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Review article

The potential use of mesenchymal stem cells for the treatment of multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system (CNS). In attempt to identify an appropriate treatment for improving the neurological symptoms and remyelination process, autologous and allogenic transplantation of mesenchymal stem cells (MSCs) have been introduced as an effective therapeutic strategy in MS. MSCs are a heterogeneous subset of pluripotent non-hematopoietic stromal cells that are isolated from bone marrow, adipose tissue, placenta and other sources. MSCs have considerable therapeutic effects due to their ability in differentiation, migration, immune-modulation and neuroregeneration. To date, numerous experimental and clinical studies demonstrated that MSCs therapy improves the CNS repair and modulates functional neurological symptoms. Here, we provided an overview of the current knowledge about the clinical applications of MSCs in MS. Furthermore, the major challenges and risks of MSCs therapy in MS patients have been elucidated.

1. Introduction

Multiple sclerosis (MS) is a chronic disabling disease of central nervous system (CNS) that affect > 2.3 million people in the world [5,66]. Pathological evidence defined MS as an inflammatory demyelinating disease caused by infiltration of autoreactive lymphocytes to the CNS [54,86]. Relapsing–remitting MS (RRMS) is considered as the most common form of MS which patients experience partial recovery between relapses. Over time, 80% of RRMS may advance to secondary progressive MS (SPMS). Approximately 20% of cases are suffer from primary progressive MS (PPMS) that show progressive form of MS from the beginning, without any relapse periods [26]. There are several disease-modifying therapies (DMT) that reduce the number and severity of relapses in RRMS. Over last decades, various therapeutic strategies have developed to delay the progression of MS through immunosuppression and immunomodulation [18,31]. In recent years, some effective therapies such as injectable or oral administration of drugs including interferon beta, fingolimod, glatiramer acetate and teriflunomide have been introduced for treating MS.

Interestingly, stem cell therapy has been emerged as promising therapeutic approach in MS disease [31]. In recent years, stem cells transplantation or reprogramming of somatic cells toward desired cells have been considered as an effective approach to treat various disease states, especially neurodegenerative and neurological disorders [8,9]. Several experimental and clinical studies reported that stem cells may serve as a potential therapy in MS [18,62,67]. Stem cells are unspecialized cells that enable to produce the large scale of identical cells and perpetuate themselves or differentiate to other types of cells in particular tissue under certain physiological or experimental condition [53]. Given the ability of these cells in proliferation and differentiation, stem cells could in turn be used to attenuate the progression of disease and regenerate irreversible damage and neuronal loss in the CNS-related injuries [35,45]. There are at least five types of stem cells including embryonic stem cells (ESCs), hematopoietic stem cells (HSCs), neural stem cells (NSCs), mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) that produce neural cells [18,24,71]. For the first time, an immunoablative therapy with HSCs was conducted on MS patients in 1995 [7]. After that, different types of stem cells have been used to prevent chronic demyelination and progressive axonal atrophy [2,27,42,64,87]. Despite the several benefits of HSCs, secondary malignant disease, Epstein-Barr virus (EBV)-induced lymphoma and thrombocytopenia have been hampered the applications of HSCs in clinical therapy [1]. Additionally, ESCs obtained by *in vitro* fertilization are epigenetically unstable and vulnerable to environmental or culture condition [78]. Furthermore, to prevent teratocarcinoma organization, iPSCs should be differentiated to desired cells before transplantation [19]. Interestingly, it has been demonstrated that transplantation of autologous or allogenic MSCs through cells replacement,

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neuroprotective effects and secretion of immunoregulatory factors improve immunomodulation and remyelination process in the CNS [55].

Here, we presented the current literatures on MSCs (autologous and allogenic) transplantation in MS patients and explored the potential therapeutic mechanisms of MSCs in MS. We also discussed the major challenges of MSCs for clinical therapy.

2. Mesenchymal stem cells

MSCs are multipotent progenitor cells that can potentially differentiate into multilineage cells. For the first time, MSCs were isolated from bone marrow as colony firming unit fibroblast (CFU-F) by Friedenstein et al. in 1967 [49]. Furthermore, MSCs were also isolated from other tissues such as adipose tissue, umbilical cord, fetal liver, muscle and lung. It has been shown that isolated stem cells are able to differentiate into mesenchymal cells. In addition, these cells are also capable to differentiate into ectodermic and endodermic cells and generate skeletal myocytes, neurons and visceral mesoderm cells under specific experimental condition [85]. MSCs criteria are described by positive expression of CD73, CD90, CD105 and negative expression of CD34, CD45, CD11b, CD14, CD19, CD79a and human leukocyte antigen-DR (HLA-DR) [77]. Beyond the potential ability of MSCs in repopulation and differentiation, their feasibility to autologous transplantation makes them as an ideal candidate in clinical applications. > 2000 patients with different types of diseases, including like graft-*versus*-host disease (GVHD), hematologic malignancy, organ transplantation, neurological diseases, and autoimmune diseases received autologous MSCs for their treatment [41].

3. Therapeutic mechanisms of MSCs in MS disease

3.1. Migration

Different characteristics of MSCs including their ability for migration to the injury site, differentiation to neural lineage and immunomodulation by secreting neurotropic and anti-inflammatory factors, make them as attractive therapeutic strategy in MS disease [83]. Blood brain barrier (BBB) is a semi-permeable boarder that restricts the passage of macromolecules and cells across the BBB. Following BBB disruption, MSCs can cross the BBB through deficient areas [15,75]. Furthermore, it has been shown that numerous chemokines, growth factors and receptor interactions such as stromal cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4), stem cell factor/c-kit, HGF/c-Met, vascular endothelial growth factor (VEGF)/VEGF receptor, platelet-derived growth factor (PDGF)/PDGF receptor, monocyte chemoattractant protein-1 (MCP-1)/C-C chemokine receptor type 2, and high mobility group box 1/receptor are involved in homing and migration of MSCs [83]. Among these, CXCR4 and SDF-1 interaction play important role in migration of MSCs into the tissue upon specific chemotactic triggers [88]. It has been demonstrated the correct targeting of transplanted MSCs increases following overexpression of SDF-1 [75]. Moreover, previous studies indicated that MSCs show leukocyte-like rolling and tethering with endothelium to cross the BBB [74]. Pluchino et al. reported that VLA-4 is responsible for MSCs interaction with BBB-endothelial cells in experimental autoimmune encephalomyelitis (EAE) mice [65]. Another study on rat model of traumatic brain injury revealed that engraftment of MSCs is highly dependent on the expression of VLA-4 in MSCs and interaction with endothelial VCAM-1 [52]. Furthermore, matrix metalloproteinases (MMPs) such as MMP2 and membrane type 1-MMP have also important role in passage of MSCs through endothelial membrane [72]. Teo et al. described two further mechanisms for MSCs crossing through the endothelial membrane including transcellular diapedesis and paracellular diapedesis. It has been postulated that MSCs can cross the endothelial membrane through an individual endothelial cell or through spaces between the endothelial cells [79].

In addition, the environmental factors have also crucial role on capability of MSCs for homing to the injured site [62]. Indeed, MSCs can alter their outer membrane receptors and secrete factors under inflammatory cytokines such as TNF-α and IL-1 and growth factors such as platelet derived growth factor-AB (PDGF-AB) and insulin growth factor-1 (IGF-1) [62]. However, gene engineering or pre-conditioning of MSCs facilitate their migration to the lesion areas. Subsequently, previous studies reported that overexpression of CCR7, SDF-1 and IGF-1 by gene engineering improves the migration of MSCs into the inflamed region [36,40]. Gonzales-Portillo et al. revealed that mannitol increases the number of gap junction and BBB permeability by endothelial cells contraction [34]. It has been demonstrated that culture condition has a key role in expression of homing molecules. It has been shown that if cells are cultured for long duration, the expression of chemokine receptors as well as chemotactic responses of MSCs will decrease. Tondreau et al. reported the expression of VLA-4 and MMPs in MSCs were lost between passages 3 and 5 of cell culture [80]. Moreover, the origin of MSCs is also important in migratory capability of these cells. Rossi et al. suggested that isolated MSCs from the adipose tissue (Ad-MSCs) and umbilical cord Wharton's jelly (UC-MSCs) express more migratory factors than bone marrow-derived MSCs (BM-MSCs) [73]. It has been shown that CCR1 are expressed only by Ad-MSCs [62] and the expression level of integrin-α4 in Ad-MSCs and UC-MSCs are more than BM-MSCs [23].

3.2. Immunomodulation

MS is an autoimmune demyelinating disease that primarily occurs after migration and infiltration of pathogenic T cells to the CNS and secretion of different cytokines such as IL-1β, IL-6, IL-17, TNF-α and INF-γ [90]. Additionally, humoral immune mechanisms play key role in initiation and progression of MS [43,51]. MSCs are considered as immunomedulator cells *via* direct or paracrine interaction with immune cells. Actually, MSCs suppress T cells proliferation, inhibit the production of pro-inflammatory cytokines and regulate the ratio of Th2/Th1 [29]. MSCs also arrest the cell cycle of B cells and inhibit their division and antibody production [17]. Moreover, MSCs affect natural killer cells (NKC) and dendritic cells and inhibit their activation and maturation [68,76]. Additionally, MSCs exert the immunosuppressive activity by regulation of regulatory T-cell (Treg)'s function [29]. Several MSCs-derived soluble factors including transforming growth factor-β1 (TGF-β1), prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), indoleamine-pyrrole 2, 3-dioxygenase (IDO), nitric oxide (NO), and interleukin-10 (IL-10) have been proposed to mediate the immunosuppressive effects of MSCs. However, these soluble factors are minimally expressed in non-inflammatory conditions; inflammatory factors such as IL-1, TNF-α and IFN-γ stimulate MSCs to produce anti-inflammatory factors [29,46,69]. Peron et al. demonstrated that human endometrial MSCs reduce the infiltration of Th1 and Th17 into the CNS and ameliorate behavioral manifestations of EAE. In this regard, the probable strategy for amelioration of EAE were mediated through up-regulation of IL-10, IL-27, IDO, and Treg [63].

Previous studies showed the types of secretory factors are dependent on the origin of MSCs. Payne et al. demonstrated that in EAE mice, BM-MSCs *via* secretion of different kinds of soluble factors exert stronger effect on modulating T-cell's responses compared with UC-MSCs and Ad-MSCs [62]. In addition, the immunomodulatory effects of MSCs depend on the type of disease and inflammatory status. In fact, it has been shown that MSCs altered their therapeutic effect under environmental condition. In this regard, Rafei et al. demonstrated that MSCs conditioned media inhibits phosphorylation of STAT3 in CD4 T-cell derived from EAE mice. MSC-driven MMP is responsible to do this by proteolysis of MSC-driven CCL2 and its conversion to an antagonistic derivative. Besides, it has been shown that antagonizing of CCL2 suppresses phosphorylation of AKT and is led to up-regulation of B7H.1 in CD4 T-cell. The interaction of B7H.1 and programmed death-1 (PD-1)

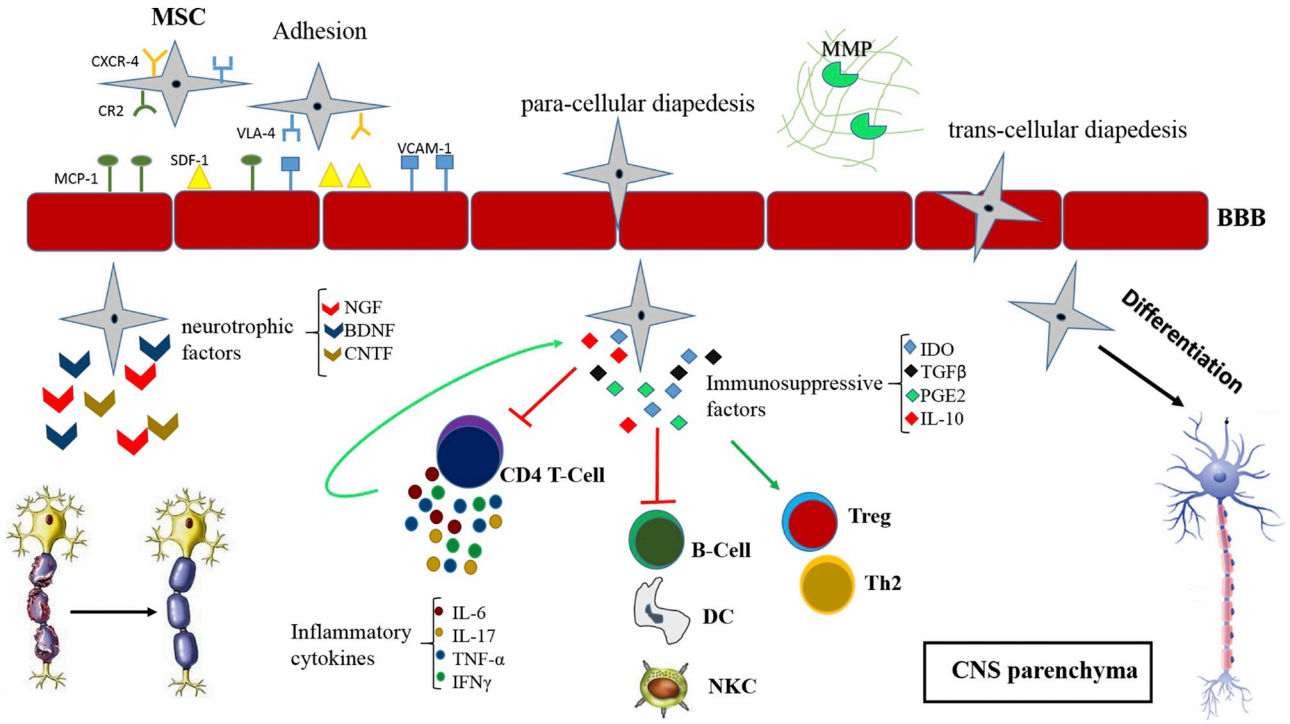

Fig. 1. Therapeutic mechanisms of MSCs in MS disease. MSCs can cross the BBB (transcellular diapedesis and paracellular diapedesis) and migrate to the inflammatory sites through interaction with adhesion molecules and their receptors (CXCR4-SDF1, CR2-MCP-1, and VLA4-VCAM1). MMPs have an important role in degrading extracellular matrix. MSCs can differentiate to neurons, astrocyte and oligodendrocytes. In addition, MSCs secrete immunosuppressive factors such as IDO, TGFβ, PGE2, and IL-10 to suppress the proliferation of inflammatory immune cells (CD4 T-Cells, B-Cell, DC, and NKC), maturation, activation and secretion of inflammatory cytokines. Inflammatory cytokines stimulate the MSCs to secrete immunosuppressive factors. Besides, MSCs increase the levels of anti-inflammatory cytokines followed by up-regulation of Treg and Th2. MSCs also release neurotrophic factors (NGF, BDNF, and CNTF) to improve cell survival and neural function.

arrest CD4/CD8 cell cycle mitigated proliferation and reduced the secretion of IL-2 [67]. Furthermore, several studies on EAE model showed the presence of sufficient amount of MSCs in CNS tissue and lymphoid organs ameliorate EAE manifestation through reduction of Th1, Th17, and the inflammatory cytokines. Additionally, MSCs increase the expression of anti-inflammatory cytokines followed by up-regulation of Treg and Th2 in EAE mice [3,67]. In this regard, it seems that direct contact between MSCs and T-cells is important in immunosuppressive activity of MSCs [29]. It has been demonstrated that under inflammatory condition, several adhesion molecules such as CD274, vascular cell adhesion molecule-1 and galectin-1 are overexpressed in MSCs that increase cell-cell contact and improve immunomodulation [29,33,70]. Additionally, low levels of ICAM-1 and VCAM-1 are expressed in MSCs. It has been suggested that ICAM-1 and VCAM-1 have important role in interaction of MSCs with T lymphocytes and suppress the inflammatory process [62,85]. Inflammatory cytokines secreted from T lymphocytes stimulate the expression of ICAM-1 and VCAM-1 in MSCs. Ren et al. revealed that MSCs deficiency in either ICAM-1 or VCAM-1 expression impaired the immunosuppressive effects of MSCs [70]. Although it should be noted that an important part of MSCs most probably is deactivated by autophagy following their administration in EAE mice. Therefore, it has been reported that impeding the autophagy improves immunomodulation through increasing T-cell proliferation and up-regulation of prostaglandin-endoperoxide synthase 2 (PTGS2) and its downstream factor as PGE2 [21].

3.3. Differentiation and neuroregeneration

The most important problem in treatment of CNS degeneration is the inability of neural tissue to fully repair itself. However, in demyelinating MS disease, neurodegenerative lesions induce permanent damages in patients. Recently, the therapeutic use of MSCs due to their capability in differentiation to other types of cells has been considered as a useful approach for treating MS patients [4,59]. MSCs can differentiate toward mesodermal and non-mesodermal cells such as neurons, astrocytes and oligodendrocytes *in vitro* and *in vivo* [77,85]. Infusion of MSCs was led to migration of stem cells to the injured tissues and replacement of damaged resident cells [83]. Furthermore, the use of transplanted MSCs for therapeutic purposes is considered as an alternative strategy to recover CNS lesions [75]. MSC-derived neural progenitor cells (MSC-NPs) are the subpopulation of MSCs that exhibit neuroectodermal lineage characteristics with fewer tendencies to differentiate toward mesodermal cells. These properties make them as an appropriate choice to reduce the risk of ectopic differentiation in MSCs transplantation. Harris et al. showed that intrathecal (IT) transplantation of MSC-NPs in MS patients improves the median EDSS, muscle strength and bladder functions [37].

Previous report indicated that intranasal infusion of MSCs in patients suffer from neurodegenerative diseases was led to quick migration of the stem cells during 1 to 2 h post-transplantation, but approximately no MSCs were detected in CNS lesions over 72 h later [25]. Interestingly, despite the lack of transplanted MSCs in the CNS, improvement in disease related symptoms was observed. This effect might be related to the secretion of paracrine neurotrophic and neurotropic factors *via* exosomes or microvesivles [10,75]. It has been shown that MSCs through secreted factors induce the axonal outgrowth and increase the survival of cells *in vitro* [12,44]. Subsequent studies revealed that environment exerts critical effect on BM-MSCs to produce different neurotrophic factors [48]. Recently, Li et al. reported that transplanted BM-MSCs release paracrine factors in exosomal structures to reduce clinical symptoms, inflammatory infiltration and axonal demyelination in EAE mice. Additionally, 676 proteins including inflammatory response-related proteins, immune response-related proteins and myelination-related proteins have been also identified in BM-MSC-derived

Table 1
Clinical applications of MSCs in MS patients.

Type of study	MS type	N (Female/ Male)	EDSS	Source of MSCs	Route of administration	Number of MSCs	Single or repeat	Follow up	Side effects	Key findings	Ref.
Open label pilot trial	PPMS SPMS	10	3.5–6	BM-MSCs	IT	5.5 mL containing 8.73×10^6 cells	Single	13–26 months	Nine patients experienced a slight headache and 2 patients were diagnosed with iatrogenic meningitis with no abnormalities in CSF similar to other regular intrathecal injections.	Intrathecal injection of MSCs was associated with improvement in some patients and halted disease progression in others.	[59]
Phase 1/2 open-safety clinical trial	Progressive MS	15 (8/7)	6.7 (4–8)	Autologous BM-MSCs	Combination of IT and IV	10×10^6 to 15×10^6 cells	Single	< 25 months	Transient fever and headache were reported in 15 patients. No major adverse effects were reported during follow up.	Transplantation of MSCs in patients with MS and ALS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects.	[42]
Open label pilot trial	SPMS	10 (6/4)	6.42 (4–7.5)	Autologous BM-MSCs	IT	1.5 to 100×10^6	Single	12 months	Transient encephalopathy and seizures in one patient who was injected with the highest number of BM-MSCs.	Early signs of clinical improvement were observed in most patients by 3 months and maintained up to 1 year.	[89]
Open label pilot trial	RRMS	7 (6/1)	–	Autologous BM-MSCs	IT	10 mL containing at least 20×10^6 cells	Single	6 months	–	FOXP3 mRNA was increased in PBMC associated with clinical stability.	[57]
Open label pilot trial	SPMS PPMS RRMS	8 (3/5)	5.56 (3.5–6.5)	Autologous BM-MSCs	IV	2×10^6 cell per kg	Repeated per month, 4–8 months	4–12 months	In one patient, moderate general weakness was observed for several hours after each injection	The results showed the safety of this treatment and its moderate clinical efficacy in MS patients who are incurable using traditional approaches.	[61]
Open label pilot trial	PPMS SPMS	25 (19/6)	5.5–7	Autologous BM-MSCs	IT	$1–1.5 \times 10^6$ cells/mL density	Single	12 months	No serious complications	It was associated with some improvement in some patients and halted disease progression in others. In five patients, MSC therapy had no effect on the course of the disease.	[6,58]
Double-blind, placebo-controlled phase II trial	RRMS	9 (7/2)	3.5 (3.0–6.0)	Five patients received autologous BM-MSCs; Four patients received placebo	IV	$1–2 \times 10^6$ cells/kg	Single	6 months	No serious adverse effects	Bone-marrow-MSCs are safe and may reduce inflammatory MRI parameters supporting their immunomodulatory properties.	[50]
Open label pilot trial	PPMS SPMS	6 (4/2)	6.5–9	Autologous BM-MSCs- NPCs	IT	$5 \times 10^3–1.6 \times 10^7$	Repeated 2–5 times	7.4 years	No serious adverse effects	These findings support the safety and tolerability of IT-MSC-NP treatment in patients with progressive MS	[38]
Open-label, phase 1	PPMS SPMS	24 (16/8)	6 (3.0–6.5)	Autologous BM-MSCs	IV	$1–2 \times 10^6$ cells/kg	Single	16 months	No serious adverse effects	Autologous MSCs transplantation in MS appears feasible, safe, and well tolerated.	[14]
Open-label prospective phase 1/2a	SPMS RRMS	10 (4/6)	5.1 (± 1.73)	Autologous BM-MSCs and MSC-CM	IT	$93–168 \times 10^6$ for MSCs and 13–20 mL for CM	Single	12 months	No serious adverse effects	Both BM-MSCs and MSC-CM are safe with relative efficacy in stabilizing the disease and reversing symptoms.	[20]

(*continued on next page*)

Table 1 (*continued*)

Type of study	MS type	N (Female/ Male)	EDSS	Source of MSCs	Route of administration	Number of MSCs	Single or repeat	Follow up	Side effects	Key findings	Ref.
Open label pilot trial	RRMS SPMS	2 (1/1)	~ 3	Umbilical cord MSCs	IV	$1–2 \times 10^6$ cells/kg	Repeated 7 times	8 years	No obvious adverse reactions or residual pathological syndromes appeared during transplantation.	Umbilical cord MSCs play an important role in immune regulation and neural protection.	[56]
Triple-blinded, placebo controlled, randomized phase 1/2	SPMS	34 (21/9)	7.6–7.8	Autologous Ad-MSCs	IV	1×10^6 to 4×10^6 cell/kg	Single	12 months	No serious adverse events were identified after 12 months of follow up.	Infusion of autologous Ad-MSCs was safe and feasible in patients with SPMS.	[28]

PPMS: Primary progressive MS; SPMS: Secondary progressive MS; BM-MSCs: Bone marrow mesenchymal stem cells; IT: Intrathecal; MSCs: Mesenchymal stem cells; IV: Intravenous; RRMS: Relapsing-remitting MS; NPCs: Nucleus pulposus cells; CM: Conditioned media; Ad-MSCs: Adipose tissue derived mesenchymal stem cell.

exosomes [48]. - BM-MSC-derived exosomes contain several factors that are led to immunoregulation and neuroprotection [81]. It has been demonstrated that intraperitoneal (i.p.) injection of human amnion-MSCs in EAE mice increases the expression of nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), and brain-derived neurotrophic factor (BDNF). These factors increase the survival of transplanted cells, inhibit programming cell death and improve neuronal function [60]. Besides, Bai et al., report suggested that soluble factors secreted by MSCs in conditioned medium (CM) are regarded as an alternative therapeutic strategy in MS disease [4]. Hepatocyte growth factor (HGF) is one of the most important factors in CM and has a key role in EAE recovery, whereas blocking of HGF and its tyrosine kinase receptor (c-Met) declined the neurotrophic activity that is mediated by CM. It has been shown that the expression level of MSC-derived HGF can be enhanced by epidermal growth factor and TNF-α to promote cell survival and angiogenesis [4]. Fig. 1 depicts some therapeutic mechanisms of MSCs in MS disease.

4. Application of MSCs in MS patients

Mohyeddin Bonab et al. conducted the first study on application of MSCs in MS. They injected autologous BM-MSCs intrathecally (IT) in PPMS and SPMS patients and followed them up with monthly neurological assessment until 13–26 months and MRI scan at the end of one year. Their data indicated that IT administration of MSCs declined the signs of MS disease. However similar to other regular IT injections, the slight and transient headache was observed in 9 patients and iatrogenic meningitis was diagnosed in 2 patients. Although no abnormalities were detected in CSF of both patients and micro-biological studies were also negative [59]. After that, numerous studies have been carried out using different routes of administration, number of transplanted cells, sources of MSCs and number of injections (Table 1). Karussis et al. combined intravenous (IV) and IT administrations of autologous BM-MSCs to maximize the potential therapeutic effect of MSCs in progressive MS patients. Immunological, neurological and MRI assessments in 24–48 h, 1, 3 and 6 months after injection showed an improvement in disease manifestations, decrease in lymphocyte proliferation and increase in the proportion of CD4, CD25 and Treg cells [42]. Another study found that IT administration of MSCs without IV injection generates no systemic response in MS patients. In this regard, Mohyeddin Bonab et al. showed that IT transplantation of BM-MSCs in 23 MS patients was not caused any significant changes in expression of FOXP3, IFN-ϒ, TGF-β, IL-4, IL-10 and IL-6 in peripheral blood mononuclear cells (PBMCs). However, previous reports revealed an improvement in visual acuity, visual evoked response latency and increasing optic nerve area [16,89]. Besides, the tolerance of repeated infusions of autologous MSCs has a key role in therapeutic response. Several studies reported that repeated infusion of MSCs were tolerated well by patients with no serious side effect [38,56]. Odinak et al. suggested that monthly infusion of MSCs for 4–8 months were tolerated well and generated moderate clinical efficacy in 6/8 of patients. In contrast, one study reported transient encephalopathy and seizures in one patient followed by high concentration of MSCs (100×10^6) [61]. Moreover, different sources of MSCs such as UC-MSCs and Ad-MSCs have beneficial effects on neural protection and immune regulation [28,56]. For the first time, Dahbour et al., suggested that IT administration of conditioned medium of autologous MSCs (MSC-CM) followed by injection of BM-MSCs are safe method with relative efficacy in stabilizing the disease and reversing symptoms [20].

5. Challenges and risks of MSCs administration in clinical therapy

5.1. Challenges of MSCs

In spite of MSCs efficiency to regulate immune system and attenuate the progression of MS disease, there are several challenges that need to

be resolved. Indeed, define a standardized method about route of administration, number of MSCs and time of repetition are necessary [13,30]. Several clinical trials on MS patients revealed that IV injection (systemic administration) and IT infusion (local administration) are the main methods for transplantation of MSCs [32,85]. It has been shown that IV administration is non-invasive and most convenient procedures that generate systemic concentration of MSCs in patients. However, due to the circulation of stem cells through different tissues and trapping them in systemic organs, a small number of cells enter the CNS as an impaired tissue in MS patients. Although several studies on RRMS, SPMS and PPMS indicated that IV injection of MSCs has remarkable immunoregulatory effect and neuroprotective activity [14,28,50,56,61]. However, it seems that IT administration is more effective than systemic injection because high number of MSCs can be detected in the brain following local injection. IT injection of stem cells bypasses the BBB by delivering MSCs directly into the CSF [47,58]. Previous studies on MS patients showed that IT administration of MSCs reduced disease progression and no changes in expression of cytokines were detected in systemic circulation. The results of this study suggested the immunomodulatory or neuroregenerative effects of MSC are exerted locally in the CNS [6].

In spite the proper concentration of MSCs in CNS of MS patients, the IT administration of MScs has critical complications. The IT injection is an invasive procedure and induces inflammation, edema and trauma in the injection site. Nevertheless, Mohyeddin Bonab et al. studied the IT transplantation of BM-MSCs in MS patients. The results indicated that IT transplantation is completely safe and feasible for therapeutic approach and patients had not any problems even one year after injection [59]. Another problem about MSCs transplantation is the number of cells that would be entered through each type of administration. The cause of variation in the results of same procedure in similar patients show that there is no standard protocol to reduce clinical symptoms and obtain appropriate concentration of MSCs in the CNS [30].

5.2. Risks of MSCs

There are some concerns about potential risks behind the use of MSCs including infusion related toxicity, infection, ectopic tissue formation, cancer and paradoxical disease activation [30]. Infection is one of the acute risks that might be occurred in both donor and receiver. In donors, infection could be happen following MSCs obtaining. The injection site of receivers is regarded as a suitable region for infectious of micro-organisms. Furthermore, application of immunosuppressive agents increases the incidence of infection. Infusion related toxicity is another acute risk of stem cell therapy [13]. Different stages of MSCs preparation, their maintenance in culture medium and freezing medium containing several allergen substances like fetal bovine serum and dimethylsulfoxide can induce toxicity in the receivers [11,39]. Additionally, the graft cell dose and number of passages affect the possible toxicity [13]. In the regard of malignancy and ectopic tissue formation, all the studies have been performed theoretical and based on our knowledge, there is no case to report [82]. The other main risk in MSCs therapy is paradoxical disease activation. Previous study showed that MSCs suppress the proliferation of Th1 and Th17 and their related cytokines production, but further studies surprisingly revealed that the reciprocal Th1 and Th17 regulation by MSCs. Darlington et al. reported that MSCs stimulate the proliferation Th17 and IL-17 production in MS patients [22]. Another reciprocal function is related to polarization of MSCs based on the type of toll-like receptor (TLR) expressed on MSCs. In this regard, the MSCs that primed by TLR4, function as pro-inflammatory mediators while MSCs that primed by TLR3, predominantly express immunosuppressive factors [84].

6. Conclusions

In the last two decades, MSCs have been emerged as a powerful and safe strategy in cell-based therapy. The MSCs therapy is not only important in terms of anti-inflammatory properties and neuroregeneration, but also the ease of isolation, cell expansion and administration; make them as an appropriate cell source for stem cell therapy. However, there are still some ambiguities related to standard protocols for laboratory management of MSCs. Optimal cells dosage, time of repetition and route of administration should be addressed before clinical applications of MSCs in MS. Additionally, a careful evaluation of cell free stem cell products such as conditioned media and exosomes and also combination therapy with anti-inflammatory drugs and other source of stem cells should be carried out in future.

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Declaration of competing interest

The authors declare no conflict of interest related to this study.

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