Stem Cell Therapy: A Great Leap Forward in Alzheimer's Treatment

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder and one of the substantial socioeconomic and medical calamities of our time. It is characterized by progressive neurodegenerative disorder featuring dementia and cognitive impairment. It is caused by synaptic failure and the excessive aggregation of two types of misfolded proteins, namely, amyloid-β (Aβ) and tau protein. AD is a complex disease that affects neurons in different parts of the brain. The treatment of AD is difficult with currently available medications and treatment approaches due to inadequate knowledge of its etiology and versatile nature of its pathology. Stem cell holds a promising approach to regenerate the tissue systems and has been explored in various studies of neurodegenerative disorders and provides great research opportunity. Stem cell research-based therapies emit a new hope for AD treatment as a regenerative approach. This chapter focuses on recent advances in stem cell therapies according to cell types and pathophysiology of AD along with human clinical trials of stem cell therapies for the AD.

Keywords

Stem cell · Alzheimer's disease · Amyloid precursor protein

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9.1 Introduction

In 1907, Alois Alzheimer first reported Alzheimer's disease (AD) (Choi et al. 2014a, b). However, 60–80% of dementia cases are caused by AD, characterized by memory loss and cognitive disorder which affects the quality of life. AD is a progressive neurodegenerative disorder, where the symptom of dementia is gradually elevated over a number of years. In the early stages of the AD, mild memory loss occurs, but in the later stage, the patients lose the ability to converse and the ability to respond to their environment. AD severely affects the human health, as it is the sixth leading cause of mortality in the United States. The average life duration of Alzheimer's patient is 8 years after the AD's symptoms become noticeable, but survival range can vary from 4 to 20 years, depending on the age, lifestyle, diet, and health condition. In 2010, the estimated economic burden of AD's treatment was $172 billion in the United States and $604 billion worldwide that will be tripled by 2050 (Wimo et al. 2010). In India, approximately 3.7 million people were suffering from AD, and this number is expected to double by the year 2030 (Alzheimer's and Related Disorders Society of India (ARDSI) 2010).

Two types of AD are reported: (i) familial and (ii) sporadic. Familial AD is caused by an autosomal genetic mutation in the genes responsible for Aβ plaques. This genetic mutation is related to the amyloid precursor protein (APP), presenilin-1 (PSEN-1), and presenilin-2 (PSEN-2). However, familial AD is rare in prevalence and less than 5% of familial AD cases are reported (Selkoe 2001; Prasher et al. 1998; Rosen et al. 2010; Marchetti and Marie 2011; Genin et al. 2011). Sporadic AD is ubiquitous in nature and caused by the interaction between genetic profile and environmental factors (Duncan and Valenzuela 2017; Persson et al. 2014). The cardinal pathologic features of AD include the aggregation of two types of misfolded proteins (amyloid beta and tau) (Allen et al. 2011; Eckman and Eckman 2007). Amyloid beta (Aβ) protein is a pathological cleavage product of the APP. Aβ protein accumulates into plaques and minor oligomers. Mutations in APP genes or in APP processing pathway genes are linked to the inherited familial AD (Huang and Mucke 2012). Tau is a microtubule-associated protein that accumulates intracellularly as neurofibrillary tangles (NFTs) which is a pathological feature closely linked with cognitive decline in the AD. However, mutations in tau protein lead to cause frontotemporal dementia, not AD (Huang and Mucke 2012).

A rising accord inside the field is that treatment of AD patients with currently available medicines comes late, which is the result of vital neuronal cell loss within the brain. To combat these problems, human embryonic stem cell (hESC)/induced pluripotent stem cell (iPSC)/mesenchymal stem cell (MSC)-derived neural cells have been suggested as powerful replacement therapy for AD (Fig. 9.1). In this chapter, the current state of research in the etiology of AD, probable challenges, and techniques for using stem cell-based treatment will be discussed briefly. Recent studies that have developed promising cell types and clinical investigations that could be used to combat this detrimental disease in the future will also be highlighted.

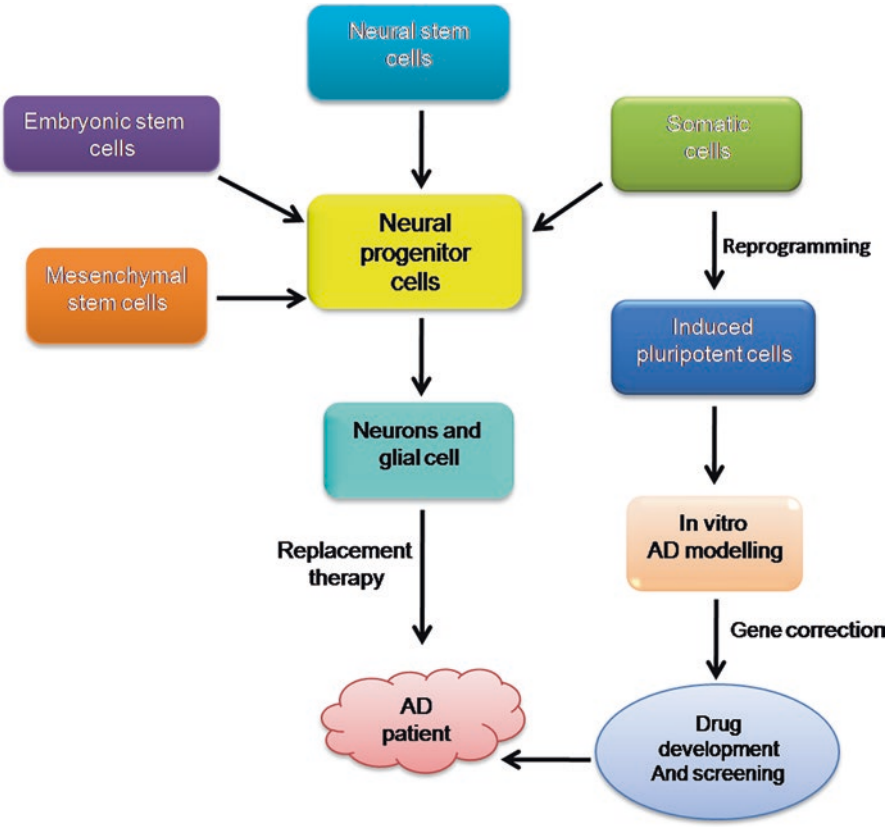

Fig. 9.1 Stem cell therapy in AD

9.2 Pathophysiology of Alzheimer's Disease

AD is distinguished by extracellular amyloid plaques and intracellular NFT features. Amyloid-β (Aβ) protein is the major constituent of plaques associated with AD (Fig. 9.2). The pathophysiology of AD involves several neurotransmitters system and processes (Lin et al. 2001). Three hallmarks of the AD are β-amyloid plaques, neurofibrillary tangles, and neuronal cell death.

Recently, recognized characteristics of AD include degeneration of synapses, aneuploidy, neuronal loss, granulovacuolar degeneration, and amyloid plaques. Three types of amyloid plaques are known in the brain of AD patients:

1. *Diffuse plaques*: contain no amyloid core
2. *Neuritic plaques*: consist of a central amyloid core surrounded by neurites
3. *Burnt-out plaques*: consist of an isolated amyloid core

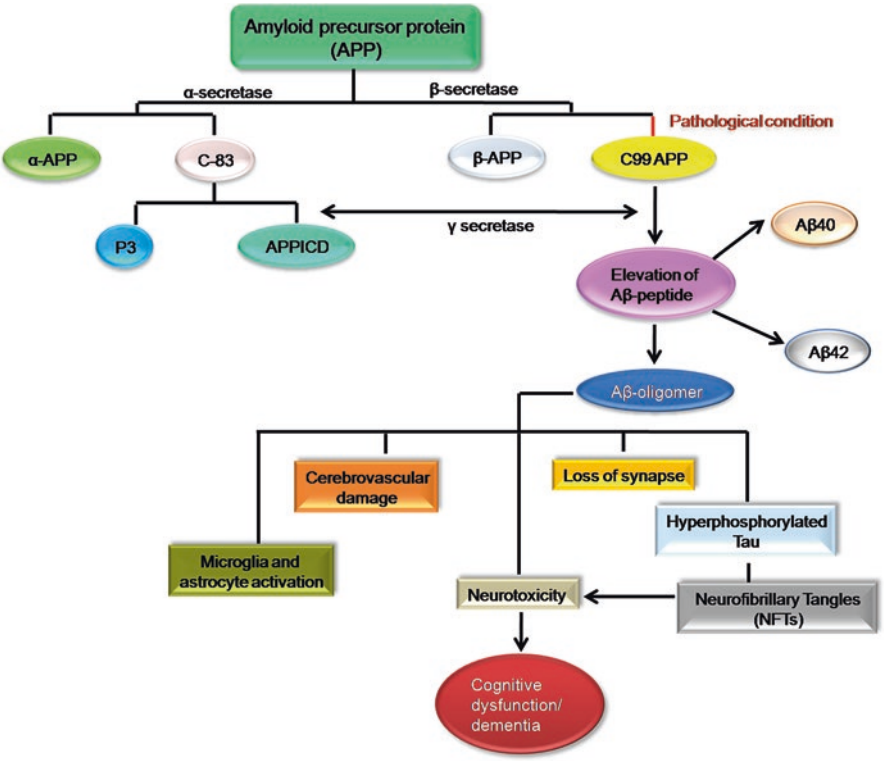

Fig. 9.2 Pathogenesis of AD represented by interacting damage pathways lead by soluble oligomers of the amyloid beta peptide

Apart from the amyloid plaques and tangles, globular and non-fibrillar proteins are continuously released in the AD patient's brain. Cellular changes include short-term and rapid degeneration of neurons which leads to neuronal death when Aβ proteins remain globular.

A few theories related to AD such as the cholinergic, Aβ, tau, and inflammation hypothesis have been explained. Some of them are listed below to understand the mechanism of this disorder:

1. *Changes in brain structure*: The characteristic of the AD on a macro level is the progressive loss of brain tissue. The cortex atrophies are responsible for memory formation in the brain.
2. *Degenerative processes in AD*: AD is characterized on a micro level by three neuropathologic hallmarks: extracellular β-amyloid plaques, intracellular NFTs, and neuronal degeneration. β-Amyloid plaques play an important role in AD pathogenesis which is known as "amyloid cascade" (Swerdlow 2007).

9.3 β-Amyloid Hypothesis

β-Amyloid plaques are aggregates of insoluble peptides formed after the cleavage of APP. Three enzymes, namely γ-secretase, β-secretase, and α-secretase, participate in the APP cleavage. However, APP cleavage by β-secretase followed by γ-secretase produces a soluble 40-amino acid peptide. In addition, γ-secretase cleaves APP that forms nonsoluble 42-amino acid peptide Aβ42 or Aβ which aggregates as β-amyloid plaques. There are three genes involved in the formation of Aβ: APP, PS1, and PS2. PS1 and PS2 genes code for presenilin which is a subunit of γ-secretase. Tau protein hyperphosphorylation occurs after plaque formation in the brain (Selkoe 2002). Neurofibrillary tangles (NFTs) result from damage of neuronal microtubules caused by tau protein modification (Imbimbo et al. 2005). Tau protein disrupts the collapse structure of microtubules and destroys the neuron's transport and communication system. Modifications in tau lead to its oligomerization and NFT production (Maccioni et al. 2010).

9.4 Cholinergic Hypothesis

Loss of cholinergic neurons is one of the pathologies of AD. In that case, more than 75% of cholinergic neurons are reduced in AD patient's brain (Perry et al. 1978). However, acetylcholine is involved in memory; thus, loss of cholinergic activity relates with impairment of memory. Acetylcholine attaches to the post-synaptic receptors: muscarinic and nicotinic. Pre-synaptic nicotinic receptors influence the release of acetylcholine, serotonin, norepinephrine, and glutamate which have a role in AD pathophysiology.

9.5 Glutamatergic Hypothesis

Glutamatergic neurons form the projections which influence the cognition in the brain. AD pathology is linked to only one type of receptor, that is, NMDA receptor which then undergoes low-level activation in AD patient's brain. However, dysregulation of the glutamate NMDA receptor is responsible for neuronal damage which interferes with normal signal transduction (Danysz et al. 2000). It can lead to the production of APP which is related to plaque development and tau hyperphosphorylation.

9.6 Oxidative Stress Hypothesis

Aβ generates the reactive oxygen and nitrogen species which have an unpaired extra electron and also induces lipid peroxidation. The free radicals cause cellular and molecular damage in neuronal cells. The brain can be damaged from oxidative stress because of high oxygen utilization rate and antioxidant enzymes as compared

with the other organs. Upregulation of cytokines and DNA damage in neurons have an essential role in AD progression.

9.7 Chronic Inflammation Hypothesis

β-Amyloid deposition in neurons and NFTs causes inflammation in response to cellular damage. Inflammation leads to the increased number of prostaglandins, produced by COX-1 and COX-2, localized in distinct areas of the brain. Inflammation occurs within or adjacent to the neuritic plaque. Antichymotrypsin, macroglobulin in neuritic plaques, and activated microglia codes for interleukin-1 and interleukin-6 also are detectable in case of the inflammation-related AD.

9.8 Cholesterol and Other Factors

Cholesterol is also implicated in AD pathogenesis. Elevated cholesterol levels raise Aβ production, and thus, the risk of AD progression increases (Reiss 2005). During the AD progression, brain regions become altered, and reduced serotonin levels play an important role in depression and anxiety which are common in an AD patient (Mössner et al. 2000; Lai et al. 2005).

9.9 Stem Cells Used in Alzheimer's Treatment

Stem cells are undifferentiated cells that possess self-renewal and differentiation property. Self-renewal is described as the ability to undergo numerous cell cycle divisions, resulting in identical daughter cells, and differentiation capability is the development of specialized cells from the undifferentiated stem cells (Tabassum et al. 2017). On the virtue of origin, stem cells can be categorized into embryonic stem cells (ESCs) and adult stem cells, and based on potency, these cells are categorized into totipotent, multipotent, pluripotent, and unipotent. Due to the differentiation properties of stem cells into neuronal-like cells, they can be used for the treatment of Alzheimer's disease. The human body generates four types of stem cells: neural stem cells (NSCs), MSCs, ESCs, and iPSCs. These cells have unique properties; thus, they are the most suitable candidates for stem cell therapy.

Embryonic Stem Cells (ESCs) ESCs are pluripotent stem cells which are obtained from the inner cell mass of the blastocyst that gives rise to all cell types except placenta. Researchers successfully differentiated the ESCs into several specific neural cell types including dopaminergic neurons in vitro (Krencik et al. 2011; Malmersjo et al. 2009). The direct transplantation of ESCs showed high risks of teratoma formation due to their potent differentiation ability (Kooreman and Wu 2010). Moreover, various rodent studies demonstrated that the transplantation of ESC-derived NSCs shows no tumorigenesis, but to confirm these results, further research is needed

(Araki et al. 2013; Tang et al. 2008). Along with tumorigenesis, rejection of transplanted ESC-derived tissues by the immune system occurred (Pearl et al. 2012).

Induced Pluripotent Stem Cells (iPSCs) iPSCs are pluripotent stem cells which are reprogrammed from adult fibroblasts by using four transcription factors including Oct3/4, Sox2, Klf4, and c-Myc that are pretty much similar to the ESCs (Takahashi and Yamanaka 2006). These cells are reprogrammed into pluripotency state, having the capability to differentiate into different types of cells including neurons (Cooper et al. 2010) and neurospheres (Nori et al. 2011). Researchers used the iPSC-derived glia cells regarding the inflammatory response in Alzheimer's disease (Holtman et al. 2015). In 2014, Takamatsu revealed that iPSC-derived macrophages express neprilysin and β-amyloid-degrading protease (Takamatsu et al. 2014). However, certain unsolved problems are still present regarding the clinical usage of iPSCs such as tumor formation, immunogenicity, long-time safety, genetic defects, and optimal reprogramming (Tolosa et al. 2016; Araki et al. 2013). Therefore, iPSC-based treatment for AD has been more focused on the establishment of cell-based disease models as compared to treatments (Choi et al. 2014a, b; Yagi et al. 2012; Sproul et al. 2014). Israel and coworkers highlighted the cholinergic neurons of the basal forebrain because of their dysfunction in the early stage of AD (Israel et al. 2012). We know that there is a widespread degeneration in the later stage of the AD, so the protocol using iPSCs should be more elaborated (Pen and Jensen 2017).

Neuronal Stem Cells (NSCs) NSCs are found within the brain. In the past few decades, it was thought that the process of neurogenesis takes place in the fetus; however, the recent studies demonstrated that neurogenesis also occurs in an adult's brain. NSCs were found in the sub-granular zone and sub-ventricular zone of the brain (Taupin 2006; Mu and Gage 2011). These cells are differentiated into neurons, astrocytes, and oligodendrocytes (Taupin 2006). Due to the differentiation capability, NSCs are considered as the best choice for the replacement of injured neurons. In 2001, for the first time, Qu and coworkers proved the replacement of injured neuron by implanting human NSCs into the mature rat's brain (Qu et al. 2001). The results showed that NSCs survived and differentiated into neurons and astrocytes in rat's brain. Moreover, memory impairment was also observed in mature rats after the transplantation when evaluated with the control (Qu et al. 2001). However, NSC isolation from the adult's brain is complicated, so current studies mainly use fetal NSCs, which could also raise ethical problems. To combat these problems, researchers focused on the MSCs, and it was found that bone marrow MSCs (BM-MSCs), adipose tissue (AT-MSCs), and umbilical cord blood MSCs (UC-MSCs) could be trans-differentiated into neuronal cells (Brazelton et al. 2000; Mezey et al. 2000; Kim et al. 2012a, b).

Mesenchymal Stem Cells (MSCs) MSC-based therapy has an advantage over other cell-based therapy because it can be given intravenously and has blood barrier penetration and low tumorigenicity (Oh et al. 2015; Ra et al. 2011). The in vitro transplantation of MSCs in AD cell model augmented the metabolic activity and survival which help to rescue the patients with AD. Co-culturing of human MSCs and mouse microglia cells increased the expression of neprilysin (Aβ-degrading enzyme) (Kim et al. 2012a, b). BM-MSCs show the immunomodulatory capability by releasing the soluble factors including TGF-β, IL-6, IL-10, and PGE2 (Ramasamy et al. 2007; Aggarwal and Pittenger 2005). These factors inhibit the functioning of monocyte-derived dendritic cells and modify the phenotype of the natural killer cell (Sotiropoulou et al. 2006). In 2012, Chen and coworkers demonstrated that AT-MSCs can be differentiated into astrocytes and neuronal-like cells (Chen et al. 2012). The transcriptional profile of AT-MSCs showed some similarity with BM-MSCs (Peroni et al. 2008). AT-MSCs also secrete various neurotrophic factors (Gutiérrez-Fernández et al. 2013; Yang et al. 2012). UC-MSCs can be also differentiated into neuron-like cells. Researchers studied these cells in mouse model having Alzheimer's disease and clinically (Kang et al. 2016). Table 9.1 summarizes the studies of stem cell therapy on AD-diseased animal models.

9.10 Some Clinical Trials of Stem Cell Therapies for Alzheimer's Disease

Since 2011, animal model evidence supported the approval of MSC-based therapies in clinical trials for patients with Alzheimer's disease. UC-MSCs were preferred, and the route of administration of stem cell is intravenous (Table 9.2).

9.11 Conclusion and Future Prospects

Stem cell therapy exhibits therapeutic benefits in several neurodegenerative disorders. Stem cell transplantation increases the expression of synaptic protein markers in AD animal models. The transplantation of MSCs elevated the level of Aβ-degrading enzyme and reduced the level of Aβ due to microglial expression. With the ongoing development of reprogramming technology, there is an immense potential in the utilization of iPSCs in the treatment of AD. For reprogramming, somatic cells from patients could be used to generate iPSCs. After that, it can be differentiated into neural precursor cells for transplantation. This means that tissue rejections will never again an issue and there will be negligible ethical problems. Also, it can ameliorate the modeling of neurodegenerative diseases like AD, because iPSCs could differentiate into neurons, having the inimitable genetic phenotype of the patient. Thus, stem cell-derived neuronal cells create a cellular model which offers the closest relation to the sporadic form of the AD disease and expectantly translated into human studies to find a cure for the AD.

Table 9.1 Outline of studies of stem cell therapy on Alzheimer's-diseased animal models

S. no.	Models for study	Type of stem cell transplanted	Site of administration of stem cell	Outcome of the study	References
1.	DS model mice (Ts65Dn)	Murine NSCs	Hippocampus	Reduction of tau-positive clusters in trisomic and disomic mice	Kern et al. (2011)
2.	Ibotenic acid-induced NBM lesion mice	Murine ESCs and ESC-derived NSCs	Frontal association cortex and barrel field of S1 cortex	NPC restored memory, ES lowers working memory and induced massive teratoma formation	Wang et al. (2006)
3.	Acute Aβ-induced model mice	Murine BM-MSCs	Hippocampus (dentate gyrus)	BM-MSCs enhanced microglial activation. Lowers Aβ deposits of acutely induced AD mice	Lee et al. (2009)
4.	APP/PS1 transgenic mice	BM-MSC	Intra-hippocampus	Reduction of senile plaques.Significant increased DeltaNp73 protein expression.	Wen et al. (2011)
5.	Triple transgenic AD model mice (3 X Tg-AD)	Murine NSCs	Hippocampus	NSC transplantation rescued learning and memory loss. No change in Aβ, tau pathology but elevated synaptic density in mice's hippocampus	Blurton-Jones et al. (2009)
6.	Transgenic AD model mice (Tg2576)	Human ASCs	1. Intravenous 2. Hippocampus (bilateral dentate gyrus)	Rescued memory impairment and recover spatial learning; diminish amyloid plaque formation, upregulated interleukin-10 and neurotrophic factors in the brain of Tg2576 mice	Kim et al. (2012a, b)
7.	Rat Fimbria-Fornix transaction	Murine NSCs and NSC-derived glial cells	Basal forebrain	Recovered memory and learning; number of p75NGFR-positive neurons increased	Xuan et al. (2009)
8.	1. Aged rats (30 months) 2. Ibotenic acid-induced NBM lesion rats	Murine BM-MSC	Hippocampus (CA-1 region)	1. Aged rats learn quickly 2. Ibo-induced memory impairment	Babaei et al. (2012)

(continued)

Table 9.1 (continued)

S. no.	Models for study	Type of stem cell transplanted	Site of administration of stem cell	Outcome of the study	References
9.	1. Matured rats (6 months) 2. Aged rats (24 months) – memory impaired and unimpaired	Human NSCs	Right lateral ventricle	Cognitive function gets better in immature and aged memory-impaired groups. Morphologically functional hNSC-derived cells were found in the hippocampus and cortex	Qu et al. (2001)
10.	Rat hippocampus l Aβ injection	EPI-NSCs	Hippocampus	Improvement in cognitive tasks increased neuron number and differentiation into a different cell type	Esmaeilzade et al. (2012)
11.	APP and presenilin-1 (PSEN-1) double-transgenic mice	Human UC-MSCs	Hippocampus	Spatial learning and memory improved. Reduction of Aβ load and tau hyperphosphorylation, proinflammatory cytokine release from microglia inhibited	Lee et al. (2012)
12.	AF64A cholinotoxin injection in rats impaired	Human NSCs	Right lateral ventricle	Rats receiving NSCs over-expressing ChAT showed a full resurgence in learning and memory functions, whereas those receiving NSCs only remained a memory	Park et al. (2012)

Table 9.2 List of some main clinical trials of stem cell therapies for Alzheimer's disease

Trial number	Title	Type of stem cells and administration	Status (start-end date)	Sponsor	Location
NCT02833792	A Phase IIa Study of Allogeneic Human Mesenchymal Stem Cells in Subjects with Mild to Moderate Dementia Due to Alzheimer's Disease	Human adult ischemia-tolerant MSCs via intravenous administration	June 2016–June 2020	Stemedica Cell Technologies, Inc., United States	United States
NCT01297218	Open-Label, Single-Center, Phase 1 Clinical Trial to Evaluate the Safety and the Efficacy of NEUROTSTEM®-AD in Patients with Dementia of the Alzheimer's Type	Human umbilical cord blood-MSC via intravenous administration	February 2011–April 2012	Medipost Co. Ltd.	Korea
NCT02054208	A Phase I, Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Potential Efficacy of Longeveron Allogeneic Human Mesenchymal Stem Cell (LMSCs) Infusion Versus Placebo in Patients With Alzheimer's Disease	Longeveron MSCs (high dose or low dose) via peripheral intravenous infusion	August 2016–August 2018	Longeveron LLC, United States	United States
NCT01547689	Open-Label, Single-Center, Self-Control, Phase I/II Clinical Trial to Evaluate the Safety and the Efficacy of UC-MSC in Patients with Alzheimer's Disease	Human umbilical cord blood-MSC via intravenous administration	March 2012–December 2016	Affiliated Hospital to Academy of Military Medical Sciences Peking University Third Hospital	China
NCT02899091	A Randomized, Double-Blind, Placebo-Controlled, Phase I/IIa Clinical Trial for Evaluation of Safety and Potential Therapeutic Effect After Transplantation of CB-AC-02 in Patients with Alzheimer's Disease	CB-AC-02 (placenta-derived mesenchymal stem cells) via injection	September 2016 (not yet recruiting)	CHABiotech CO., Ltd	Korea

(continued)

Table 9.2 (continued)

Trial number	Title	Type of stem cells and administration	Status (start-end date)	Sponsor	Location
NCT01617577	Efficacy and Safety of Filgrastim as a Pro-cognitive Agent in Alzheimer's Disease	Subcutaneous filgrastim (G-CSF)	June 2012–December 2012	University of South Florida	United States, Florida
NCT02912169	An Open-Label, Non-randomized, Multi-center Study to Assess the Safety and Effects of Autologous Adipose-Derived Stromal Vascular Fraction (AD-SVF) Cells Delivered Intravenous (IV) and Intranasal in Patients with Alzheimer's Disease	Autologous adipose-derived stromal vascular fraction (AD-SVF) cells via intravenous (IV) and intranasal administration	September 2016–November 2017	Ageless Regenerative Institute, United States	United States, Florida
NCT02600130	A Phase I Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Potential Efficacy of Longeveron Allogeneic Human Mesenchymal Stem Cell (LMSCs) Infusion Versus Placebo in Patients With Alzheimer's Disease	Longeveron MSC via peripheral intravenous	August 2016–October 2019	Longeveron LLC	United States, Florida
NCT03297177	Use of Autologous Stem Cell Use in Neurological Non-neoplastic Disorders and Disease	Autologous stem/stromal cells derived from subdermal fat deposit via the intravenous parenteral route	January 2020–January 2023	Healeon Medical Inc., United States	United States, Massachusetts

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