

Stem Cell Therapy for Neurodegenerative Diseases

Jong Zin Yee¹, Ki-Wook Oh^{2,3}, Seung Hyun Kim^{2,3}

¹Hanyang University College of Medicine, Seoul, Korea

²Department of Neurology, Hanyang University College of Medicine, Seoul, Korea

³Cell Therapy Center for Neurologic Disorders, Hanyang University Hospital, Seoul, Korea

Neurodegenerative diseases are the hereditary and sporadic conditions which are characterized by progressive neuronal degeneration. Neurodegenerative diseases are emerging as the leading cause of death, disabilities, and a socioeconomic burden due to an increase in life expectancy. There are many neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and multiple sclerosis, but we have no effective treatments or cures to halt the progression of any of these diseases. Stem cell-based therapy has become the alternative option to treat neurodegenerative diseases. There are several types of stem cells utilized; embryonic stem cells, induced pluripotent stem cells, and adult stem cell (mesenchymal stem cells and neural progenitor cells). In this review, we summarize recent advances in the treatments and the limitations of various stem cell technologies. Especially, we focus on clinical trials of stem cell therapies for major neurodegenerative diseases.

Key Words: Neurodegenerative Diseases; Stem Cells; Cell Transplantation

Correspondence to: Seung Hyun Kim
Department of Neurology, Hanyang
University College of Medicine,
222 Wangsimni-ro, Seongdong-gu,
Seoul 04763, Korea
Tel: +82-2-2290-8371
Fax: +82-2-2296-8370
E-mail: kimsh1@hanyang.ac.kr

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INTRODUCTION

Neurodegenerative diseases, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD), Huntington's disease (HD), and multiple sclerosis (MS), are characterized by progressive degeneration of particular neuronal cells. Neurodegenerative disorders are believed to share a common pathophysiologic mechanism that allows the deposition of abnormal proteins in selectively vulnerable neuron populations. However, the exact mechanisms of neurodegeneration are too complicated to cure or treat these disorders [1]. Failures in clinical trials of single pathogenic targets lead us to a new field to explore investigational treatments for neurodegenerative diseases. The prevalence and social burden of these disorders are increasing with an aging population. Regarding the lack of effective treatment, stem cell-based therapy is emerging as an alternative treatment strategy. Stem cell-based therapy takes advantage of multiple types of stem cells to modify disease pathophysiology, support neurons, and non-neuronal cells, or directly replace cells.

In this review, we introduce various stem cell therapies for neurodegenerative diseases and focus on clinical trials in the main neurodegenerative diseases, including ALS, AD, and PD.

STEM CELL THERAPY STRATEGIES AND APPLICATIONS

Stem cells have unique properties; self-renewal and differentiation capacity. There are several types of stem cell, including embryonic stem cells (ESC), induced pluripotent stem cells (iPSC), and adult stem cells (mesenchymal stem cells [MSCs] and neural progenitor cells [NPCs]) (Table 1). MSCs, a type of adult stem cells, are multipotent cells of mesenchymal origin and have been isolated from bone marrow, placenta, adipose tissue, cord blood, amniotic fluid, synovial fluid, dermal tissues, and deciduous teeth [2,3]. MSCs can be differentiated not only into mesodermal cell lineages but also endodermal and ectodermal cell lineages via stimulation. MSCs have been vastly explored, considering their ability to secrete many cytokines and neurotrophic factors to control immune

Table 1. Stem cell types and sources

	Embryonic stem cell (ESC)	Adult stem cell		Induced pluripotent stem cell (iPSC)
		Mesenchymal stem cell (MSC)	Neural progenitor cell (NPC)	
Cell sources	Inner cell mass of blastocyst	Mesodermal origin tissue (bone marrow, adipose tissue, umbilical cord blood, etc.)	Neural tissue	Skin fibroblast
Differentiation potency	Pluripotent	Multipotent	Unipotent	Pluripotent
Ethical concerns	Destruction of human embryo		No major ethical concerns	

responses and enhance neuronal protection [4,5]. Adult stem cells such as MSCs are widely used in clinical trials because MSCs avoid the ethical concerns of ESC and provide the possibility of autologous transplantation. iPSC-based cell therapy for human clinical applications remains controversial, given very limited preclinical data.

There are two stem cell therapy strategies: cellular replacement and neuroprotection. Replacement of cells is grafting into a particular damaged neuronal subtype. Transplanted cells may be integrated into host tissue, making synapses reconstitute neural networks like the original structure. Neuroprotection is to support residual neurons. Several mechanisms have been suggested to explain the neuroprotective mechanism of stem cells, including their potent anti-inflammatory capacity, direct release of antiapoptotic and neurotrophic factors, and the ability to induce the proliferation of local neural progenitor cells [6-9].

Previous cell-based therapy has focused mostly on cellular replacement; however, because of problems associated with differentiation, the establishment of an appropriate neural network, and subsequent formation of a functional network, this approach has a limited effectiveness. Thus, neuroprotection has been indicated as a more practical application both in pre-clinical and clinical settings [10]. Understanding that while replacement therapy may be appropriate for diseases such as PD, in which a particular neuronal subpopulation is damaged, neuroprotection using stem cells is preferred to treat ALS, which is widely involved in long neural axis, considering it can support the remaining motor neurons.

AMYOTROPHIC LATERAL SCLEROSIS

ALS is a rapidly progressive neurodegenerative disease selective degenerating motor neurons in the motor cortex, brain stem, and spinal cord. As the disease progresses, it presents muscle weakness and atrophy, and with progression to paralysis, leading to the death due to respiratory failure within 3-5 years of onset. It has been found to be a multifactorial process due to the selective vul-

nerability of motor neurons and complex interactions with damaged non-neuronal cells [11]. In the past 20 years, possible disease mechanisms have been suggested; oxidative stress, mitochondrial dysfunction, cytoskeletal abnormalities, abnormal axonal transport, glutamate excitotoxicity, protein misfolding, microglial and astrocyte dysfunction, defective immune reaction, and impaired growth factor signals and neurotrophic factor signals [12]. Developing insight from preclinical studies also began to provide a clue on how to treat ALS. However, poor understanding of the primary mechanism for neurodegeneration contributes a barrier to drug development. Riluzole, which has a modest effect, is the only FDA approved drug [13].

Thus, there has been interest in stem cell therapies to provide an alternative treatment strategy for transplantation of stem cells for cellular replacement and neuroprotective effects [14,15]. A wide range of effects of stem cells might be beneficial for the treatment of ALS.

A number of animal studies have provided evidence that the transplantation of stem cells, including ESC, NPC, and MSC, through various routes make animal models live longer and restore functions, suggesting that these therapies may improve clinical outcomes [16-23]. Adipose tissue-derived MSC (AdMSC) transplantation has shown to slow motor neuronal death and alleviate clinical manifestations and pathologies in mouse models through neuroprotection and immunomodulation [24]. Mainly, patient-derived iPSC can be differentiated into motor neurons, enabling the autologous transplantation [25].

Results of cell-based therapy in animal models provide a rationale to imply that these approaches have the potential to have effects in human trials. Several studies have shown that various types of stem cell approaches are safe, feasible, and have preliminary efficacy in patients with ALS [26-35]. Because of safety and ethical concerns, MSC has been widely explored [36]. Replacement of damaged motor neurons in ALS is not currently practical in humans; the focus instead is on neuroprotection. Table 2 shows summary of ALS clinical trials.

Table 2. Clinical trials for amyotrophic lateral sclerosis

NCT number	Start	Cell Type	Autologous	Location	Phases	Arm	Blind	Funded	Delivery route	Duration of trial
NCT00855400	2007	BM-MNC	Autologous	Spain	I/II	NA	Open label	IIT	Intraspinal with laminectomy T3-4	NA
NCT01984814	2008	BM-MNC	Autologous	India	II	Parallel, retrospective control	Open label	IIT	NA	56 mo
NCT02242071	2008	NA	NA	India	I	Single	Open label	IIT	NA	2 yr
NCT01348451	2009	NSC	Allogeneic spinal cord	USA	I	Single	Open label	SIT	Intraspinal with laminectomy	4 yr
NCT02193893	2010	Progenitor cells	Auto BM	Poland	I	Parallel	Open label	IIT	Intrathecal	1 yr
NCT01082653	2010	NA	Auto BM	USA	I	Single	Open label	SIT	NA	1 yr
NCT01142856	2010	BM-MSC	Autologous	USA	I	Single	Open label	IIT	Intrathecal	2 yr
NCT01254539	2010	BM-MNC	Autologous	Spain	I/II	Two	Double blind	IIT	Intraspinal with laminectomy T3-4 (I), Intrathecal (II)	NA
NCT01363401	2011	BM-MSC	Autologous	Korea	I/II	Parallel	Open label	SIT	Intrathecal	4 mo
NCT01051882	2011	BM-MSC	Autologous	Israel	I/II	Parallel	Open label	SIT	Intramuscular or intrathecal	6 mo
NCT01640067	2011	NSC	NA	Italy	I	Single	Open label	IIT	Intraspinal (lumbar)	At least 3 yr
NCT01494480	2012	UC-MSC	NA	China	II	Single	Open label	IIT	Intrathecal	2 yr
NCT01609283	2012	Ad-MSC	Autologous	USA	I	Single	Open label	IIT	Intrathecal	2 yr
NCT01759797	2012	BM-MSC	NA	Iran	I	Single	Open label	IIT	Intravenous, intraventricular	6 mo
NCT01933321	2012	Hematopoietic stem cells	NA	Mexico	II/III	NA	Open label	IIT	Intrathecal, intravenous	12 mo
NCT01777646	2012	BM-MSC	Autologous	Israel	II	Single	Open label	SIT	Intramuscular and intrathecal	6 mo
NCT01758510	2012	BM-MSC	Allogeneic	Korea	I	Single	Open label	IIT	Intrathecal	6 mo
NCT01730716	2013	NSC	Allogeneic spinal cord	USA	II	Single	Open label	SIT	Intraspinal	2 yr
NCT01771640	2013	BM-MSC	Autologous	Iran	I	Single	Open label	IIT	Intrathecal	6 mo
NCT02116634	2014	MSC	NA	Iran	I/II	NA	Open label	IIT	Intrathecal	2 yr
NCT02017912	2014	BM-MSC	Autologous	USA	II	Parallel	Double blind	SIT	Intramuscular and intrathecal	6 mo
NCT01759784	2014	BM-MSC	NA	Iran	I	Single	Open label	IIT	Intraventricular	NA
NCT02492516	2014	Ad-MSC	Autologous	Iran	I	Single	Open label	IIT	Intravenous	12 mo (safety), 2 mo (function)
NCT02286011	2014	BM-MNC	Autologous	Spain	I	Parallel	Double blind	SIT	Intramuscular	2 yr
NCT02478450	2015	GRP	Allogeneic brain	USA	I/II	Parallel (4 cohort)	Open label, partially blinded	SIT	Intraspinal (cervical and lumbar)	9 mo

Ad, adipose tissue-derived; BM, bone marrow-derived; ESC, embryonic stem cell; GRP, glial-restricted precursor cell; IIT, Investigator Initiated Trial; NA, not available; MNC, mononuclear cells; MSC, mesenchymal stem cells; NPC, neurogenic progenitor cell; SIT, Sponsor Initiated Trial; UC, umbilical cord-derived.

After the clinical trial (phase I/II) was conducted, bone marrow-derived MSC (BM-MSC) (HYNR-CS, NEURONATA-R) was included in the revision of the regulations on orphan drug designation and approved as a New Drug Application by the Korean Food and Drug Administration [26].

ALZHEIMER DISEASE

AD is characterized by progressive memory dysfunction due to neuronal degeneration, cognitive decline, and dementia. It shows a neuronal loss, especially cholinergic neurons and the destruction of synaptic networks throughout the whole brain cortex, hippo-

campus, basal forebrain, and amygdala. An AD patient's brain typically has pathologic hallmarks, which are beta amyloid (A β) plaque and neurofibrillary tangle [37]. The A β plaque is formed by the generation of an A β peptide through enzymatic cleavages of the amyloid precursor protein (APP), whereas the neurofibrillary tangle is created by tau proteins [38]. In addition to the progressive loss of neurons, the decrease of neurogenesis is exacerbated in AD [39].

The current treatment option for AD is only to regulate the activity of cholinergic neurons. Upregulation of these neurons by cholinesterase inhibitors improves AD patient's performance, but there is no cure for AD [40]. Considering the destructive nature of

AD and no curative treatment, stem cell therapy for AD, which protects neurons, increases neurogenesis or replaces lost neurons, may slow the progression of the disease thoroughly or halt it completely.

Several cell-based therapies for AD have been tried in animal models. Various types of stem cell were used: rat neurogenic stem cell (NSC) and NSC-derived glia transplantation in rat models [41], NPC transplantation in mouse models [7,42], mouse ESC, human ESC transplantation in rodent models [43-45], AdMSC transplantation into the brain cortex of mouse models [46,47], BM-MSC transplantations in rodent models [48-53], and umbilical cord blood-derived MSC (UC-MSC) and human placenta-derived MSCs (hP-MSCs) in rodent models [54-57]. In the case of iPSCs, exploring AD pathologies and drug screenings have been tried in several studies [58,59]. One study found gamma-secretase inhibitors and modulators can reduce A β 42 secretion in iPSC-derived neurons differentiated from patient's fibroblasts [60].

Despite these successes in animal models, there is only one completed clinical trial, which was a phase I study performed at Samsung Medical Center [61]. In this study, they investigated the safety and the tolerability of NEUROSTEM[®]-AD (hUC-MSCs), and the maximum tolerated dose (MTD). In 2015, they were approved to conduct phase I, IIa clinical trial from the FDA over the next 2 years.

PARKINSON DISEASE

PD is manifested by the progressive loss of dopaminergic (DA) neurons in the substantia nigra. Patients with PD display several motor symptoms including gait disturbance, unstable posture, tremors, and rigidity [62]. The pathologic hallmark of PD is the Lewy bodies, which is the clumps of alpha-synuclein, in the mid-brain and the brain stem [59].

Current treatments are drugs such as Levodopa, a dopamine precursor, neural lesion surgery and deep brain stimulation, which are only symptomatic, have various harmful effects and uncertain long-term efficacy, and become ineffective in already progressed PD. Thus, there are vast interests in stem cell technologies for the needs to cure PD.

Cell-based therapies for PD focus on the replacement of lost DA neurons. ESC and MSC were differentiated into DA neurons and then grafted into rat PD models, resulting in functional improvements [63,64]. Patient-specific DA neurons can be utilized to treat PD using iPSC [65]. Significant functional recovery and cell inte-

gration within the host tissue were observed in transplantation of these patient-specific neurons into a rodent model [4]. DA neurons induced from UC-MSCs have also been shown to relieve functional abnormalities in both rodent models and rhesus monkey models [66,67].

Although some studies choose these cellular replacement methods using stem cells as a viable approach for PD, providing neuroprotection can also be useful for maintaining existing DA neurons and slowing disease progression. Among stem cells, MSC transplantations are the most suitable for clinical setting considering their neurotrophic and immunomodulatory effects and potential as effective delivery vehicles. In a rat model, MSC transplantation had a protective effect against DA neuronal death [68]. AdMSC administration has also provided effectiveness due to the neurotrophic and immunomodulatory effects in rodent models [69]. Genetically engineered MSCs and NPCs to produce growth factors made prolonged secretions of growth factor in situ, and transplantation of these engineered cells protected DA neurons and gave functional improvement in animal PD models [70-74]. Various studies using other types of stem cells were also well documented [63,75-77]. The limitations of these approaches are transient survival of transplanted stem cells, and the possibility of contamination with fibroblasts, which has been shown to have an effect to accelerate neuronal death in mouse PD models [78,79].

Taken together, the combination of cellular replacement and neuroprotection may improve the efficacy of cell therapies for PD. Some clinical trials have shown varying results, and there is little evidence that stem cell therapies are safe and effective for PD patients [80]. Two phase I/II clinical trials using AdMSC and NSC are ongoing.

CONCLUSION

The burden of neurodegenerative diseases is growing with the acceleration of an aging population. However, there is no effective or curative therapy for neurodegenerative diseases. Recent advances in stem cell techniques will fulfill unmet medical needs of neurodegenerative diseases. There are several issues that need to be addressed to move forward: safety and ethical concerns, type of stem cells, delivery route, dose, and efficacy, and cost-effectiveness. An understanding of all facets of stem cell and pathomechanism is necessary to successfully translate the application of cell-based therapy for neurodegenerative diseases. Future therapeutic

strategies may focus on a combinational approach, replacement and neuroprotection strategies, using two or more types of stem cells, genetic engineering or gene therapy to achieve maximal efficiency and efficacy.

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