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Stem Cell Therapy – Approach for Multiple Sclerosis Treatment

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Abstract

Context: Multiple sclerosis (MS) is an autoimmune and inflammatory disease that affects the central nervous system (CNS). In MS, activated T-cells for self-antigens, such as myelin, attack erroneous targets in the CNS and result in axonal demyelination and neurological disability. Stem cell (SC) therapy has potential applications in treating neurological disorders.

Evidence Acquisition: The reasoning for use of SCs from different sources, as a therapeutic option in MS, arose from the expectation that they have the capacity to remyelinate and differentiate into oligodendrocyte precursor cells. Many SC types are under testing for treating MS and, the most common, are neural SC (NSC), embryonic SC (ESC), mesenchymal SC (MSC) and hematopoietic SC (HSC).

Results: The NSCs, namely adult NSCs, bone marrow-derived-NSCs and neural progenitor cells, are capable of differentiation into oligodendrocytes and induce remyelination. The MSCs influence on the rate of repair of all endogenous progenitors. The autologous HSC transplantation is an option in cases that do not respond to standard therapy and also meliorate the symptoms and limit progression of disease. The ESCs have shown neuroprotection in cases of MS, through a yet unclear immunosuppression mechanism.

Conclusions: Recently, cell transplantation has introduced a novel approach for treatment of neurological disorders, such as MS. Therefore, focusing on safety issues, while bridging from the basic SC sciences to the clinical transplantation trials, has a crucial role in cellular therapy programs. This review will discuss in detail the experimental and clinical use of these SC populations and their probably mechanisms in the treatment of multiple sclerosis.

Keywords: Cell- and Tissue-Based Therapy, Stem Cells, Mesenchymal Stromal Cells, Multiple Sclerosis, Hematopoietic Stem Cells, Myelin Sheath

1. Context

Multiple sclerosis (MS) is an autoimmune and chronic inflammatory multifocal demyelinating disease of the central nervous system (CNS) (1-12). Demyelination can occur via hereditary demyelinating and metabolic disorders, viral infections, nutritional and toxic disorders, and also in association with trauma and stroke, known as CNS lesions. The MS is characterized by three mechanisms, including demyelination, remyelination failure and axonal loss. In order to select the best approach for MS treatment, two objectives must be kept in mind: to prevent progression and to repair damages that have already been constituted (13-15). There are different medications that were introduced for the treatment of patients with relapsing MS, such as interferon beta-1a (Avonex®, Biogen, Cambridge, MA, USA/Rebif®, Merk Serono, Darmstadt, Germany), recombinant interferon β-1b (Betaferon®, Boehringer Ingelheim, Ingelheim, Germany), natalizumab, as a α4 integrin antagonist monoclonal antibody (Tysabri®, Biogen, Cambridge, MA, USA), teriflunomide (Aubagio®, Genzyme, Cambridge, MA, USA), dimethyl fumarate (Tecfidera®, Biogen, Cambridge, MA, USA), alemtuzumab (Lemtrada®, Genzyme, Cambridge, MA, USA), clatiramer acetate (Copaxone®, Teva Pharmaceutical Industries, Petah Tikva, Israel), fingolimod (Gilenya®, Novartis, Basel, Switzerland), etc. (3, 9, 16-25). Although several patients with MS respond fairly well to these medications, oth-

ers continue to show deterioration in motor and cognitive functions (20). Nowadays, another approach for the treatment of MS is stem cells (SCs) therapy. The SCs are unspecialized cells that belong to the group of multipotent cells. Although these cells are undifferentiated, they are capable to proliferate or reproduce themselves, and they can differentiate into other types of body cells, with specialized functions (26). The SCs have been regarded as a promising treatment for neurodegenerative disease, such as MS (27, 28). There are many investigations about the potential of four SC types, including neural stem cells (NSCs), embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and non-expanded adipose stromal vascular fraction or expanded adipose tissue-derived MSCs in MS stem cell therapy (1, 29, 30). Therefore, we will review their capability in the treatment of MS.

2. Evidence Acquisition

2.1. Search Strategy

This review was performed using "cell therapy", "mesenchymal stem cells", "Multiple sclerosis", "stem cells", and "stem cell transplantation", as search terms, and PubMed, as search engine. Subsequently, the search period was set from 1988 to 2014.

2.2. A Brief History of Stem Cell Therapy for Multiple Sclerosis

In 1977, exogenous myelinating cells were injected into demyelinated lesions, in the CNS, by Bill Blakemore. He demonstrated successful remyelination in CNS after cell transplantation. Similar studies showed promising results and cell therapy was suggested for treatment of neurodegenerative disorders, such as MS. After about four decades, findings of several clinical cell transplantation trials on MS were reported. In most of these studies, autologous bone marrow derived SCs were injected, intravenously (31). Furthermore, in 1995, autologous HSC transplantation was performed for refractory MS (11). Recently, SC therapy has been recommended for treatment of various degenerative diseases, including MS (1, 6), using different types of SCs (4, 32, 33).

2.3. Potential of Neural Stem Cells for the Treatment of Multiple Sclerosis

The NSCs can be isolated from the adult CNS, from the subventricular zone (SVZ) of the lateral ventricle wall, which is a major germinal region that is used for isolation of NSCs and, consequently, are termed as SVZ-NSCs (34, 35). The fundamental properties of these cells are self-renewal, multipotency and long distance migration, within the inflamed CNS (36-41). These properties make NSCs suitable for cellular therapy in brain. However, there is increasing evidence that NSCs have neuroprotective and immunomodulatory properties (42-46). Many studies exist that reported beneficial effects of NSCs therapy, in neurologic disorders, in several animal models of different neurologic disease, such as: Huntington disease, Parkinson disease (PD), MS, stroke, spinal cord injuries and amyotrophic lateral sclerosis (47). Therefore, for NSCs to be useful in the treatment of MS, they would need to differentiate into both oligodendrocytes and neurons. Several investigations have shown that NSCs can differentiate into mature oligodendrocytes, in animal models of dysmiyelination (43, 48-53) and neurons, in animal model of cerebral degeneration (54). Recently, other investigations reported the therapeutic potential of adult NSCs (aNSCs) in MS (40, 42, 43, 55). Another type of NSCs, investigated in neurodegenerative diseases, are bone marrow-derived NSCs (BM-NSCs), and these cells have neurogeneratory potential and immunomodulatory effects (56, 57). The BM-NSCs are preferred to SVZ-NSCs, through ethics. Neural progenitor cells (NPCs) are other neural cells that, similarly to NSCs, are capable of differentiation into oligodendrocytes and remyelination. Furthermore, NPCs have anti-inflammatory properties in the CNS, by producing a variety of cytokines and neutrophins (58, 59). These findings clearly confirmed the tremendous potential of NSCs therapy for the treatment of patients with MS, even though it seems that more investigations are need for the confirmation of viability of the method of hNSCs isolation and evaluation of clinical efficacy of NSCs therapy, in animal model.

2.4. Mesenchymal Stem Cells as a Therapeutic Strategy for Multiple Sclerosis

The MSCs are capable transdifferentiation into cells of the endodermal and ectodermal origin, including possible neural transdifferentiation and immunomodulating properties. Because of this ability of MSCs, they have been described as multipotent stromal cells (60-63). These cells can be prepared from a variety of sources, including bone marrow, amniotic fluid, deciduous teeth, adipose tissue, umbilical cord, synovial membranes, peripheral blood, etc. However, bone marrow has been shown as the main source of MSCs (64-69). Recently, numerous studies have focused on MSCs, for cell therapy in many neurodegenerative disorders, including MS (70-73). There are several clinical trials and, also, basic studies that used human MSCs, as a candidate for treatment of MS (Table 1). The MSCs can migrate into injured CNS and differentiate into cells expressing neural and glial cell markers (74). Indeed, MSCs can differentiate into neuronal cells and this differentiation is confirmed by biomedical, anatomical and electrophysiological characteristics (75). Harris et al. investigated the potential of MSCs on promoting repair and recovery after intrathecal injection, into mice with experi-

mental autoimmune encephalomyelitis (EAE). Their results had shown an improved neurological function, compared to controls, and suggested that MSCs can influence the rate of repair of all endogenous progenitors in spinal cords. Therefore, MSCs can be used in MS patients for promoting CNS repair (76). Reduction of expanded disability status scale (EDSS) was observed when Karussis et al. used autologous MSCs injected intrathecal plus intravenous, in patients with MS (77). Investigations of the effects of intrathecal injection of autologous MSCs in MS patients have shown clinical improvement in treated patients (78). Neurotrophin-3 (NT-3)-modified MSCs, via recombinant adenoviral vector (Adv), implanted into a region of ethidium bromide (EB) induced remyelination in the rats with demyelinated spinal cord. Results have shown that AdvNT-3-MSC implants upgrade the endogenous remyelinating cells, to participate directly in myelination. These data suggest that genetically modification of MSCs could be a potential therapeutic approach for elevating the efficacy of MSC treatment for MS and other neurodegenerative disease (79). However, our data and other publications, about the use of MSCs in MS patients, have revealed the feasibility and safety of MSC therapy.

Table 1. Published Studies Using Human Mesenchymal or Mononuclear Stem Cells for the Treatment of Multiple Sclerosis[a]

Stem Cell Type	Number of Patients	Type of Disease	Route of Administration	Study Findings	Phase	Ref.
Bone marrow MSCs	15	advanced MS	intrathecal, intravenous	clinical feasibility, safety, and immediate immunomodulatory effects - no major adverse effects	I, II	(77)
Bone marrow MSCs	10	advanced MS, relapsing-remitting MS, and secondary progressive MS	intrathecal	clinical not radiological efficacy - no adverse effect	I	(78)
Bone marrow MSCs	25	advanced MS	intrathecal	improvement and stabilization of the disease course - no adverse effect	I	(80)
Unsorted bone marrow stem cells	6	relapsing progressive MS	intravenous	therapeutic potential	I	(81)
Bone marrow MSCs	10	secondary progressive MS	intravenous	evidences of structural, functional, and physiological improvement	I/IIa	(82, 83)
Bone marrow MSCs derived neural stem cells	-	-	-	influence the rate of repair through effects on endogenous progenitors in the spinal cord in MS	in vitro study	(84)
Bone marrow MSCs	8	progressive MS	intravenous	safety of the protocol and the moderate clinical efficacy - After 12 months, the improvement and stabilization - no significant side-effects	I	(85)
Bone marrow MSCs	7	relapsing-remitting MS	intrathecal	MSCs effectiveness in obtaining a sufficient number of Treg lymphocytes	-	(86)
Bone marrow MSCs	-	-	-	monitoring the immunological effects of MSCs	in vitro study	(87)
Allogeneic umbilical cord MSCs	1	primary progressive MS	intrathecal, intravenous	a potent immunosuppressive effect	-	(88)
Bone marrow MSCs	10	primary and secondary progressive MS	intrathecal	functional improvement in pyramidal, cerebellar and sensory pathways, and bowel function in some patients - decreasing in the number of plaques in one patient in MRI	I	(89)
Human placenta MSCs	16	secondary progressive and relapsing MS	intravenous	safety and well tolerability - mild to moderate adverse events (headache, nausea, infusion site reactions)	Ib	(90)
Bone marrow MSCs	25	relapsing-remitting, secondary progressive, progressive relapsing	-	MSCs inhibit proliferation of mitogen/myelin-stimulated T Cells in MS patient - immune suppression by MSC in MS patients	in vitro study	(7)

[a]Abbreviations: MS: Multiple sclerosis; MSCs: Mesenchymal stem cells.

2.5. Hematopoietic Stem Cell Transplantation in Multiple Sclerosis

Hematopoietic stem cells (HSCs) are multipotent SCs that give rise to all the blood cell types, from the lymphoid and myeloid lineages. There has been an increasing use of HSC transplantation (HSCT) over the last years, for the treatment of hematological and non-hematological neoplasms and several autoimmune diseases, including MS (91, 92). More than 600 published reports investigated bone marrow HSCT for the treatment of MS (93-95). The identifying characteristic of MS is inflammatory demyelination, with neurodegeneration (71). In MS, activated T-cells, specific for self-antigens, such as myelin, migrate into CNS and result in axonal demyelination (96). First line therapy for patients with MS is immunosuppression/immunomodulation therapy that is generally employed with success (97). However, several patients do not respond to these therapies and relapse with neurological deterioration. Patients with relapse can benefit from allogeneic or autologous HSCT, as a viable therapeutic option. The HSCT, as a therapeutic intervention in MS treatment, was suggested in 1995 and initial results were reported beginning with 1997 (98, 99). Several studies, in both animal models of MS and clinical trials have shown that HSCT can induce MS remission and improvement (12). However, a few studies argued that HSCT has no effect on MS improvement. The EAE-diseased mice were treated with allogeneic HSCT, during the acute phase of MS, and all mice went into a complete remission and did not show relapses (100, 101). Also, autologous HSCT, in EAE mice, resulted in complete remission (102, 103). Takahashi et al. transduced TREM-2 (an innate immune receptor) in bone marrow-derived myeloid precursor cells and intravenously injected it to mice with EAE, an animal model of MS. They observed that TREM-2 transduced myeloid precursors ameliorate clinical symptom of MS in mice with EAE, by clearance of nervous tissue debris and degenerated myelin (104). Resident perivascular macrophage and microglia, in the CNS, were physiologically derived from myeloid progenitors of HSCs, during development as well as throughout life span (105-107). Moreover, it has been presented that several HSCs are recruited to sites of neurological damage, to become functional perivascular macrophage and microglia like cells (29, 108, 109). Macrophages efficiently remove cellular debris in acute injuries of the neural system. This is accompanied by amelioration of inflammation and neuroinflammatory diseases recovery (110-112). Another study evaluated clinical and neurological outcomes, after autologous HSCT in 22 patients with progressive MS. They showed that most patients with progressive MS improve after HSCT (113). The proposed mechanism for improvement of MS symptoms, by autologous HSCT is immune system alteration (114). Fassas et al. reported treatment of 15 patients with progressive MS and a median expanded disability status scale (EDSS) of 6.0 by HSCT after conditioning. During 6 months follow up, there were no death and no worsening in neurological symptoms and EDSS was improved in seven of 15 patients (98). Saiz et al. transplanted HSC on five patients with progressive MS and median EDSS of 6.5, after carmustine, cyclophosphamide and antilymphocyte globulin conditioning. They achieved improvement in four patients, revealed on MRI, whereas the neurological symptoms worsened in the fifth patients (115). Large series of MS patients, including 85 cases, were evaluated by the European Group for Blood and Marrow Transplantation (EBMT) Autoimmune Disease Working Party. Totally, 70% and 26% of patients were in secondary progressive phase and primary progressive phase of MS, respectively. The median EDSS of patients was 6.5 (ranging from 4.5 to 8.5). They were subjected for HSCT after conditioning. During a median 16 months follow up, the chance of progression-free survival was 74%, at 3 years. Five patients died from treatment related causes, including: infection and cardiac failure (116). Patients with both hematological neoplasms and autoimmune diseases inconsistently respond to HSCT. Mandalfino et al. transplanted HSC on three cases with hematological malignancy and co-existent MS. They observed that patients achieved neurological improvement, following HSCT (117). However, Lu et al. reported a case of MS associated with chronic myelogenous leukemia in a 39-year-old woman, which showed continuation of MS activity after allogeneic HSCT (118). Another study on five autopsy cases, in patients with MS that were cured by autologous HSCT, showed that MS activity continued in spite of high dose cytotoxic/immunosuppressive therapy (119). The HSCT is still in experimental therapy. However, these studies are heterogeneous in number of patients, follow up duration, status of MS symptoms in patients, conditioning regimen. However, results suggest that hematopoietic stem cell transplantation can improve MS symptoms in the progressive phase.

2.6. Embryonic Stem Cells Application in Multiple Sclerosis Treatment

The ESCs are pluripotent cells that derived from the inner cell mass of an early stage embryo, called blastocyst. They are able to differentiate into all cell types in the body. The actual limitation, in preparation of sufficient human oligodendrocyte precursor cells, orients the research towards obtaining tissue specific progenitor cells from human ESCs. Several researchers have differentiated mouse ESCs into oligodendrocyte, with myelogenic properties (120-123). Also, other groups showed that human ESCs can be directed into neural cells (124-127). In recent studies, scientists discovered several systems, such as small molecules and specific transcription factors, that control embryonic stem cells fate to produce neurons (128-131) and oligodendrocytes (132, 133). Human ESCs-derived oligodendrocytes are capable of remyelination (132, 134, 135). However, there are always the risks of tumorigenicity in neural cells derived from ESCs, which limit clinical trials

(55). Especially in human, ESC-based therapies might give rise to teratomas from undifferentiated ESCs or incompletely differentiated neural cells (136, 137). Aharonowiz et al. transplanted human ESC-derived neural progenitors into mice with EAE (138). They observed that clinical symptoms of EAE were remarkably reduced after transplantation. Histological evaluation revealed that transplanted neural progenitors migrate to the mice brain, especially in host white matter. However, remyelination and production of mature oligodendrocytes were not clearly seen. They concluded that the therapeutic effect of neural progenitor's transplantation was mediated by an immunosuppressive neuroprotective mechanism. Further studies are required to define the efficacy of ESCs-derived neural cell therapy in MS patients.

3. Results

Because NSCs can differentiate into mature oligodendrocytes and neurons, in animal models of cerebral degeneration, they are regarded as a perspective for MS. Other types of NSCs, including NSCs, BM-NSCs and NPCs, have proved their capacity of differentiation into oligodendrocytes and remyelination.

The MSCs promote repair and recovery after intrathecal injection, suggesting an influence on the rate of repair of all endogenous progenitors in spinal cords, confirmed by amelioration of EDSS.

The autologous HSCT has been proven efficient in selected cases of MS patients who do not respond to first line immunosuppression/immunomodulation therapy. The most evident responses to HSCT were seen especially in patients with relapsing MS. Nevertheless, the progressive phase of MS can also benefit from an improvement in symptomatology.

Although with the risk of development of teratomas from undifferentiated of incompletely differentiated cells, ESCs have shown a potential immunosuppression mechanism responsible for neuroprotection in cases of MS.

4. Conclusions

Nowadays, cellular therapy has opened a new paradigm in treatment of several disorders, including MS, as a neurodegenerative disease. Therefore, cell and SC transplantation have introduced promising hope in this area. On the other hand, there are several safety concerns about the clinical applications of SCs. Therefore, it is necessary to eliminate these risks before translating from the basic and experimental sciences to clinical transplantation trials. In summary, more experimental and clinical trials are needed to lead investigators in this area of research.

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Footnote

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