing the dementia progression. Still, even though the drug treatment effects are quite critical, it should be added that AD patients' daily care is considered costly in emotional and economic aspects. The drugs available to treat AD are expensive and focus only on symptom relief [13].

Due to these circumstances, the scientific literature suggests the use of cell therapy for AD. It is emphasized that pluripotent stem cells (PSCs) and gene-modified cells started to be used in the search for innovative and effective treatment since they can continuously form, renovate or differentiate into many cell types of the body. The continuous new cell generation ensures physiological conditions and repair mechanisms after injuries or diseases in some circumstances. In the case of the CNS, it does not recover quickly after extensive degenerative events. Brain transplant therapies by stem cells have significantly been investigated. Different lines have been explored, such as embryonic stem cells, neural stem cells, and mesenchymal stem cells [14].

Mesenchymal stem cells (MSCs), reported as the study's subject, are cells capable of engrafting into the brain and can differentiate after in situ transplantation into neurons and neuroglia [15]. The neural differentiation of MSCs is identified by their ability to stimulate neural progenitor neurogenesis and neural cell survival by expressing neurotrophic factors [16]. Besides, transplantation of MSCs into the CNS inhibits apoptosis and supports neural cells' neurogenesis [17]. Thus, MSCs are suggested for the treatment of neurodegenerative disease [18,19].

Given the circumstance of AD improper treatments and recent cell therapy breakthroughs, the study aimed to describe the potential use of MSCs to treat AD through a systematic review.

2. METHODS

2.1. Study Design

A systematic review methodology was chosen for the MSCs scientific investigation related to the treatment of AD. MeSH adopted the research strategy through the keywords: Mesenchymal Stem Cells;

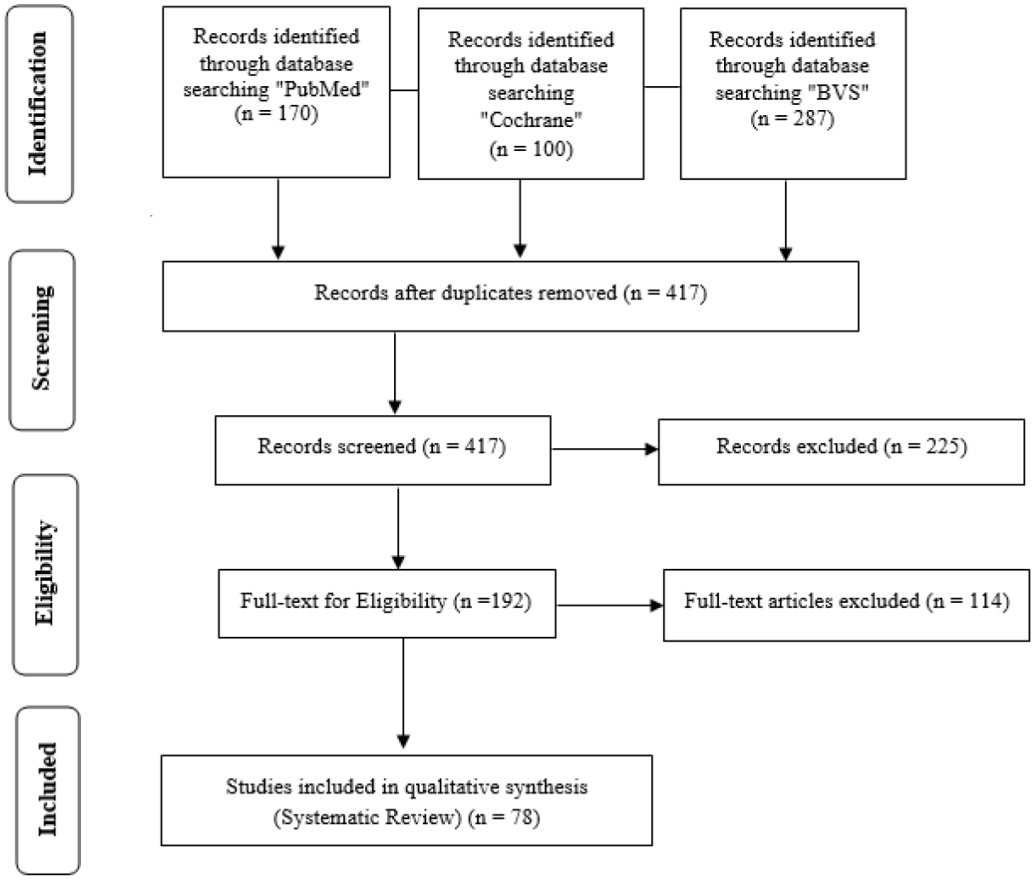

Figure 1: Flowchart.

Alzheimer Disease; Clinical Trials; Infusion; Dementia. This research was performed from January 2020 to February 2021. A total of 557 studies were then compared and submitted to eligibility analysis. In the end, 78 studies were selected according to PRISMA rules for systematic reviews (Figure **1**) (Transparent reports of systematic reviews and meta-analyses - HTTP: //www.prisma-statement.org/).

2.2. Databases and Research Methodology

The PubMed, VHL and Cochrane Library databases were investigated for the literature review. Also, a keyword combination using Boolean operators "AND" and "OR" was used. The papers and abstracts were examined. After searching for the terms in MeSH, clinical trial information of patients treated with MSCs was obtained from Clinical Trials Gov (https://clinicaltrials.gov/).

2.3. Study Selection and Bias Risk Assessment

Full-text articles were selected, studies wrote in English, titles and abstracts containing the topic "mesenchymal stem cells used in neurodegenerative or Alzheimer's disease treatment" were considered. Ten independent reviewers performed the research. Data extraction was performed by reviewers 1, 2, 8 and 9 and thoroughly reviewed by reviewers 3, 4, 5 and 6. The researchers (7 and 10) decided upon some issues, made the final decision on selecting the papers, and conducted the final review of the study. The Cochrane instrument was adopted to assess the quality of such studies [20].

3. LITERATURE REVIEW AND DISCUSSION

3.1. Alzheimer's Disease Pathogenesis

AD has mutations in the β-amyloid precursor protein genes, PSEN1 and PSEN2, each encoding their respective proteins [21,22]. The distinguishing characteristic of AD is the extracellular β-amyloid (Aβ) protein accretion in senile plaques, followed by intracellular neurofibrillary tangle clustering of abnormally hyperphosphorylated Tau proteins [23-25], causing severe cellular burden resulting in neuronal damage [26]. It is highlighted that Tau is an intracellular microtubule-associated protein within neurons and is vital for structural support and axonal transportation. When hyperphosphorylated, it causes microtubule collapse and clumping in NFTs. The other significant issue is the amyloid precursor protein cleavage by β-secretase and γ-secretase, which leads to extracellular buildup and agglomeration of Aβ fragments, visible as amyloid plaques in the AD brain [27,28]. Importantly, amyloid plaques first appear in the cerebral frontal cortex and then spread throughout the CNS cortical region, ultimately causing neuronal dysfunction [29]. Bonda *et al*. [26] report that oxidative distress is also a prominent factor for AD, and amyloid plaques and NFTs may adapt to high oxidative distress. Furthermore, it is notable that in addition to the plaques and NFTs involvement, age and genetics are also risk factors for AD development [5]. For Wyse *et al*. [30], the decreased levels of acetylcholine, acetylcholinesterase and acetyltransferase in the hippocampus and neocortex and reduced levels of neurons in the cholinergic nuclei of the basal prosencephalon are the reasons for the cholinergic hypothesis of the disease.

3.2. Main MSCs Mechanisms Used in AD

MSCs therapy is more advantageous and less invasive when administered intravenously; moreover, it reaches the CNS after crossing the blood-brain barrier, has low tumorigenicity, and alters the immune response profile [31,32]. Thus, MSCs have attracted particular attention in the AD treatment due to their excellent accessibility, simple handling, extensively studied properties and wide range of differentiation potential [33,34].

The beneficial MSCs effects seem to be mediated by their secreting factors, which stimulate proliferation, differentiation, and neurogenic niche survival [32,35-41]. Studies suggest that anti-inflammatory and immunomodulatory properties contribute to recovery, which involves many cytokines [37-39,42,43].

Bone marrow-derived MSCs (BMMSCs) are also important to mention. BMMSCs have been investigated further [44] and earn their immunomodulatory capacity through the soluble release factors, including IL-6, IL-10, TGF-β, and PGE2 [45-47]. They are known to inhibit the function of monocyte-derived dendritic cells and alter the natural killer cell [48,49]. Besides this therapy, adipose tissue is a good MSCs source. Adipose-derived mesenchymal stem cells (AdMSCs) can differentiate into neuron-like cells and astrocytes [50]. They appear to share a common Stemness transcriptional profile with BMMSCs [51,52] and secrete neurotrophic agents [53-58]. MSCs, also can be umbilical cord-derived (UCMSCs) and differentiate into neuron-like cells. UCMSCs are investigated in an AD mice model [59], and a suggested action

mechanism is the activation of M2-like microglia [42,60]. Due to these characteristics, MSCs have stood out in the scientific community. Furthermore, they exhibit a great proliferative potential to migrate, integrate and differentiate into neural cells [61-63].

Bali *et al*. [64] reported the therapeutic effects of MSCs, pointing out neuroprotection by secreted agents, neuron regeneration, immunomodulatory effects on the cells responsible for the disease development, as well as the proliferation of endogenous cells.

In the research by Cui *et al*. [65], administration of MSCs was observed in APP/PS1 AD mice. The authors report that there was the secretion of miR-21-enriched exosomes, increasing the mice's memory capacity and decreased Aβ plaque depositions. Furthermore, another paper has shown activin A released from MSCs in coculture of human MSCs with neural cells derived from the subventricular area of 5XFAD mice. The therapy caused the neural cells to develop and grow [66].

Another relevant data is that the MSCs manipulation produces promising results increasing the MSCs effects on the neural tissue, and the MSCs increase neurogenesis and the neural progenitor cells differentiation into mature neurons, augmenting the Wnt pathway [32]. The authors describe that neurogenesis occurred in the subgranular zone of the hippocampus dentate gyrus, acting as an endogenous repair mechanism in AD. Exosomes and microvesicles released from modified MSCs are enhanced in agents of interest to boost treatment effects. Overexpression of Aβ-degrading enzymes and/or negative regulation of secretive enzymes relating to Aβ formation with transfection of different RNAs may help improve disease symptoms [67]. Furthermore, Brn-4 protein in MSCs can inhibit Aβ build-up in the brain, but the presence of miR-937 prevents the mRNA translation of Brn-4 into protein [68,69].

According to Delbeuck *et al*. [4], there is synapse reduction in the CNS and consequently, neuronal loss; thus, one of the main mechanisms through which the strength and number of synapses are regulated is through the release of neurotrophin activity, reduced early in the disease progression, influencing learning and memory capacity. Therefore, MSCs can produce various neurotrophins, capable of enhancing brain plasticity and improving neuronal survival. According to Terry *et al*. [70], human mesenchymal stem cell transplantation (hMSCs) may be a valid option to alleviate AD symptoms.

3.3. Clinical Trials

In 2019 [71], human allogeneic umbilical cord hMSCs were used in phase 1 of a clinical trial in six patients suffering from mild to moderate AD, in order to assess its safety, potential side effects, and efficacy of intravenous hMSC infusions in patients suffering from AD (Clinicaltrials.gov, NCT04040348). It is believed that the stem cell infusion method might be safe. However, the clinical effect of the method on the pathogenesis of AD needs to be further verified. Thus, this research advocates a secondary outcome measure, observing cognitive function over time by the Alzheimer's Disease-Cognitive Assessment Scale, the Folstein test that includes the Mini-Mental State Examination. In addition, serum levels of biomarkers and inflammatory within 65 weeks such as interleukin-6, neurofilament light, β-amyloid 40 and 42 in pg/mL. Serum apolipoprotein E levels assessed in mg/dL; PRA values, verifying plasma renin activity in serum blood in ng/mL per hour; serum Tau protein level in blood in ng/L and cerebrospinal fluid biomarker levels, and also assessing the change in hippocampal volume by MRI brain volumetric studies.

Another study with allogeneic hMSCs was observed on 40 patients suffering from AD [72]. The study is in phase 2, aiming to evaluate the safety and tolerability of hMSCs manufactured by Stemedica versus placebo, administered intravenously in individuals suffering from mild to moderate dementia due to AD, and to observe the efficacy of hMSCs as evidenced by neurological, functioning, and psychiatric parameters (Clinicaltrials.gov NCT02833792). The study provides primary result measurements, referring to the administration safety and adverse patient effects, as well as the efficacy guided by secondary result measurements. Thus, hMSCs are an alternative source of multipotent self-renewing cells, and several previous studies show that they have both paracrine and autocrine activity in damaged tissues, including the brain. Indeed, they secrete a variety of cytokines and growth factors having anti-inflammatory agents, as well as immunomodulatory property such as vascular endothelial growth factor, hepatocyte growth factor, among others, that are involved in angiogenesis, healing, and repair processes [73].

In the Kim *et al*. [74] study, the authors stereotactically transplanted human umbilical cord-

Table 1: Ongoing Clinical Trials of Mesenchymal Stem Cells in Patients Suffering from Alzheimer's Disease, at Clinicaltrials.gov

Name and start (date) of the study	Country	Title	n[1]	Age	Cell / Dosage	Placebo	Measurement Results	
							Primary	Secondary
NCT04040348 October 2019	United States	Alzheimer's Disease Stem Cells Multiple Infusions	6	50-85 years old	hMSCs / 100 million cell infusion (4x)	No	TE-SAEs	ADAS-Cog; MMSE of Folstein test; GDS; ADRQL; IL-6; NfL; Aβ40; Aβ42; ApoE; PRA; Tau protein CSF; change in hippocampal volume
NCT02833792 June 2016	United States	Allogeneic Human Mesenchymal Stem Cells for Alzheimer's Diseas	40	50-85 years old	hMSCs / 1.5 million cell infusion per kilogram (1x)	Yes	Safety of aMBMC administration	Efficacy of aMBMC administration
NCT02672306 October 2017	China	Safety and Exploratory Efficacy Study of UCMSCs in Patients With Alzheimer's Disease (SEESUPAD)	16	50-85 years old	UCMSCs / NA	Yes	ADAS-Cog	ADAS-Cog; MMSE; CIBIC-plus; ADCS-ADL; NPI; changes in AD Biomarkers;
NCT03691909 September 2018	United States	A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-AdMSCs) for the Treatment of Rheumatoid Arthritis (HB-AdMSCs)	15	18-65 years old	HB-AdMSCs / Cell infusion (1x)	No	Incidence of Treatment-Emergent Adverse Events [Safety and Tolerability]	TNF; IL-6; CRP; ESR; levels of Joint Count 66/68 (# joints - tender and swollen) during the trial

(n[1]) [1]Number of total participants; (hMSCs) human Mesenchymal Stem Cells; (UCMSCs) Human Umbilical Cord-derived Mesenchymal Stem Cells; (TE-SAEs) Treatment-Emergent Serious Adverse Events; (ADAS-Cog) Alzheimer's Disease Assessment Scale-Cognitive; (MMSE) Mini Mental State Examination; (GDS) Geriatric Depression Scale; (ADRQL) Alzheimer's Disease Related Quality of Life; (IL-6) Interleukin-6; (NfL) Neurofilament light; (Aβ40) Amyloid Beta 40; (Aβ42) Amyloid Beta 42; (ApoE) Apolipoprotein E; (PRA) Plasma Renin Activity; (CSF) Cerebrospinal Fluid; (CIBIC-plus) Clinician's Interview-Based Impression of Change; (ADCS-ADL) Alzheimer's Disease Cooperative Study Activities of Daily Living; (NPI) Neuropsychiatric Inventory; (NA) Not available; (HB-AdMSCs) Hope Biosciences - Adipose-derived Mesenchymal Stem Cells; (TNF) Tumor Necrosis Factor; (CRP) C-reactive protein; (ESR) erithrosedimentation rate.

derived MSCs into the hippocampus and the precuneus. The authors report that the patients had no severe adverse events, and no significant clinical effect on the cognitive decline was observed. Another relevant aspect is that cell therapy using induced MSCs and PSCs shows great treatment potential for various neurodegenerative diseases, such as Parkinson's and AD. Results have shown favorable effects regarding inflammation modulation. Moreover, they may promote other beneficial effects, such as neuronal growth.

Several clinical trials with MSCs are in progress on AD patients (Table **1**); however, phase 1 and 2 results have not yet been published. Preclinical trials of BMMSCs in animals suffering from AD have achieved good results and are adequate to start clinical trials on humans suffering from AD. Intravenous infusion is the optimal procedure to implant stem cells. Moreover, umbilical cord stem cells are the most commonly used cell source in AD treatment [75]. For Shruster *et al*. [76], stem cell therapy has been suggested as a strategy to replace damaged circuits and is able to restore learning and memory abilities by reconstructing damaged cholinergic neurons in AD patients. Thus, neural transplantation may provide an alternative treatment for AD towards a permanent cure.

It has been observed several studies on various stem cell sources and manipulation methods that can be used to safely generate functional cells, so MSC-based therapy may be one of the most favorable and efficient solutions for AD.

3.4. Future Perspectives

Approved drug therapies for Alzheimer's disease are intended to prevent the disease progression and have effects to alleviate symptoms [30,77]. However, stem cells may have a significant impact on future strategies for the treatment of AD, due to studies indicating MSCs as an appropriate strategy to promote endogenous neurogenesis in the AD subjects' brains [32,78].

4. CONCLUSION

MSCs therapy, a growing area of research, is very important for clinical medicine and has the potential to expand our understanding of neurodegenerative diseases, especially AD. The MSCs infusion and transplantation method may be a safe and effective approach for treating AD, bringing valuable improvements in disability and psychological behaviors. However, more clinical trials with MSCs in AD patients are expected, in addition to deciphering the genetic differences that predispose an individual to develop this dysfunction.

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POTENTIAL CONFLICT OF INTEREST STATEMENT

The authors declare to have no conflict of interest.

REFERENCES

[1] Anand R, Gill KD, Mahdi AA. Therapeutics of Alzheimer's disease: past, present and future. Neuropharmacology 2014; 76 Pt A: 27-50. https://doi.org/10.1016/j.neuropharm.2013.07.004

[2] Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. Cell 2012. 148: 1204-1222. https://doi.org/10.1016/j.cell.2012.02.040

[3] Imtiaz B, Tolppanen AM, Kivipelto M, Soininen H. Future directions in Alzheimer's disease from risk factors to prevention. Biochem Pharmacol 2014; 88: 661-670. https://doi.org/10.1016/j.bcp.2014.01.003

[4] Delbeuck X, Van der Linden M, Collette F. Alzheimer's disease as a disconnection syndrome? Neuropsychol Rev 2003; 13: 79-92. https://doi.org/10.1023/a:1023832305702

[5] Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science 1992; 256: 184-185. https://doi.org/10.1126/science.1566067

[6] Paula VJR, Guimarães FM, Forlenza OV. The role of Tau protein in the pathophysiology of frontotemporal dementia. Rev Psiquiatr Clín 2009; 36: 197-202. https://doi.org/10.1590/S0101-60832009000500004

[7] Cirrito JR, Holtzman DM. Amyloid beta and Alzheimer disease therapeutics: the devil may be in the details. J Clin Invest 2003; 12: 321-323. https://doi.org/10.1172/JCI19420

[8] Courtney C, Farrell D, Gray R, *et al*. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004; 363; 2105-15. https://doi.org/10.1016/S0140-6736(04)16499-4

[9] Solomon B. Immunological approaches as therapy for Alzheimer's disease. Expert Opin Biol Ther 2020; 2: 907-17. https://doi.org/10.1517/14712598.2.8.907

[10] Kumar S. Memantine: pharmacological properties and clinical uses. Neurol India 2004; 52: 307-09. Available from: https://pubmed.ncbi.nlm.nih.gov/15472417/

[11] Jarvis B, Figgitt DP. Memantine. Drugs Aging 2003; 20: 465-76. https://doi.org/10.2165/00002512-200320060-00005

[12] Zemek F, Drtinova L, Nepovimova E, *et al*. Outcomes of Alzheimer's disease therapy with acetylcholinesterase inhibitors and memantine. Expert Opin Drug Saf 2014; 13: 759-774. https://doi.org/10.1517/14740338.2014.914168

[13] Edwards Iii GA, Gamez N, Escobedo G Jr, Calderon O, Moreno-Gonzalez I. Modifiable risk factors for Alzheimer's disease. Front Aging Neurosci 2019; 11: 146. https://doi.org/10.3389/fnagi.2019.00146

[14] Hass R, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. Cell Commun Signal 2011; 9: 12. https://doi.org/10.1186/1478-811X-9-12

[15] Zhang H, Huang Z, Xu Y, Zhang S. Differentiation and neurological benefit of the mesenchymal stem cells transplanted into the rat brain following intracerebral hemorrhage. Neurol Res 2006; 28. https://doi.org/104-112.10.1179/016164106X91960

[16] Crigler L, Robey RC, Asawachaicharn A, Gaupp D, Phinney DG. Human mesenchymal stem cell subpopulations express a variety of neuro-regulatory molecules and promote neuronal cell survival and neuritogenesis. Exp Neurol 2006; 198: 54-64. https://doi.org/10.1016/j.expneurol.2005.10.029

[17] Yoo SW, Kim SS, Lee SY, *et al*. Mesenchymal stem cells promote proliferation of endogenous neural stem cells and survival of newborn cells in a rat stroke model. Exp Mol Med 2008; 40: 387-397. https://doi.org/10.3858/emm.2008.40.4.387

[18] Hamada H, Kobune M, Nakamura K, *et al*. Mesenchymal stem cells (MSC) as therapeutic cytoreagents for gene therapy. Cancer Sci 2005; 96: 149-156. https://doi.org/10.1111/j.1349-7006.2005.00032.x

[19] Dezawa M. Systematic neuronal and muscle induction systems in bone marrow stromal cells: the potential for tissue reconstruction in neurodegenerative and muscle degenerative diseases. Med Mol Morphol 2008; 41: 14-19. https://doi.org/10.1007/s00795-007-0389-0

[20] Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), Cochrane handbook for systematic reviews of interventionsversion 5.2.0 (updated June2017), Cochrane, 2017. Available from: www.training.cochrane.org/handbook

[21] Zhan Y, Zheng H, Wang C, *et al*. A novel presenilin 1 mutation (F388L) identified in a Chinese family with early-onset Alzheimer's disease. Neurobiol Aging 2017; 50: 168.e1-168.e4. https://doi.org/10.1016/j.neurobiolaging.2016.10.010

[22] Filadi R, Pizzo P. Defective autophagy and Alzheimer's disease: is calcium the key? Neural Regen Res 2019; 14: 2081-2082. https://doi.org/10.4103/1673-5374.262584

[23] Xu X. Gamma-secretase catalyzes sequential cleavages of the AbetaPP transmembrane domain. J Alzheimers Dis 2009; 16: 211-224. https://doi.org/10.3233/JAD-2009-0957

[24] Chabrier MA, Cheng D, Castello NA, Green KN, LaFerla FM. Synergistic effects of amyloid-beta and wild-type human Tau on dendritic spine loss in a floxed double transgenic model of Alzheimer's disease. Neurobiol Dis 2014; 64: 107-117. https://doi.org/10.1016/j.nbd.2014.01.007

[25] Zhang FQ, Jiang JL, Zhang JT, Niu H, Fu XQ, Zeng LL. Current status and future prospects of stem cell therapy in Alzheimer's disease. Neural Regen Res 2020; 15: 242-250. https://doi.org/10.4103/1673-5374.265544

[26] Bonda DJ, Wang X, Lee HG, Smith MA, Perry G, Zhu X. Neuronal failure in Alzheimer's disease: a view through theoxidative stress looking-glass. Neurosci Bull 2014; 30: 243-252. https://doi.org/10.1007/s12264-013-1424-x

[27] Salloway S, Sperling R, Fox NC, *et al*. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014; 370: 322-333. https://doi.org/10.1056/NEJMoa1304839

[28] Duncan T, Valenzuela M. Alzheimer's disease, dementia, and stem cell therapy. Stem Cell Res Ther 2017; 8: 111. https://doi.org/10.1186/s13287-017-0567-5

[29] Palmer AM. Neuroprotective therapeutics for Alzheimer's disease: progress and prospects. Trends Pharmacol Sci 2011; 32: 141-147. https://doi.org/10.1016/j.tips.2010.12.007

[30] Wyse RD, Dunbar GL, Rossignol J. Use of genetically modified mesenchymal stem cells to treat neurodegenerative diseases. Int J Mol Sci 2014; 15: 1719-1745. https://doi.org/10.3390/ijms15021719

[31] Ra JC, Shin IS, Kim SH, *et al*. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. Stem Cells Dev 2011; 20: 1297-308. https://doi.org/10.1089/scd.2010.0466

[32] Oh SH, Kim HN, Park HJ, Shin JY, Lee PH. Mesenchymal stem cells increase hippocampal neurogenesis and neuronal differentiation by enhancing the Wnt signaling pathway in an Alzheimer's disease model. Cell Transplant 2015; 24: 1097-1109. https://doi.org/10.3727/096368914X679237

[33] Divya MS, Roshin GE, Divya TS, *et al*. Umbilical cord blood-derived mesenchymal stem cells consist of a unique population of progenitors co-expressing mesenchymal stem cell and neuronal markers capable of instantaneous neuronal differentiation. Stem Cell Res Ther 2012; 3: 57. https://doi.org/10.1186/scrt148

[34] Park D, Yang G, Bae DK, *et al*. Human adipose tissue-derived mesenchymal stem cells improve cognitive function and physical activity in ageing mice. J Neurosci Res 2013; 91: 660-670. https://doi.org/10.1002/jnr.23182

[35] Munoz JR, Stoutenger BR, Robinson AP, Spees JL, Prockop DJ. Human stem/progenitor cells from bone marrow promote neurogenesis of endogenous neural stem cells in the hippocampus of mice. Proc Natl Acad Sci U S A 2005; 102: 18171-18176. https://doi.org/10.1073/pnas.0508945102

[36] Zilka N, Zilkova M, Kazmerova Z, Sarissky M, Cigankova V, Novak M. Mesenchymal stem cells rescue the Alzheimer's disease cell model from cell death induced by misfolded truncated Tau. Neuroscience 2011; 193: 330-337. https://doi.org/10.1016/j.neuroscience.2011.06.088

[37] Kim JY, Kim DH, Kim JH, *et al*. Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-β plaques. Cell Death Differ 2012; 19: 680-691. https://doi.org/10.1038/cdd.2011.140

[38] Kim KS, Kim HS, Park JM, *et al*. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. Neurobiol Aging 2013; 34: 2408-2420. https://doi.org/10.1016/j.neurobiolaging.2013.03.029

[39] Yun H, Kim H, Park K, *et al*. Placenta-derived mesenchymal stem cells improve memory dysfunction in an A1–42-infused mouse model of Alzheimer's disease. Cell Death Dis 2013; 4: e958. https://doi.org/10.1038/cddis.2013.490

[40] Teixeira FG, Carvalho MM, Neves-Carvalho A, *et al*. Secretome of mesenchymal progenitors from the umbilical cord acts as modulator of neural/glial proliferation and differentiation. Stem Cell Rev Rep 2015; 11: 288-297. https://doi.org/10.1007/s12015-014-9576-2

[41] Naaldijk Y, Jäger C, Fabian C, *et al*. Effect of systemic transplantation of bone marrow-derived mesenchymal stem cells on neuropathology markers in APP/PS1 Alzheimer mice. Neuropathol Appl Neurobiol 2017; 43: 299-314. https://doi.org/10.1111/nan.12319

[42] Yang H, Xie Z, Wei L, *et al*. Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an AβPP/PS1 transgenic mouse model. Stem Cell Res Ther 2013; 4: 76. https://doi.org/10.1186/scrt227

[43] Kwak KA, Lee SP, Yang JY, Park YS. Current perspectives regarding stem cell-based therapy for Alzheimer's disease. Stem Cells Int 2018; 2018: 6392986. https://doi.org/10.1155/2018/6392986

[44] Li M, Guo K, Ikehara S. Stem cell treatment for Alzheimer's disease. Int J Mol Sci 2014; 15: 19226-19238. https://doi.org/10.3390/ijms151019226

[45] Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005; 105: 1815-1822. https://doi.org/10.1182/blood-2004-04-1559

[46] Beyth S, Borovsky Z, Mevorach D, *et al*. Human mesenchymal stem cells alter antigen-presenting cell maturation and induce T-cell unresponsiveness. Blood 2005; 105: 2214-2219. https://doi.org/10.1182/blood-2004-07-2921

[47] Ramasamy R, Fazekasova H, Lam EW, Soeiro I, Lombardi G, Dazzi F. Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. Transplantation 2007; 83: 71-76. https://doi.org/10.1097/01.tp.0000244572.24780.54

[48] Ryan JM, Barry F, Murphy JM, Mahon BP. Interferon-gamma does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells. Clin Exp Immunol 2007; 149: 353-363. https://doi.org/10.1111/j.1365-2249.2007.03422.x

[49] Sotiropoulou PA, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. Stem Cells 2006; 24: 74-85. https://doi.org/10.1634/stemcells.2004-0359

[50] Chen J, Tang YX, Liu YM, *et al*. Transplantation of adipose-derived stem cells is associated with neural differentiation and functional improvement in a rat model of intracerebral hemorrhage. CNS Neurosci Ther 2012; 18: 847-854. https://doi.org/10.1111/j.1755-5949.2012.00382.x

[51] Case J, Horvath TL, Ballas CB, March KL, Srour EF. *In vitro* clonal analysis of murine pluripotent stem cells isolated from skeletal muscle and adipose stromal cells. Exp Hematol 2008; 36: 224-234. https://doi.org/10.1016/j.exphem.2007.09.003

[52] Peroni D, Scambi I, Pasini A, *et al*. Stem molecular signature of adipose-derived stromal cells. Exp Cell Res 2008; 314: 603-615. https://doi.org/10.1016/j.yexcr.2007.10.007

[53] Gutiérrez-Fernández M, Rodríguez-Frutos B, Ramos-Cejudo J, *et al*. Effects of intravenous administration of allogenic bone marrow- and adipose tissue-derived mesenchymal stem cells on functional recovery and brain repair markers in experimental ischemic stroke. Stem Cell Res Ther 2013; 4: 11. https://doi.org/10.1186/scrt159

[54] Ikegame Y, Yamashita K, Hayashi S, *et al*. Comparison of mesenchymal stem cells from adipose tissue and bone marrow for ischemic stroke therapy. Cytotherapy 2011; 13: 675-685. https://doi.org/10.3109/14653249.2010.549122

[55] Leu S, Lin YC, Yuen CM, *et al*. Adipose-derived mesenchymal stem cells markedly attenuate brain infarct size and improve neurological function in rats. J Transl Med 2010; 8: 63. https://doi.org/10.1186/1479-5876-8-63

[56] Lu S, Lu C, Han Q, *et al*. Adipose-derived mesenchymal stem cells protect PC12 cells from glutamate excitotoxicity-induced apoptosis by upregulation of XIAP through PI3-K/Akt activation. Toxicology 2011; 279: 189-195. https://doi.org/10.1016/j.tox.2010.10.011

[57] Wei X, Zhao L, Zhong J, *et al*. Adipose stromal cells-secreted neuroprotective media against neuronal apoptosis. Neurosci Lett 2009; 462: 76-79. https://doi.org/10.1016/j.neulet.2009.06.054

[58] Yang KL, Lee JT, Pang CY, *et al*. Human adipose-derived stem cells for the treatment of intracerebral hemorrhage in rats via femoral intravenous injection. Cell Mol Biol Lett 2012; 17: 376-392. https://doi.org/10.2478/s11658-012-0016-5

[59] Kang JM, Yeon BK, Cho SJ, Suh YH. Stem cell therapy for Alzheimer's disease: a review of recent clinical trials. J Alzheimers Dis 2016; 54: 879-889. https://doi.org/10.3233/JAD-160406

[60] Darlington D, Deng J, Giunta B, *et al*. Multiple low-dose infusions of human umbilical cord blood cells improve cognitive impairments and reduce amyloid-β-associated neuropathology in Alzheimer mice. Stem Cells Dev 2013; 22: 412-421. https://doi.org/10.1089/scd.2012.0345

[61] Mendrone Jr A. Peripheral blood as a source of stem cells. Rev Bras Hematol Hemoter 2009; 31: 19-24. https://doi.org/10.1590/S1516-84842009005000026

[62] Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, Nolta JA. Mesenchymal stem cells for the treatment of neurodegenerative disease. Regen Med 2010; 5: 933-946. https://doi.org/10.2217/rme.10.72

[63] Fesharaki M, Razavi S, Ghasemi-Mobarakeh L, *et al*. Differentiation of human scalp adipose-derived mesenchymal stem cells into mature neural cells on electrospun nanofibrous scaffolds for nerve tissue engineering applications. Cell J 2018; 20: 168-176. https://doi.org/10.22074/cellj.2018.4898

[64] Bali P, Lahiri DK, Banik A, Nehru B, Anand A. Potential for stem cells therapy in Alzheimer's disease: do neurotrophic factors play critical role? Curr Alzheimer Res 2017; 14: 208-220. https://doi.org/10.2174/1567205013666160314145347

[65] Cui GH, Wu J, Mou FF, *et al*. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. FASEB J 2018; 32: 654-668. https://doi.org/10.1096/fj.201700600R

[66] Park SE, Lee J, Chang EH, *et al*. Activin A secreted by human mesenchymal stem cells induces neuronal development and neurite outgrowth in an *in vitro* model of Alzheimer's disease: neurogenesis induced by MSCs via activin A. Arch Pharm Res 2016; 39: 1171-1179. https://doi.org/10.1007/s12272-016-0799-4

[67] Liew LC, Katsuda T, Gailhouste L, Nakagama H, Ochiya T. Mesenchymal stem cell-derived extracellular vesicles: a glimmer of hope in treating Alzheimer's disease. Int Immunol 2017; 29: 11-19. https://doi.org/10.1093/intimm/dxx002

[68] Tan XF, Qin JB, Jin GH, *et al*. Effects of Brn-4 on the neuronal differentiation of neural stem cells derived from rat midbrain. Cell Biol Int 2010; 34: 877-882. https://doi.org/10.1042/CBI20100214

[69] Liu Z, Wang C, Wang X, Xu S. Therapeutic effects of transplantation of as-miR-937-expressing mesenchymal stem cells in murine model of Alzheimer's disease. Cell Physiol Biochem 2015; 37: 321-330. https://doi.org/10.1159/000430356

[70] Terry AV Jr, Buccafusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. J Pharmacol Exp Ther 2003; 306: 821-7. https://doi.org/10.1124/jpet.102.041616

[71] Baumel B. Alzheimer's disease stem cells multiple infusions. ClinicalTrials.gov 2019. Available from: https://clinicaltrials.gov/ct2/show/study/NCT04040348

[72] Santosh K. Allogeneic human mesenchymal stem cells for Alzheimer's disease. ClinicalTrials.gov 2016. Available from: https://clinicaltrials.gov/ct2/show/study/NCT02833792

[73] Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells 2007; 25: 2739-2749. https://doi.org/10.1634/stemcells.2007-0197

[74] Kim HJ, Seo SW, Chang JW, *et al*. Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: a phase 1 clinical trial. Alzheimers Dement (N Y) 2015; 1: 95-102. https://doi.org/10.1016/j.trci.2015.06.007

[75] Liu XY, Yang LP, Zhao L. Stem cell therapy for Alzheimer's disease. World J Stem Cells 2020; 12: 787-802. https://doi.org/10.4252/wjsc.v12.i8.787

[76] Shruster A, Melamed E, Offen D. Neurogenesis in the aged and neurodegenerative brain. Apoptosis 2010; 15: 1415-1421. https://doi.org/10.1007/s10495-010-0491-y

[77] Salem AM, Ahmed HH, Atta HM, Ghazy MA, Aglan HA. Potential of bone marrow mesenchymal stem cells in management of Alzheimer's disease in female rats. Cell Biol Int 2014; 38: 1367-1383. https://doi.org/10.1002/cbin.10331

[78] Sadatpoor SO, Salehi Z, Rahban D, Salimi A. Manipulated mesenchymal stem cells applications in neurodegenerative diseases. Int J Stem Cells 2020; 13: 24-45. https://doi.org/10.15283/ijsc19031

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