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REVIEW ARTICLE

A Review on Alzheimer's disease and mesenchymal stem cell therapy

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A B S T R A C T

Alzheimer's disease (AD) is a progressive neurological ailment that manifests as difficulties in completing everyday activities, disorientation, and memory loss. Several innovative drug therapies have failed in clinical trials because they cannot stop or encourage the regeneration of injured brain cells. Furthermore, many medications only give symptomatic alleviation. As a result, a better knowledge of stem cell therapy's process might lead to new and effective treatments for this severe disease. Recent preclinical evidence suggests that stem cells can be used to treat or model AD. The mechanisms of stem cell based therapies for AD include stem cell mediated neuroprotection and trophic actions, antiamyloidogenesis, beneficial immune modulation, and the replacement of the lost neurons. This study examined the present status of many Mesenchymal stem cell-based therapeutics in AD pathogenesis. Furthermore, we have emphasized current clinical research that may be useful in treating Alzheimer's disease.

Keywords: *Alzheimer's disease, Beta amyloid, Neuroinflammation, Stem cells*

Introduction

Alzheimer's disease (AD) is one of the leading cause of age-related dementia, which is characterized by gradual loss of memory and inability to learn. AD is caused by the accumulation of β-amyloid (Aβ) peptides, leading to loss of functioning neurons and decreased synaptic activity.[1, 2] The World Health Organization adopted a global action plan on dementia and intimated societies regarding the increase in its prevalence.[3] According to WHO, the number of patients with dementia has increased to 50 million,[3] worldwide, and this number is believed to double by 2040.[4] AD is a neurodegenerative disease, causing more significant memory impairment and having a higher disability rate than aging, putting an increased burden on the healthcare system and caregivers.[5, 6] AD is also associated with higher mortality due to the number of causes, including neuronal death and cerebral atrophy.

Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, are multipotent stem cells that can self-replicate and undergo multiline-age differentiation.[7, 8] Due to this reason, MSCs are considered

to be one of the most promising aspects to treat neurodegeneration.[9] Moreover, other properties of MSCs, such as immunomodulation, high biosafety, and role in stimulation of endogenous neural precursors, make them ideal candidates for treating neurodegenerative diseases, including AD.[9] Moreover, MSCs can be easily derived from a variety of sources in humans, such as adipose tissue, bone marrow, umbilical cord or amniotic fluid. Previous attempts of treatment with stem cells in AD mainly focused on replacing impaired neurons.[8] MSCs have the potential to slow down neurodegeneration and repair damaged neural tissue, which makes them an alternative approach to treat AD.[8] These roles are accomplished by the secretion of neurotrophins and regulatory factors involved in angiogenesis.[10-12] The role of MSCs in immunomodulation, migratory capability and regeneration has been confirmed in various disease models, including diabetic nephropathy, myocardial infarction, brain injury and dermatitis.[13-16] In recent years, several *in-vivo* studies on AD animal models have showed that MSCs were effective in altering disease pathology and improving cognitive function.[17-18]

Pathogenesis of Alzheimer's disease

The pathology of AD is very complex. The cholinergic theory, the amyloid cascade hypothesis, and the tau propagation hypothesis have all been presented to characterize the genesis of AD based on observable clinical and neuropathological symptoms.[19-20] However, an accumulation of phosphorylated tau aggregation and neuroinflammation is AD's most notable and distinguishing characteristic.[21, 22] The amyloid cascade theory states that AD development's most critical triggering events are A precursor protein (APP) metabolism and A42 buildup.[23] According to this theory, the buildup of A peptide is to blame for the loss of synapses and neuronal cell death.[24, 25] Furthermore, A may lodge around the brain's tiny blood vessels, leading to the formation of cerebral amyloid angiopathy (CAA), a prevalent neuropathological disorder that most often affects AD patients and is thought to be caused by a failure of A clearance.[26] All other reasons, such as tau pathology and neuroinflammation, have been proven to eventually lead to a buildup.[27] Figure 1 shows how the tau hypothesis links AD pathology to hyper phosphorylation and intracellular deposition of NFTs of the micro tubular protein tau.[28] It also shows that the illness may be accelerated by spreading the abnormal type of tau protein from one cell to the next. Few studies connecting both concepts show that amyloid plaque aggregation causes the activation of different kinases, resulting in hyper phosphorylation of the tau protein.[29]

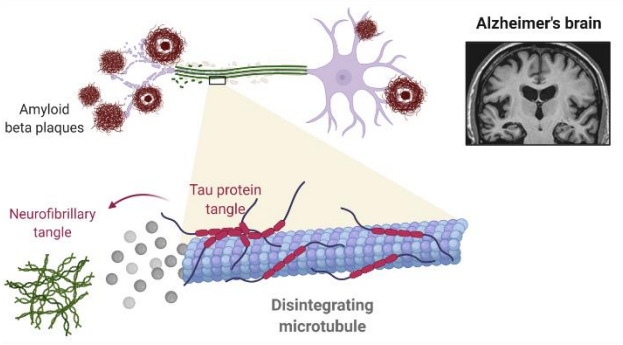

Figure 1: Pathophysiology of Alzheimer's Current treatment of AD

One of the characteristic features of AD is loss of functional neurons and synaptic activity, leading to memory impairment, loss of motor control, and dementia.[30] One practical approach to treat this is by increasing the concentration of acetylcholine (Ach) in the synaptic cleft, which is possible by inhibition of the Acetylcholinesterase (AChE) enzyme.[31] Based on this mechanism, four drugs are currently used for the treatment of AD, including rivastigmine, donepezil galantamine and memantine.

The treatment of AD capable of curing underlying pathology has not been developed, which results in an inevitable increase in the number of AD patients. Both preclinical and clinical studies have provided a great deal of evidence that the accumulation of Aβ controls many downstream processes of AD.[32-35] Therefore, most studies on drug development in AD targeted decreased Aβ production or enhanced clearance. However, thus far, these approaches have failed in later phases of almost all clinical trials. Therefore, the hour needs to develop effective AD therapies to tackle this global health problem.

Pre-clinical studies

We summarized preclinical studies in Table 1 and possible mechanism of actions shown in Figure 2. Research found that treating APP/PS 1 transgenic mice with human amniotic mesenchymal stem cells (hAM-MSCs) reduced deposition and improved memory and that these benefits were linked to an increase of activated

microglia and control of neuroinflammation as shown in Table 1.[36] The stimulation of the cell survival signaling system by bone marrow-derived mesenchymal stem (BM-MSCs) reduced A-induced apoptotic cell death in primary cultured hippocampus neurons. These anti-apoptotic properties of BM-MSCs were also shown in an acutely generated Alzheimer's disease mouse model created by administering A intrahippocampal. Furthermore, in the *in-vivo* model, BM-MSCs reduced A-induced oxidative stress and spatial memory impairment, indicating that BM-MSCs mitigate A-induced neurotoxicity and cognitive decline by decreasing apoptotic cell death and oxidative stress in the hippocampus.[37] Another research found that BM-MSCs may find their way into wounded brains and increase the number of positive cells for choline acetyltransferase (ChAT), survivin, and selective AD indicator-1 (seladin-1) nestin gene expression. According to histopathological analysis, BM-MSCs may eliminate beta-amyloid plaques from the hippocampus.[38] According to research, Engrafted MSCs expressing exogenous (C-X3-C motif) ligand 1 (CX3CL1) decreased the production of the inflammatory cytokine TNF- and enhanced synapse-related protein expression. Compared to a control group, transplantation of MSCs containing CX3CL1 and Wnt3a (CX3CL1-Wnt3a-MSC) dramatically reduced learning and memory deficits. The prevention of microglial neurotoxicity and stimulation of hippocampus neurogenesis were linked to improved neurobehavioral capabilities in APP/PS1 mice treated with CX3CL1-Wnt3a-MSC. Transplantation of CX3CL1-Wnt3a-MSC also inhibited the activity of glycogen synthase kinase 3 beta through regulating phosphoinositide 3-kinase/activated protein kinase B (PI3K/AKT) signaling (GSK3b).[39] Ding, M., et al. demonstrated that injecting human umbilical cord mesenchymal stem cells (hucMSC-exosomes) into these mice might help remove A deposition and cure cognitive dysfunctions. Furthermore, it was shown that injecting hucMSC-exosomes into mice's brains might control microglia activity, reducing neuroinflammation. Pro-inflammatory cytokines were higher in mice's peripheral blood and brains, whereas anti-inflammatory cytokines were lower.[40] Research found that transplanting amyloid precursor protein (APP) and presenilin1 (PS1) double-transgenic mice with human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSC) dramatically enhanced spatial learning and memory deterioration. Furthermore, in hUCB-MSC transplanted APP/PS1 animals, amyloid-peptide (A) deposition, -secretase 1 (BACE-1) levels, and tau hyper-phosphorylation were significantly decreased.[18] Another research found that conditioned medium from adipose tissue mesenchymal stem cells (ATSC-CM) lowered the inflammatory markers IL-1 and TNF-. By lowering TLR expression, ATSC-CM alleviated memory deficits, decreased beta amyloid production, boosted neuron survival, and reduced inflammation. [41] MSC transplantation successfully alleviates learning impairments in the 5xFAD mouse model, according to the findings of the research, and MSCs have a clear influence on Ab42 levels in the brains of 5xFAD mice.[42] Behavioral modifications decreased the expression of APP, BACE1, and Ab and the activity of b-secretase and c-secretase, according to the findings of research in which placenta-derived mesenchymal stem cells (PD-MSCs) were transplanted into Ab1–42-infused mice. Furthermore, the transplantation of PD-MSCs reduced the activation of glial cells and the production of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Furthermore, we discovered that in Ab1–42-infused animals, PD-MSCs inhibited the production of inflammatory cytokines, reduced neuronal cell death, and enhanced neuronal cell development from neural progenitor cells.[43] Glycoprotein of the rabies virus (RVG-tagged) after being delivered intravenously, exosomes generated from mesenchymal stem cells showed enhanced targeting to the cortex and hippocampus, reduced plaque formation and A levels, and reduced astrocyte activation. According to the Morris water maze test, brain focused exosomes produced from MSCs were superior than unmodified exosomes in improving cognitive performance in APP/PS1 mice.[44] Human placenta amniotic membrane-derived mesenchymal stem cells (hAMMSCs) were administered intravenously into C57BL/6J-APP transgenic mice in another investigation. hAMMSCs improved spatial learning and memory function and were linked to a reduction in the number of amyloid plaques in the brain.[45] According to previous studies research, intracerebral transplantation of human menstrual blood-derived stem cells (MenSCs) significantly enhanced the spatial learning and memory of APP/PS1 mice. In APP/PS1 mice, MenSCs also dramatically decreased amyloid plaques and reduced tau hyper-phosphorylation.

Surprisingly, intracerebral transplantation of MenSCs enhanced multiple A degrading enzymes and controlled a panel of proinflammatory cytokines associated with an altered microglial phenotype, suggesting that MenSCs in the brains of APP/PS1 mice had an anti-inflammatory and degrading effect.[46] Several studies we found that showed significant results to attenuates Alzheimer's disease by several mechanisms like decrease Aβ deposition, decrease oxidative stress and inflammatory mediators and also improve cognitive decline as shown in Figure 2. These stem cell may be a therapeutic agent for treatment of Alzheimer's disease.

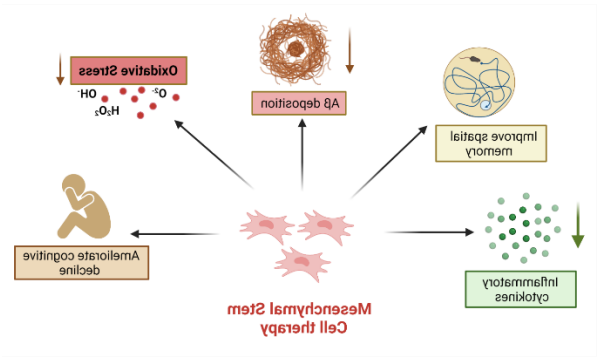

Figure 2: Effects of Mesenchymal stem cells

Table 1: Preclinical studies

Stem cells	Study model	Mechanism	Reference
Human amniotic mesenchymal stem cells	APP/PS 1 transgenic mice	Decrease Aβ deposition and improve memory	[36]
Bone marrow-derived mesenchymal stem cells	Primary cultured hippocampal neurons	Ameliorate Aβ-induced apoptotic cell death.	[37]
Bone marrow-derived mesenchymal stem cells	Sprague–Dawley rats	Remove beta-amyloid plaques from hippocampus	[38]
Engrafted MSCs carrying exogenous ligand 1	APP/PS1 mice	Transplantation of MSCs carrying CX3CL1 significantly improve the learning and memory impairment	[39]
Human umbilical cord mesenchymal stem cells containing exosomes	AβPPswe/PS1dE9 double-transgenic mice	Improved cognitive dysfunction and help to clear Aβ deposition in these mice	[40]
Human umbilical cord blood-derived mesenchymal stem cells	APP and (PS1) double-transgenic mice	hUCB-MSC improved spatial learning and memory decline	[18]
Adipose tissue mesenchymal stem cells conditioned medium (ATSC-CM)	Wistar rats	ATSC-CM) reduced IL-1β and TNF-α as inflammation markers	[41]
Adult mesenchymal cells	5xFAD mouse model	The results indicate that MSC transplants effectively reduce learning deficits in the 5xFAD mouse model and demonstrate a clear impact of MSCs on the levels of Ab42 in the brains of 5xFAD mice	[42]
placenta derived mesenchymal stem cells	Ab1–42-infused mice	Attenuated the expression of APP, BACE1, and Ab, as well as the activity of b-secretase and c-secretase	[43]
RVG-tagged Mesenchymal stem cells derived exosomes	APP/PS1 double transgenic mice	RVG-tagged Mesenchymal stem cells derived exosomes decrease Aβ levels, and activation of astrocytes was reduced.	[44]

Clinical studies

To date, many clinical studies have been conducted to study the safety, clinical efficacy, and tolerability of MSCs in patients with AD. However, most of the trials are ongoing with no published results. A systematic search was performed to identify the clinical trials, both completed and ongoing. 16 clinical trials, registered on Clinical Trials.gov, were retrieved, which are summarized in Table 2.

Table 2: Characteristics of clinical trials conducted on mesenchymal stem cells therapy in Alzheimer's disease

NCT, *status*	Country, year	Study design	Study phase	Stem cell type	No. of participants (n)	Follow up period	Interventions	Study outcomes
NCT01297218 & NCT01696591 (extended follow-up study), *completed*	Republic of Korea, 2011	Open label, single center, single arm	1	hUCB-MSCs	9	Initial: 12 weeks Extended: 24 months	Low dose: 2.5 × 10^5 cells/5 µL per entry site High dose: 5.0 × 10^5 cells/5 µL per entry site	The administration of hUCB-MSCs into hippocampi showed no serious ADEs during 24-month follow-up period. Moreover, administration was feasible and well tolerated among AD patients [49]
NCT02054208, *completed*	Republic of Korea, 2014	Double-blind, Single-center, two arm	1/2a	hUCB-MSCs	45 Stage 1: 9 Stage 2: 36	24 weeks	Low dose: Intraventricular administration of 1 x 10^7cells/2mL. High dose: Intraventricular administration of 3 x 10^7cells/2mL. Placebo: 2ml normal saline	Repeated administrations of hUCB-MSCs were well tolerated and feasible among AD patients. However, three serious ADEs, including fever, nausea and vomiting were seen in two participants that required extended hospitalization [52]
NCT03117738, *completed*	USA, 2017	Randomized, double-blind, placebo-controlled, two arm	1/2	Autologous AD-MSCs	21	30 weeks 52 weeks	Drug: AstroStem Dose: 2 × 108 AD-MSCs Placebo: Saline with 30% auto-serum	Not yet published results [53]
NCT02600130, *completed*	USA, 2016	Randomized, double-blinded, placebo-controlled, three arm	1	LMSCs	25	52 weeks	Cohort 1: Peripheral IV infusion of 20 million LMSCs Cohort 2: Peripheral IV infusion of 100 million LMSCs Cohort 3: Placebo (Plasmalyte A and 1% human serum albumin)	Not yet published results [56]
NCT03172117 (extended follow-up study for NCT02054208), *ongoing*	Republic of Korea, 2017	Double-blind, Single-center, two arm	1/2a	hUCB-MSCs	45 Stage 1: 9 Stage 2: 36	24 weeks	Low dose: Intraventricular administration of 1 x 10^7cells/2mL. High dose: Intraventricular administration of 3 x 10^7cells/2mL. Placebo: 2ml normal saline	Not yet published results [52]
NCT04228666, *withdrawn*	USA, 2020	Open label, non-randomized, single arm	1/2a	Autologous AD-MSCs	0	52 weeks	Intravenous administration of HB-adMSCs Dose: 2 x 10^8 cells.	Not available [58]
NCT04855955, *available*	USA, 2021	Single patient, clinical study	N/A	AD-MSCs	1	N/A	Drug: AD-MSCs	Not yet published results [55]

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NCT02833792, *ongoing*	USA, 2016	Randomized, single-blind, placebo-controlled, multi-center, crossover study	2a	hMSCs	40	18 months	Drug: hMSCs Placebo: Ringer lactate solution	Not yet published results [57]
NCT04040348, *ongoing*	USA, 2019	Open label, single center, single arm	1	hMSCs	6	52 weeks	100 million cells allogeneic hMSC	Not yet published results [58]
NCT04388982, *ongoing*	China, 2021	Open label, single center, single arm	1/2	Allogenic adipose MSCs-Exos	9	48 weeks	Low dose: 5μg MSCs-Exos Mild dose: 10μg MSCs-Exos High dose: 20μg MSCs-Exos	Not yet published results [59]
NCT02899091, *ongoing*	Republic of Korea, 2016	Randomized, Double-blind, Placebo-controlled, two arm	1/2a	CB-AC-02: A human placenta derived MSC candidate	24	48 weeks	CB-AC-02, 2.0 x 10^8 cells Placebo	Not yet published results [60]
NCT04684602, *ongoing*	USA, 2020	Non-randomized, open label, multicenter	1/2	hUCB-MSCs	5000	12 months	Drug: PrimePro™/ PrimeMSK™ injection	Not yet published results [61]
NCT04482413, *ongoing*		Randomized, double blind, active controlled, two arm	2b	AD-MSCs	80	28 weeks	Drug: IV AstroStem containing 2 x 10^8 cells/20 mL of saline with 30% auto-serum Placebo: 5 mg of Donepezil	Not yet published results [54]
NCT01547689, *unknown status*	China, 2012	Open label, single center, self-controlled single arm	1/2	hUCB-MSCs	30	10 weeks	IV infusion containing 20 million cells （0.5×10^6 UC-MSCs per kg ）	Not yet published results [50]
NCT02672306, *unknown status*	China, 2017	Randomized, double blind, two arm	1/2	hUCB-MSCs	16	48 weeks	hUC-MSCs 20 million cells per subject (0.5×10^6 UCMSCs per kg) Placebo: IV normal saline	Not yet published results [62]

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A two-staged, phase 1 clinical trial has been conducted on 9 patients with dementia associated with AD.[47] The trial evaluated the safety and tolerability of hUCB-MSCs, manufactured as NEUROTSTEM®-AD. During stage 1 of the trial, the patients were followed up for 12 weeks, post-hUCB-MSCs administration into the hippocampi to identify the acute adverse drug events (ADEs). Pain in the surgical site (n=9) and headache (n=4) were the most common ADEs found. Other common ADEs included headache (n=3) and dizziness (n=3). A stage 2, an extended follow-up study was performed on the patients who completed stage 1 of the trial. During the 24-month follow-up period, no patient reported any serious ADE. Hence, the trial showed that the hUMB-MSCs administration was safe and well-tolerated among patients with AD with no dose-limiting toxicity (DLT).[47-49] However, the efficacy of hUMB-MSCs had not been confirmed due to study limitations, including the limited number of participants and the absence of a control group.[47-49] Therefore, future clinical trials with active comparator or placebo-controlled group and extended follow-up are needed to establish the efficacy of this treatment.

To overcome the limitations of the previous trials,[47,48] another phase 1/2a trial was conducted in the Republic of Korea.[50] The primary purpose of this trial was to study DLT and exploratory efficacy of NEUROSTEM®-AD (hUCB-MSCs) in patients with mild to moderate AD. This two-arm trial studied the effect of repeated IV injections of hUCB-MSCs in the treatment group compared to the placebo-controlled group in two stages. The first stage of trial utilized hUCB-MSCs dose-escalation, followed by randomized and multiple-dose parallel design in the second stage. Fever was the most common ADE reported after IV administration of hUCB-MSCs. Other acute ADEs included headache, nausea and vomiting, which were all subsided within 2 days. However, three participants required extended hospitalization due to ADEs in the low dose group. Finally, five out of 9 participants completed 3-year comprehensive observational study with no other reported ADEs. According to Kim et al., the results of this trial were similar to the phase 1 study conducted in 2011 (NCT01297218,[49] and repeated hUCB-MSCs administrations into lateral ventricle were found safe and tolerated among patients with AD.[51, 52] The phase 2a trial is still ongoing and the clinical efficacy of hUCB-MSCs administration can only be established after extended follow-up and upon completion of this phase.[52]

A combined phase 1/2 clinical trial was conducted to study the safety, and clinical efficacy of adipose tissue-derived MSCs (AD-MSCs) manufactured as AstroStem.[53] 21 participants were included in the trial, which were randomly assigned to treatment and placebo group. Nine repeated IV administrations of AstroStem were given to the participants in the treatment group every 2 weeks. Later, the participants were followed up for 30 and 52 weeks to evaluate treatment-related ADEs and the clinical efficacy of the treatment. Pulmonary embolism, stage IV squamous cell carcinoma, and diarrhea were the most common reported ADEs. Other ADEs included fatigue, weight loss, dysphagia, glaucoma, and dehydration. The Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog) score of 5.9 (6.8) was reported in AstroStem group as compared to 3 (5.4) in the placebo group. [53] A similar randomized, 2-arm, phase 2b study using the same treatment (AstroStem) is undergoing. [54] This study is conducted with 2 treatment arms to evaluate the effectiveness of IV AstroStem compared to donepezil; a cholinesterase inhibitor used to improve mental function. The patients will be followed up at 28 and 40 weeks to study primary and secondary outcomes.[54] A single patient, clinical study focusing on assessing AD-MSCs therapy based on disease severity is registered on Clinical Trials.gov.[55]

To study the safety and clinical effectiveness of Longeveron MSCs (LMSCs), a phase 1, randomized, placebo-controlled clinical trial has been conducted among AD patients.[56] This 3-arm study recruited 25 participants, which were randomly assigned (2:2:1) to the low dose, high dose, and placebo groups. The participants were followed up at regular intervals up to 52 weeks. Although the study has been completed, the results are yet to be published.[56] A phase 2a clinical trial utilizing allogenic human MSCs is ongoing.[57] This study's primary and secondary objectives are to assess the safety and efficacy of hMSCs, respectively. A total of 40 participants will be recruited and randomly assigned to treatment and placebo cohorts (20 patients each). The treatment cohort will receive a drug containing hMSCs, while the placebo cohort will receive ringer lactate solution. Independent review boards will monitor the safety and efficacy.[57] Another phase 1 study,

started in 2019 on hMSCs treatment among AD patients is not yet completed.[58] To assess the effectiveness of hMSCs in the treatment of AD, the results of these ongoing studies will be vital.

Conclusion

Due to their easy isolation and better differentiation potential, MSCs are the most widely used stem cells in human clinical trials. However, the promising results of MSCs therapy in animal models have not yet been successfully translated in the human clinical trials. Although few clinical trials with published results demonstrated safety and tolerability of MSCs therapy in humans during the 24-month follow-up period, but the ADRs associated with this therapy are still a matter of question. Extended, large scale clinical trials are needed to further confirm the safety and feasibility of MSCs therapy. Moreover, the efficacy and therapeutic benefits of this therapy are still to be established. Most of the clinical trials were conducted in patients with mild to moderate AD and hence, the clear picture can only be obtained by the inclusion of patients with severe AD in the later phases of clinical trials. Having said that, it is evident that the MSCs therapy has a great potential to alter disease pathology, as shown during pre-clinical studies. As most of the clinical trials are in early phases, it is possible, with better and vigorous research, that MSCs can become the most effective therapy against AD..

References

1. Alzheimer's Association. 2012 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2012; 8(2):131-68. DOI: https://doi.org/10.1016/j.jalz.2012.02.001
2. Gauthier S, Scheltens P, Cummings J, editors. Alzheimer's Disease and Related Disorders. CRC Press; 2005.
3. WHO, Dementia. 2021. Available from :URL: https://www.who.int/news-room/fact-sheets/detail/dementia
4. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. Lancet 2016; 388:505-517. DOI: https://doi.org/10.1016/S0140-6736(15)01124-1
5. Joe E, Ringman JM. Cognitive symptoms of Alzheimer's disease: clinical management and prevention. Bri Med J. 2019; 367. DOI: https://doi.org/10.1136/bmj.l6217
6. Alzheimer's , 2020 Alzheimer's disease facts and figures. Alzheimer's & Dementia, 202; 16(3)391-460. DOI: https://doi.org/10.1002/alz.12068
7. Soria Lopez, J.A., H.M. González, and G.C. Léger, Chapter 13 - Alzheimer's disease, in Handbook of Clinical Neurology, Elsevier. 2019. 231-255.
8. Chakari-Khiavi F, Dolati S, Chakari-Khiavi A, Abbaszadeh H, Aghebati-Maleki L, Pourlak T, et al. Prospects for the application of mesenchymal stem cells in Alzheimer's disease treatment. Life Sci. 2019; 231:116564. DOI: https://doi.org/10.1016/j.lfs.2019.116564
9. Mukhamedshina YO, Gracheva OA, Mukhutdinova DM, Chelyshev YA, Rizvanov AA. Mesenchymal stem cells and the neuronal microenvironment in the area of spinal cord injury. Neural Regen Res. 2019; 14(2):227. DOI: https://doi.org/10.4103/1673-5374.244778
10. Yuan O, Lin C, Wagner J, Anderson JS, Archard JA, Deng P, et al., Exosomes Derived from Human Primed Mesenchymal Stem Cells Induce Mitosis and Potentiate Growth Factor Secretion. Stem Cells Dev, 2019; 28(6):398-409. DOI: https://doi.org/10.1089/scd.2018.0200
11. Deng P, Anderson JD, Yu AS, Annett G, Fink KD, Nolta JA. Engineered BDNF producing cells as a potential treatment for neurologic disease. Expert Opin Biol Ther. 2016; 16(8):1025-33. DOI: https://doi.org/10.1080/14712598.2016.1183641
12. Showalter MR, Wancewicz B, Fiehn O, Archard JA, Clayton S, et al. Primed mesenchymal stem cells package exosomes with metabolites associated with immunomodulation. Biochem Biophys Res Commun. 2019; 512(4):729-35. DOI: https://doi.org/10.1016/j.bbrc.2019.03.119
13. Park BW, Jung SH, Das S, Lee SM, Park JH, Kim H, et al. In vivo priming of human mesenchymal stem cells with hepatocyte growth factor–engineered mesenchymal stem cells promotes therapeutic potential for cardiac repair. Sci Advances. 2020; 6(13):eaay6994. DOI: https://doi.org/10.1126/sciadv.aay69
14. Park HH, Lee S, Yu Y, Yoo SM, Baek SY, Jung N, et al. TGF-β secreted by human umbilical cord blood-derived mesenchymal stem cells ameliorates atopic dermatitis by inhibiting secretion of TNF-α and IgE. Stem Cells. 2020; 38(7):904-16. DOI: https://doi.org/10.1002/stem.3183
15. Ge X, Han Z, Chen F, Wang H, Zhang B, Jiang R, et al. MiR-21 alleviates secondary blood–brain barrier damage after traumatic brain injury in rats. Brain Res. 2015; 1603:150-7. DOI: https://doi.org/10.1016/j.brainres.2015.01.009
16. Zhang F, Wang C, Wen X, Chen Y, Mao R, Cui D, et al. Mesenchymal stem cells alleviate rat diabetic nephropathy by suppressing CD103+ DCs-mediated CD8+ T cell responses. J Cell Mol Med. 2020; 24(10):5817-31. DOI: https://doi.org/10.1111/jcmm.15250
17. Lee JK, Jin HK, Endo S, Schuchman EH, Carter JE, Bae JS. Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses. Stem Cells. 2010; 28(2):329-43. DOI: https://doi.org/10.1002/stem.277
18. Lee HJ, Lee JK, Lee H, Carter JE, Chang JW, Oh W, et al. Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. Neurobiol Aging. 2012; 33(3):588-602. DOI: https://doi.org/10.1016/j.neurobiolaging.2010.03.024
19. Li H, Liu CC, Zheng H, Huang TY. Amyloid, tau, pathogen infection and antimicrobial protection in Alzheimer's disease–conformist, nonconformist, and realistic prospects for AD pathogenesis. Transl Neurodegener. 2018; 7(1):1-6.

DOI: https://doi.org/10.1186/s40035-018-0139-3
20. Karran E, Mercken M, Strooper BD. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nat Rev Drug Discov. 2011; 10(9):698-712.
DOI: https://doi.org/10.1038/nrd3505
21. Murphy MP, LeVine III H. Alzheimer's disease and the amyloid-β peptide. J Alzheimer's Dis. 2010; 19(1):311-23.
DOI: https://doi.org/10.3233/JAD-2010-1221
22. Jha NK, Jha SK, Kar R, Nand P, Swati K, Goswami VK. Nuclear factor-kappa β as a therapeutic target for Alzheimer's disease. J Neurochem. 2019; 150(2):113-37.
DOI: https://doi.org/10.1111/jnc.14687
23. Tanzi RE, Bertram L. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell. 2005; 120(4):545-55.
DOI: https://doi.org/10.1016/j.cell.2005.02.008
24. Kumar P, Jha NK, Jha SK, Ramani K, Ambasta RK. Tau phosphorylation, molecular chaperones, and ubiquitin E3 ligase: clinical relevance in Alzheimer's disease. J Alzheimers Dis. 2015; 43(2):341-61.
DOI: https://doi.org/10.3233/JAD-140933
25. Sardar Sinha M, Ansell-Schultz A, Civitelli L, Hildesjö C, Larsson M, Lannfelt L, et al. Alzheimer's disease pathology propagation by exosomes containing toxic amyloid-beta oligomers. Acta Neuropathol. 2018; 136(1):41-56.
DOI: https://doi.org/10.1007/s00401-018-1868-1
26. Brenowitz WD, Nelson PT, Besser LM, Heller KB, Kukull WA. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer's disease and other cerebrovascular neuropathologic changes. Neurobiol Aging. 2015; 36(10):2702-8.
DOI: https://doi.org/10.1016/j.neurobiolaging.2015.06.028
27. Prasanna P, Rathee S, Rahul V, Mandal D, Chandra Goud MS, Yadav P, et al. Microfluidic platforms to unravel mysteries of Alzheimer's Disease: How far have we come?. Life. 2021; 11(10):1022.
DOI: https://doi.org/10.3390/life11101022
28. You Y, Perkins A, Cisternas P, Muñoz B, Taylor X, et al. Tau as a mediator of neurotoxicity associated to cerebral amyloid angiopathy. Acta Neuropathol Com. 2019; 7(1):1-5.
DOI: https://doi.org/10.1186/s40478-019-0680-z
29. Huang HC, Jiang ZF. Accumulated amyloid-β peptide and hyperphosphorylated tau protein: relationship and links in Alzheimer's disease. J. Alzheimer's Dis. 2009; 16(1):15-27.
DOI: https://doi.org/10.3233/JAD-2009-0960
30. Harvey RA, Ferrier DR. Lippincott's illustrated reviews. Pharmacology. 2005;56.
31. Golan DE, Tashjian AH, Armstrong EJ, editors. Principles of pharmacology: the pathophysiologic basis of drug therapy. Lippincott Williams & Wilkins; 2011.
32. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297(5580):353-6.
DOI: https://doi.org/10.1126/science.107299
33. Brouwers N, Sleegers K, Van Broeckhoven C. Molecular genetics of Alzheimer's disease: an update. Ann Med. 2008; 40(8):562-83.
DOI: https://doi.org/10.1080/07853890802186905
34. Blurton-Jones M, LaFerla FM. Pathways by which Aβ facilitates tau pathology. Curr Alzheimer Res. 2006; 3(5):437-48.
DOI: https://doi.org/10.2174/156720506779025242
35. Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction. Neuron. 2003; 39(3):409-21.
DOI: https://doi.org/10.1016/S0896-6273(03)00434-3
36. Zheng XY, Wan QQ, Zheng CY, Zhou HL, Dong XY, Deng QS, et al. Amniotic mesenchymal stem cells decrease Aβ deposition and improve memory in APP/PS1 transgenic mice. Neurochem Res.. 2017; 42(8):2191-207.
DOI: https://doi.org/10.1007/s11064-017-2226-8
37. K Lee J, K Jin H, Bae JS. Bone marrow-derived mesenchymal stem cells attenuate amyloid β-induced memory impairment and apoptosis by inhibiting neuronal cell death. Current Alzheimer Res. 2010; 7(6):540-8.
DOI: https://doi.org/10.2174/156720510792231739
38. 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(12):1367-83.
DOI: https://doi.org/10.1002/cbin.10331
39. Li A, Zhao J, Fan C, Zhu L, Huang C, Li Q, et al. Delivery of exogenous proteins by mesenchymal stem cells attenuates early memory deficits in a murine model of Alzheimer's disease. Neurobiol Aging. 2020; 86:81-91.
DOI: https://doi.org/10.1016/j.neurobiolaging.2019.10.012
40. Ding M, Shen Y, Wang P, Xie Z, Xu S, Zhu Z, et al. Exosomes isolated from human umbilical cord mesenchymal stem cells alleviate neuroinflammation and reduce amyloid-beta deposition by modulating microglial activation in Alzheimer's disease. Neurochem Res. 2018; 43(11):2165-77.
DOI: https://doi.org/10.1007/s11064-018-2641-5
41. Mehrabadi S, Motevaseli E, Sadr SS, Moradbeygi K. Hypoxic-conditioned medium from adipose tissue mesenchymal stem cells improved neuroinflammation through alternation of toll like receptor (TLR) 2 and TLR4 expression in model of Alzheimer's disease rats. Behav Brain Res. 2020; 379:112362.
DOI: https://doi.org/10.1016/j.bbr.2019.112362
42. Matchynski-Franks JJ, Pappas C, Rossignol J, Reinke T, Fink K, Crane A, Twite A, et al. Mesenchymal stem cells as treatment for behavioral deficits and neuropathology in the 5xFAD mouse model of Alzheimer's disease. Cell Transplant. 2016; 25(4):687-703.
DOI: https://doi.org/10.3727/096368916X690818
43. Yun HM, Kim HS, Park KR, Shin JM, Kang AR, Song S, et al. Placenta-derived mesenchymal stem cells improve memory dysfunction in an Aβ1–42-infused mouse model of Alzheimer's disease. Cell Death Differ. 2013; 4(12):e958.
DOI: https://doi.org/10.1038/cddis.2013.490
44. Cui GH, Guo HD, Li H, Zhai Y, Gong ZB, Wu J, et al. RVG-modified exosomes derived from mesenchymal stem cells rescue memory deficits by regulating inflammatory responses in a mouse model of Alzheimer's disease. Immun Ageing. 2019; 16(1):1-2.
DOI: https://doi.org/10.1186/s12979-019-0150-2
45. Jiao H, Shi K, Zhang W, Yang L, Yang L, Guan F, et al. Therapeutic potential of human amniotic membrane-derived mesenchymal stem cells in APP transgenic mice. Oncol Lett. 2016; 12(3):1877-83.
DOI: https://doi.org/10.3892/ol.2016.4857

46. Zhao Y, Chen X, Wu Y, Wang Y, Li Y, Xiang C. Transplantation of human menstrual blood-derived mesenchymal stem cells alleviates Alzheimer's disease-like pathology in APP/PS1 transgenic mice. Front Mol Neurosci. 2018:140. DOI: https://doi.org/10.3389/fnmol.2018.00140
47. The Safety and The Efficacy Evaluation of NEUROSTEM®-AD in Patients With Alzheimer's Disease. 2011 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT01297218.
48. The Long-Term Safety and Efficacy Follow-Up Study of Subjects Who Completed the Phase I Clinical Trial of Neurostem®-AD. 2012 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT01696591.
49. Kim HJ, Seo SW, Chang JW, Lee JI, Kim CH, Chin J, 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. Alzheimer's & Dementia: Transl Res Clin Interv 2015; 1(2):95-102. DOI: https://doi.org/10.1016/j.trci.2015.06.007
50. Safety and Efficiency of Umbilical Cord-derived Mesenchymal Stem Cells(UC-MSC) in Patients With Alzheimer's Disease (SEMAD). 2012 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT01547689.
51. Safety and Exploratory Efficacy Study of NEUROSTEM® Versus Placebo in Patients With Alzheimer's Disease. 2014 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT02054208.
52. Jeong H, Kim OJ, Oh SH, Lee S, Reum Lee HA, Lee KO, et al. Extracellular Vesicles Released from Neprilysin Gene-Modified Human Umbilical Cord-Derived Mesenchymal Stem Cell Enhance Therapeutic Effects in an Alzheimer's Disease Animal Model. Stem Cells Int. 2021; 2021. DOI: https://doi.org/10.1155/2021/5548630
53. A Study to Evaluate the Safety and Efficacy of AstroStem in Treatment of Alzheimer's Disease. 2017 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT03117738.
54. Study to Evaluate the Safety and Efficacy of AstroStem in Treatment of Alzheimer's Disease. 2021 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT04482413.
55. Autologous Human Adipose-Derived Mesenchymal Stem Cells in Alzheimer's Disease. 2021 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/record/NCT04855955.
56. Lomecel-B Infusion Versus Placebo in Patients With Alzheimer's Disease. 2016 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT02600130.
57. Allogeneic Human Mesenchymal Stem Cells for Alzheimer's Disease. 2016 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT02833792.
58. A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) for the Treatment of Alzheimer's Disease. 2020 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT04228666.
59. The Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients With Alzheimer's Disease. 2021 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT04388982.
60. Evaluation of the Safety and Potential Therapeutic Effects After Intravenous Transplantation of CB-AC-02 in Patients With Alzheimer's Disease. 2016 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT02899091.
61. Mesenchymal Stem Cells for the Treatment of Various Chronic and Acute Conditions. 2020 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT04684602.
62. Safety and Exploratory Efficacy Study of UCMSCs in Patients With Alzheimer's Disease (SEESUPAD). 2017 [cited 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT02672306..