Progress of Mesenchymal Stem Cell Therapy for Neural and Retinal Diseases

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Progress of mesenchymal stem cell therapy for neural and retinal diseases

Tsz Kin Ng, Veronica R Fortino, Daniel Pelaez, Herman S Cheung

Abstract
Complex circuitry and limited regenerative power make central nervous system (CNS) disorders the most challenging and difficult for functional repair. With elusive disease mechanisms, traditional surgical and medical interventions merely slow down the progression of the neurodegenerative diseases. However, the number of neurons still diminishes in many patients. Recently, stem cell therapy has been proposed as a viable option. Mesenchymal stem cells (MSCs), a widely-studied human adult stem cell population, have been discovered for more than 20 years. MSCs have been found all over the body and can be conveniently obtained from different accessible tissues: bone marrow, blood, and adipose and dental tissue. MSCs have high proliferative and differentiation abilities, providing an inexhaustible source of neurons and glia for cell replacement therapy. Moreover, MSCs also show neuroprotective effects without any genetic modification or reprogramming. In addition, the extraordinary immunomodulatory properties of MSCs enable autologous and heterologous transplantation. These qualities heighten the clinical applicability of MSCs when dealing with the pathologies of CNS disorders. Here, we summarize the latest progress of MSC experimental research as well as human clinical trials for neural and retinal diseases. This review article will focus on multiple sclerosis, spinal cord injury, autism, glaucoma, retinitis pigmentosa and age-related macular degeneration.

Key words: Mesenchymal stem cells; Stem cell therapy; Central nervous system; Retina; Clinical trial

Core tip: Central nervous system (CNS) disorders are the most challenging and difficult for functional repair. Neurons are still diminishing in many patients despite surgical and medical interventions. Stem cell therapy has been proposed as a viable option. Mesenchymal stem cell (MSC) is a widely-studied human adult stem cell population. MSCs can be conveniently obtained from different accessible tissues. MSCs have high proliferative and differentiation abilities, providing an inexhaustible source of neurons and glia. MSCs also show neuroprotective effects and possess extraordinary immunomodulatory properties. These qualities heighten the clinical applicability of MSCs when dealing with the pathologies of CNS disorders.
STEM CELL THERAPY AND MESENCHYMAL STEM CELLS

Stem cells are undifferentiated stem cells defined by their ability to self-renew and differentiate into mature cells. Stem cells are attractive because they are highly proliferative, implying that an inexhaustible number of mature cells can be generated from a given stem cell source. On this basis, cell replacement therapy has been proposed in recent years as a viable alternative for various pathologies. Cell replacement therapy hypothesizes that new retinal cells could be generated from stem cells so as to substitute the damaged cells in the diseased retina. This theory is mainly established from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). In addition to cell replacement function, stem cells could have another protective effect, the paracrine effect. The paracrine effects of stem cells are believed to modulate the microenvironment of the diseased tissues so as to protect the injured cells, promote survival and activate any available endogenous repair mechanisms. This latter observation applies mainly to the transplantation of adult stem cells.

Adult stem cells are defined as the stem cells found in fully developed tissues. The function of adult stem cells is the maintenance of adult tissue specificity by homeostatic cell replacement and tissue regeneration[1]. Adult stem cells are presumed quiescent within adult tissues, but divide infrequently to maintain their own niche by generating a stem cell clone and a transiently-amplifying cell. The transiently-amplifying cells will undergo a limited number of cell divisions before terminal differentiation into mature functional tissue cells. The existence of adult stem cells has been reported in multiple organs; these include: brain, heart, skin, intestine, testis, muscle and blood, among others.

Mesenchymal stem cells (MSCs), also called marrow stromal cells, are an adult stem cell population of stromal progenitor cells of mesodermal origin[2]. MSCs were originally identified in the bone marrow, representing 0.001%-0.01% of the bone marrow population. MSCs can also be found in other systems all over the body, such as adipose tissue, liver, umbilical cord, central nervous system (CNS) and dental tissues[3]. According to the International Society of Cellular Therapy[4], the minimal criteria to define MSCs are: (1) grown in adherence to plastic surface of dishes when maintained in standard culture conditions; (2) positive expression of cytospecific cell surface markers (CD105, CD90 and CD73) and negative expression of other cell surface markers (CD45, CD34, CD14 and CD11b); and (3) capacity to differentiate into mesenchymal lineages, under appropriate in vitro conditions. In addition to the expression of the three cell surface markers, MSCs also express CD29, CD44, CD146 and STRO-1[5].

The function of MSCs is to differentiate into osteocytes, chondrocytes, myoblasts and adipocytes[6,7]. An increasing number of studies, however, report that MSCs are capable of giving rise to cells of an entirely distinct lineage, including neuron-like cells. MSCs are not only able to differentiate into neurons for cell replacement therapy, they also exert paracrine effects by modulating the plasticity of damaged host tissues, secreting neurotrophic and survival-promoting growth factors, restoring synaptic transmitter release, integrating into existing neural and synaptic networks, and re-establishing functional afferent and efferent connections[8]. These paracrine activities have not been reported in ESCs or iPSCs. Moreover, MSCs possess strong immunosuppressive properties and inhibit the release of pro-inflammatory cytokines[9]. This allows autologous, as well as, allogeneic transplantation of MSCs without the need of pharmacological immunosuppression. Furthermore, MSCs can be transplanted directly without genetic modification or pre-treatments, and are able to migrate to the tissue injury sites[10]. In addition, there is no teratoma formation concern after transplantation[11], and no moral objection or ethical controversies involved in their attainment[12]. These advantageous properties, as well as the expansion potential of MSCs initiate the idea of clinical applications of MSCs to treat different human diseases, especially CNS disorders. Currently, over 100 MSC clinical trials for different diseases have been listed by the United States National Institutes of Health trial database (www.clinicaltrials.gov), indicating that MSC therapy is a popular trend for the field of regenerative medicine in the years to come.

This review article provides an update on the progress of MSC experimental research as well as human clinical trials for neural and retinal diseases with emphasis on multiple sclerosis, spinal cord injury, autism, glaucoma, retinitis pigmentosa and age-related macular degeneration.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disorder of the CNS, affecting over 1.3 million people worldwide. The histopathological hallmark of MS is the formation of an inflammatory plaque, which originates from a breach in the integrity of the blood-brain barrier[13]. The histologic features of lesions in MS include: lymphocyte infiltration, loss of oligodendrocytes, demyelination, and widespread axonal damage[14]. Myelin-reactive T cells, which secrete interferon- and interleukins, have been suggested to be responsible for the inflammatory demyelination seen in MS[15]. Currently, there are three treatment options approved by the Food and Drug Administration (FDA) for MS: administration of interferon beta, glatiramer acetate, or mitoxantrone[16]. However, there is still no medical cure for MS.

Experimental autoimmune encephalomyelitis (EAE), the best known and most commonly used model for MS, mechanistically defines the immune processes responsible for the clinical manifestations and development of MS[17]. This animal model provides insight for the application of immunotherapy to treat MS[18]. MSCs have been pro-
posed as a treatment for autoimmune diseases, including MS, because of their immunosuppressive properties and neural repair function\[19\]. Transplantation of human MSCs into animals with ongoing EAE results in rapid and sustained functional recovery due to a reduced number of inflammatory myelin-specific Th1 cells and astrocytes as well as an increased number of inflammatory-inhibiting Th2 cells, oligodendrocytes and neurons\[25\]. This functional benefit is a critical stepping-stone towards effective MSC therapies in MS patients.

Among all of the CNS disorders, MS has the highest number of registered clinical trials. Altogether there are 14 registered clinical trials for MS (Table 1), and two of them have been published. The study from Israel is a phase-1/2 open safety clinical trial to evaluate the feasibility, safety and immunological effects of intrathecal and intravenous administration of autologous MSCs in 15 MS patients (NCT00781872; http://clinicaltrials.gov/)\[20\]. No major adverse events have been reported in this study, and the mean Expanded Disability Status Scale (EDSS) improved from 6.7 to 5.9 (EDSS steps 1.0 to 4.5: MS patients are fully ambulatory, whereas EDSS steps 5.0 to 9.5: MS patients are impaired to ambulation). Moreover, magnetic resonance imaging visualized the MSCs in the occipital horns of the ventricles, indicating migration of the cells. In addition, the proportion of CD4+/CD25+ regulatory T cells increased, whereas the proliferative responses of lymphocytes decreased. The mesenchymal stem cells in the multiple sclerosis trial (MSCIMS) originated in the United Kingdom, is an open-label phase 2a proof-of-concept study of autologous MSCs in secondary progressive MS (NCT00395200; http://clinicaltrials.gov/)\[22,23\]. In this study, 10 patients received intravenous infusion of autologous bone marrow-derived MSCs (1.6 × 10⁶ cells per kg body weight). The “sentinel lesion approach” assessing the anterior visual pathway was used to measure the efficacy of treatment. Results show that treatment improved visual acuity, visual evoked response latency, and increased the optic nerve area of the recipients. No serious adverse events were identified. For other clinical trials, mainly autologous MSCs have been used, although one study from China uses umbilical cord MSCs (NCT01364246; http://clinicaltrials.gov/). Interestingly, an open-label phase I clinical trial from New York was designed to evaluate autologous MSC-derived neural progenitor cells in progressive MS patients (NCT01933802; http://clinicaltrials.gov/) even though neural stem cells from EAE animals mainly develop astrocytes rather than oligodendrocytes, or oligodendrocyte precursor cells and neurons\[29\].

**SPINAL CORD INJURY**

Spinal cord injury (SCI) is the most devastating and traumatic disorder among CNS conditions\[20\]. The worldwide frequency of SCI is about 40 cases per million individuals\[20\]. SCI can be caused by traffic accidents, violent assaults, falls, sport and other traumatic events. Depending on the injury location, extent, phases and time frames, SCI therapeutic strategies can vary greatly\[28\]. Most SCI patients are in the chronic phase, characterized by ongoing demyelination, local inflammation and apoptosis, decreased number of activated macrophages, and formation of glial scar and pseudocysts\[27\]. The present standard treatment for SCI patients is surgical intervention, high doses of methylprednisolone, and symptomatic therapy followed by rehabilitation\[28\]. New neuroregenerative strategies will be focused on neuroprotection and axonal regeneration in a permissive environment.

Cellular therapy aims to reconstruct the spinal cord through cellular replacement, glial scar remodeling, axonal guidance, and filling of formed syringomyelia\[26\]. In vivo administration of MSCs in different SCI animal models showed functional recovery including: increased motor activity and sensation in the paralyzed limbs, reduced cavity formation in the spinal cord, and axonal sprouting through the glial scar\[26,27\]. The objective of MSC application is to ameliorate the consequences of secondary injury by preserving the host nerve cells, rather than replacing them\[32\].

Comparable to MS studies, there are 11 registered clinical trials using MSCs for SCI treatment (Table 1), among which two studies (one from Egypt and one from South Korea) have been completed. The Korean study investigated the safety of single intravenous infusion of autologous adipose tissue-derived MSCs (4 × 10⁶ cells) in 8 male patients with chronic SCI (NCT01274975; http://clinicaltrials.gov/)\[31\]. No adverse events were observed. Although one patient showed improvement in the American Spinal Injury Association (ASIA) scale from grade A (No sensory or motor function is preserved in sacral segments S4-S5) to grade C (Motor function is preserved below the neurologic level, and most key muscles below the neurologic level have muscle grade less than 3) and three patients showed motor score improvement, this phase I clinical trial might not have the statistical power to conclude on the efficacy of treatment effect with adipose tissue-derived MSCs on SCI. The study conducted in Egypt (NCT00816803; http://clinicaltrials.gov/), is a Phase-1/2 clinical trial applying bone marrow-derived MSCs at the injury site of chronic SCI patients. However, no results of this study have been released. Finally, there are two Phase-3 clinical trials taking place in China (NCT01873547; http://clinicaltrials.gov/) and Korea (NCT01676441; http://clinicaltrials.gov/). The study in China plans to use umbilical cord MSCs to treat 100 chronic SCI patients compared to the rehabilitation-only group and no stem cell and rehabilitation group, whereas the study in Korea was designed to transplant bone marrow-derived MSCs to treat 32 chronic SCI patients. For other ongoing clinical trials in SCI, the approaches are mainly intrathecal transplantation of bone marrow-derived MSCs and adipose tissue-derived MSCs in chronic SCI patients.

**AUTISM**

Autism belongs to a spectrum of heterogeneous neuro-
Table 1  Registered clinical trials on mesenchymal stem cells for neural diseases

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Country</th>
<th>Stage of trial</th>
<th>Study</th>
<th>Estimated number of patients</th>
<th>Estimated trial end</th>
<th>Disease</th>
</tr>
</thead>
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<td>NCT00781172</td>
<td>Spain</td>
<td>Recruiting</td>
<td>Evaluation of autologous mesenchymal stem cell transplantation (effects and side effects) in multiple sclerosis</td>
<td>30</td>
<td>2013</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT01883661</td>
<td>India</td>
<td>Recruiting</td>
<td>Safety and efficacy of autologous bone marrow mesenchymal stem cells in multiple sclerosis</td>
<td>30</td>
<td>2014</td>
<td>Multiple sclerosis</td>
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<tr>
<td>NCT00395200</td>
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<td>Completed</td>
<td>MSCIMS</td>
<td>15</td>
<td>2015</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT01854957</td>
<td>Italy</td>
<td>Recruiting</td>
<td>MESEMS</td>
<td>20</td>
<td>2014</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT01730347</td>
<td>Sweden</td>
<td>Recruiting</td>
<td>Mesenchymal stem cells for multiple sclerosis</td>
<td>15</td>
<td>2015</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT01364246</td>
<td>China</td>
<td>Recruiting</td>
<td>Safety and efficacy of umbilical cord mesenchymal stem cell therapy for patients with progressive multiple sclerosis and neuromyelitis optica</td>
<td>20</td>
<td>2014</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT01056471</td>
<td>Spain</td>
<td>Recruiting</td>
<td>Autologous mesenchymal stem cells from adipose tissue in patients with secondary progressive multiple sclerosis (CMM/EM/2008)</td>
<td>30</td>
<td>2012</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT0228266</td>
<td>Spain</td>
<td>Active, not recruiting</td>
<td>Mesenchymal stem cell transplantation in MS (CMM/EM)</td>
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<td>2013</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT00813969</td>
<td>United States</td>
<td>Active, not recruiting</td>
<td>Autologous MSC transplantation in MS</td>
<td>24</td>
<td>2014</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT01933802</td>
<td>United States</td>
<td>Not yet recruiting</td>
<td>Intrathecal administration of autologous MSC-NP in patients with multiple sclerosis</td>
<td>20</td>
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<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT01606215</td>
<td>United Kingdom</td>
<td>Recruiting</td>
<td>STREAMS</td>
<td>13</td>
<td>2015</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>NCT01745783</td>
<td>Spain</td>
<td>Recruiting</td>
<td>Mesenchymal cells from autologous bone marrow, administered intravenously in patients diagnosed with multiple sclerosis</td>
<td>30</td>
<td>2014</td>
<td>Multiple sclerosis</td>
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<tr>
<td>NCT01694927</td>
<td>Chile</td>
<td>Enrolling by invitation</td>
<td>Autologous mesenchymal stem cells in spinal cord injury (SCI) patients (MSC-SCI)</td>
<td>30</td>
<td>2014</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>NCT01446640</td>
<td>China</td>
<td>Recruiting</td>
<td>Mesenchymal stem cells transplantation to patients with spinal cord injury (MSC)</td>
<td>20</td>
<td>2014</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>NCT01676441</td>
<td>South Korea</td>
<td>Recruiting</td>
<td>Safety and efficacy of autologous mesenchymal stem cells in chronic spinal cord injury</td>
<td>32</td>
<td>2014</td>
<td>Spinal cord injury</td>
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<tr>
<td>NCT01769872</td>
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<td>Recruiting</td>
<td>Mesenchymal stem cell implantation in patients with spinal cord injury</td>
<td>15</td>
<td>2014</td>
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<tr>
<td>NCT01162915</td>
<td>United States</td>
<td>Active, not recruiting</td>
<td>Transfer of bone marrow derived stem cells for the treatment of spinal cord injury</td>
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<td>2013</td>
<td>Spinal cord injury</td>
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<tr>
<td>NCT01274975</td>
<td>Korea South</td>
<td>Completed</td>
<td>Autologous adipose derived mcs transplantation in patient with spinal cord injury</td>
<td>8</td>
<td>2010</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>NCT01624779</td>
<td>South Korea</td>
<td>Recruiting</td>
<td>Intrathecal transplantation of autologous adipose tissue derived msc in the patients with spinal cord injury</td>
<td>15</td>
<td>2013</td>
<td>Spinal cord injury</td>
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<tr>
<td>NCT01393977</td>
<td>China</td>
<td>Unknown</td>
<td>Difference between rehabilitation therapy and stem cells transplantation in patients with spinal cord injury in China (SCI-B)</td>
<td>60</td>
<td>2012</td>
<td>Spinal cord injury</td>
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<tr>
<td>NCT01873547</td>
<td>China</td>
<td>Recruiting</td>
<td>Different efficacy between rehabilitation therapy and stem cells transplantation in patients with SCI in China (SCI-B)</td>
<td>300</td>
<td>2014</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>NCT01325103</td>
<td>Brazil</td>
<td>Unknown</td>
<td>Autologous bone marrow stem cell transplantation in patients with spinal cord injury</td>
<td>20</td>
<td>2013</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>NCT00816803</td>
<td>Egypt</td>
<td>Completed</td>
<td>Cell transplant in spinal cord injury patients</td>
<td>80</td>
<td>2008</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>NCT01343511</td>
<td>China</td>
<td>Completed</td>
<td>Safety and efficacy of stem cell therapy in patients with autism</td>
<td>37</td>
<td>2011</td>
<td>Autism</td>
</tr>
</tbody>
</table>

Information obtained from http://clinicaltrials.gov/. MSCs: Mesenchymal stem cells; MS: Multiple sclerosis; MSCIMS: Mesenchymal Stem Cells in Multiple Sclerosis; MESEMS: MEsenchymal StEm Cells for Multiple Sclerosis; MSC-NP: Mesenchymal Stem Cell-derived Neural Progenitors; STREAMS: Stem Cells in Rapidly Evolving Active Multiple Sclerosis.
GLAUCOMA

Glucoma is a group of chronic, degenerative optic neuropathies. It is characterized by a slow progressive degeneration of retinal ganglion cells (RGCs) and their axons, which results in visual field defects. Glucoma is the leading cause of irreversible blindness, affecting more than 60 million people worldwide. Traditional and current treatments for glucoma are based on surgical or medical interventions to slow disease progression and limit visual loss. However, in many patients, the numbers of RGCs still diminish, and glucoma cannot be completely cured.

The molecular basis of glucoma is complex. The pathophysiological mechanisms leading to RGC degeneration in glucoma include a complex interaction between primary axonal injury, neurotrophic factor deprivation, ischemia, oxidative stress, mitochondrial dysfunction and inflammation. New therapies aim to supplement neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial cell line-derived neurotrophic factor (GDNF) and nerve growth factor (NGF). However, repeated injections are needed to achieve an observable effect. To avoid multiple injections, cell-based delivery of neurotrophic factors was proposed. A phase-I clinical trial for glucoma (NCT01408472; http://clinicaltrials.gov/) using genetically modified CNTF-secreting retinal pigment epithelial cells (NT-501 CNTF implant) has already been launched—the outcomes have not been reported yet. Since MSCs can produce neurotrophic factors, including BDNF, CNTF, GDNF and basic fibroblast growth factor (bFGF), without the requirement of genetic modification, MSC transplantation has been suggested as a potential reservoir for neurotrophic factor secretion. Bone marrow-derived MSC transplantation increases RGC survival in a model of transient ischemia followed by reperfusion, and reduces RGC loss in ocular hypertension models. Similarly, transplantation of human umbilical cord blood MSCs promotes RGC survival in an optic nerve crush model even after 7 d of injury. In addition, intracranial human umbilical cord blood MSC transplantation at the site of optic tract transaction also protects RGCs and induces axonal regeneration. The neuroprotective effect of MSCs on RGC survival has clearly been proven, and the first clinical trial using bone marrow-derived MSCs on glucoma in Florida (Stem Cell Ophthalmology Treatment Study (SCOTS)) has just started in August 2013 (NCT01920867; http://clinicaltrials.gov/; Table 2). This study will be complete in 2017.

RETINITIS PIGMENTOSA AND AGE-RELATED MACULAR DEGENERATION

Retinitis pigmentosa (RP) is characterized by a classic pattern of difficulties in dark adaptation and night blindness in adolescence, loss of mid-peripheral visual field in young adulthood and central vision later in life. These are due to the severe attenuation of rod and cone photoreceptors. RP is one of the hereditary degenerative diseases, affecting 1 in 4000 individuals. Age-related
macular degeneration (AMD) is the leading cause of irreversible blindness in people aged 50 years or above in the developed world\textsuperscript{58}. It influences the central portion of the retina (the macula). Early AMD is characterized by drusen (pale yellowish lesions), or by hyperpigmentation and hypopigmentation of retinal pigment epithelium in the macula. Late AMD is divided into the “non-exudative” and “exudative” forms. The non-exudative form (geographic atrophy) starts with a sharply demarcated round or oval hypopigmented spot in which large choroidal vessels are visible, whereas the exudative form, characterized by choroidal neovascularization, is the detachment of the neuroretina or RPE from Bruch’s membrane by serous or hemorrhagic fluid\textsuperscript{59,60}.

Both RP and AMD involve photoreceptor cell death. MSC research studies targeting this common pathology can be divided into two categories: first, cell replacement-based studies aim to generate photoreceptor cells from different sources of MSCs. MSCs from the trabecular meshwork as well as the conjunctiva have been used to produce photoreceptor-like cells \textit{in vitro}\textsuperscript{61,62}. Interestingly, subretinal injection of MSCs has also been reported to induce differentiation into photoreceptor cells in a sodium iodate-induced retinal degeneration rat model\textsuperscript{63}. Second, studies based on paracrine effects hypothesize that MSCs can secrete neurotrophic factors to protect against photoreceptor degeneration in different animal models. Transplantation of bone marrow-derived MSCs can rescue photoreceptor cells of the dystrophic retina in the rhodopsin knockout mouse model\textsuperscript{64}. Moreover, intravenous injection of bone marrow-derived MSCs rescue photoreceptor cells as well as visual function in the Royal College of Surgeons rat model\textsuperscript{65}. For AMD, beside photoreceptor cell loss, retinal pigment epithelial (RPE) cells are also affected. Adipose tissue-derived MSCs can be induced to an RPE phenotype\textsuperscript{66}. In addition, adipose tissue-derived MSCs rescue mitomycin C-treated RPE cell lines (ARPE19) from death in culture\textsuperscript{67}. Furthermore, subretinal injected MSCs adopt RPE morphology and preserve the retinal layer integrity in the sodium iodate-induced retinal degeneration rat model\textsuperscript{68}.

To date, there are three ongoing registered clinical trials using MSCs on RP (Table 2). The first clinical trial aims to determine the feasibility and safety of human adult bone marrow-derived MSCs by intravitreal injection in patients with RP in Thailand (NCT01531348; http://clinicaltrials.gov/). The second clinical trial is the Stem Cell Ophthalmology Treatment Study (SCOTS) in Florida (NCT01920867; http://clinicaltrials.gov/) proposed to use autologous bone marrow-derived MSCs by different means of injection (retrobulbar, subtenon, intravitreal, intracocular, subretinal and intravenous). The third clinical trial is a Phase-1/2 open labeled study done in India to evaluate the safety and efficacy of bone marrow-derived MSCs in RP (NCT01914913; http://clinicaltrials.gov/). For AMD, there is only one registered clinical trial using bone marrow-derived MSCs (Table 2), the Stem Cell Ophthalmology Treatment Study (SCOTS) in Florida (NCT01920867; http://clinicaltrials.gov/). Results from these studies have not been reported yet.

\textbf{CONCLUSION}

MSCs have been discovered for more than 20 years\textsuperscript{55}, and have been found all over the body. MSCs can be conveniently obtained from different accessible tissues: bone marrow, blood, and adipose and dental tissue. They can also be easily expanded in standard culture conditions. In addition to the above mentioned characteristics, MSCs demonstrate neuroprotective effects, immunomodulatory properties and self-migratory activity, making them an attractive therapeutic tool. In recent years, MSC research has already begun the transition from preclinical experiments to human clinical trials. There are currently more than 60 MSC clinical trials dealing with CNS disorders and three clinical trials on retinal diseases. Although transient rash, self-limiting bacterial infections or fever might occur in some patients after MSC transplantation, serious adverse events have never been observed. This can foresee that MSC transplantation will become routine clinical practice for disease treatment in the near future. However, there are critical challenges still needed to be conquered before MSC therapy can be adopted in daily clinical practice. These include: (1) poor MSC retention \textit{in vivo}; (2) poor MSC engraftment, viability and function \textit{in vivo}; (3) unclear mechanisms of action; and (4) lack

\textbf{Table 2} Registered clinical trials on mesenchymal stem cells for retinal diseases

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Country</th>
<th>Status</th>
<th>Study</th>
<th>Phase of trial</th>
<th>Estimated number of patients</th>
<th>Estimated trial end</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01531348</td>
<td>Thailand</td>
<td>Enrolling by invitation</td>
<td>Feasibility and safety of adult human bone marrow-derived mesenchymal stem cells by intravitreal injection in patients with retinitis pigmentosa</td>
<td>Phase 1</td>
<td>10</td>
<td>2014</td>
<td>Retinitis pigmentosa</td>
</tr>
<tr>
<td>NCT01914913</td>
<td>India</td>
<td>Not yet recruiting</td>
<td>Clinical study to evaluate safety and efficacy of stem cell therapy in retinitis pigmentosa</td>
<td>Phase 1/2</td>
<td>15</td>
<td>2015</td>
<td>Retinitis pigmentosa</td>
</tr>
<tr>
<td>NCT01920867</td>
<td>United States</td>
<td>Recruiting</td>
<td>Stem cell ophthalmology treatment study</td>
<td></td>
<td>300</td>
<td>2017</td>
<td>Glaucoma, retinitis pigmentosa, age-related macular degeneration</td>
</tr>
</tbody>
</table>

Information obtained from http://clinicaltrials.gov/.
of standardized trials[79]. Moreover, few studies showed the contradictory results of MSC immunomodulatory properties. This might be explained by the heterogeneous MSC population. TLR4-primed human MSCs (MSC2) mostly secrete pro-inflammatory cytokines (IL-6, IL-8) while TLR3-primed human MSCs (MSC2) express mostly immunosuppressive mediators (IL-10, IDO, TSG-6)[73].

Addition of fewer MSCs (10-1000) would lead to a less consistent suppression or a marked lymphocyte proliferation in culture, whereas addition of 10000-40000 MSCs have an inhibitory effect[25]. Besides, there are uncertainties that must be answered. What is the optimal cell number for transplantation? Which MSC types are optimal for regenerative medicine? When is the optimal stage to receive MSC therapy? Which transplantation route is suitable for each individual CNS disorder? Further research is needed to understand the mechanisms elicited by stem cells in regenerating damaged tissues after transplantation.

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