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Feasibility of Cell Therapy in Multiple Sclerosis: A Systematic Review of 83 Studies

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ABSTRACT

Multiple Sclerosis is an inflammatory disease of the central nervous system in which T cells experience a second phase of activation, which ultimately leads to axonal demyelination and neurological disability. The recent advances in stem cell therapies may serve as potential treatments for neurological disorders. There are broad types of stem cells such as neural, embryonic, mesenchymal and hematopoietic stem cells with unprecedented hope in treating many debilitating diseases. In this paper we will review the substantial literature regarding experimental and clinical use of these stem cells and possible mechanisms in the treatment of MS. These results may pave the road for the utilization of stem cells for the treatment of MS.

Keywords: Multiple sclerosis, Stem cells therapy, Human embryonic stem cells, Hematopoietic stem cells, Mesenchymal stem cells, Neural stem cells

INTRODUCTION

Multiple Sclerosis is an inflammatory disease of the central nervous system in which T cells experience a second phase of activation, which ultimately leads to axonal demyelination and neurological disability.[1] MS in most patients is characterized with axonal loss underlying long-term progressive disability. Disease-modifying treatments reduce the progression rate of the disease, but do not stop it. Both drug therapy and neurorehabilitation have shown to ease the burden of some symptoms, though neither influences disease progression.[2-4]

Stem cells are unspecialized cells in the body that have the ability to proliferate or reproduce, and differentiate into other type of body cells with specialized functions.[5,6] Stem cell therapies may serve as potential treatments for neurodegenerative disease.[6, 7]

There are broad types of stem cells such as neural (NSCs), embryonic (ESCs), mesenchymal (MSCs) and hematopoietic stem cells (HSCs) with unprecedented hope in treating many debilitating diseases. In this paper, we will review the substantial literature regarding experimental and

clinical use of these stem cells and possible mechanisms in the treatment of MS.

MATERIALS AND METHODS

Study Selection

We performed a comprehensive electronic search on the Pub Med and ISI web of science for all studies of Multiple Sclerosis (MS) based on the cell therapy using following terms: "Tissue Therapy", "Neural stem cells", "Mesenchymal stem cell", "hematopoietic or haematopoietic peripheral blood stem cell", "Multiple Sclerosis" and all possible combinations between 1/1/1990 and 31/12/2012. These search terms were confirmed with a MeSH database. Out of 28272 studies, 77 that met our primary criteria of interest were selected (Fig. 1). Finally, 11 titles and abstracts of articles were screened.

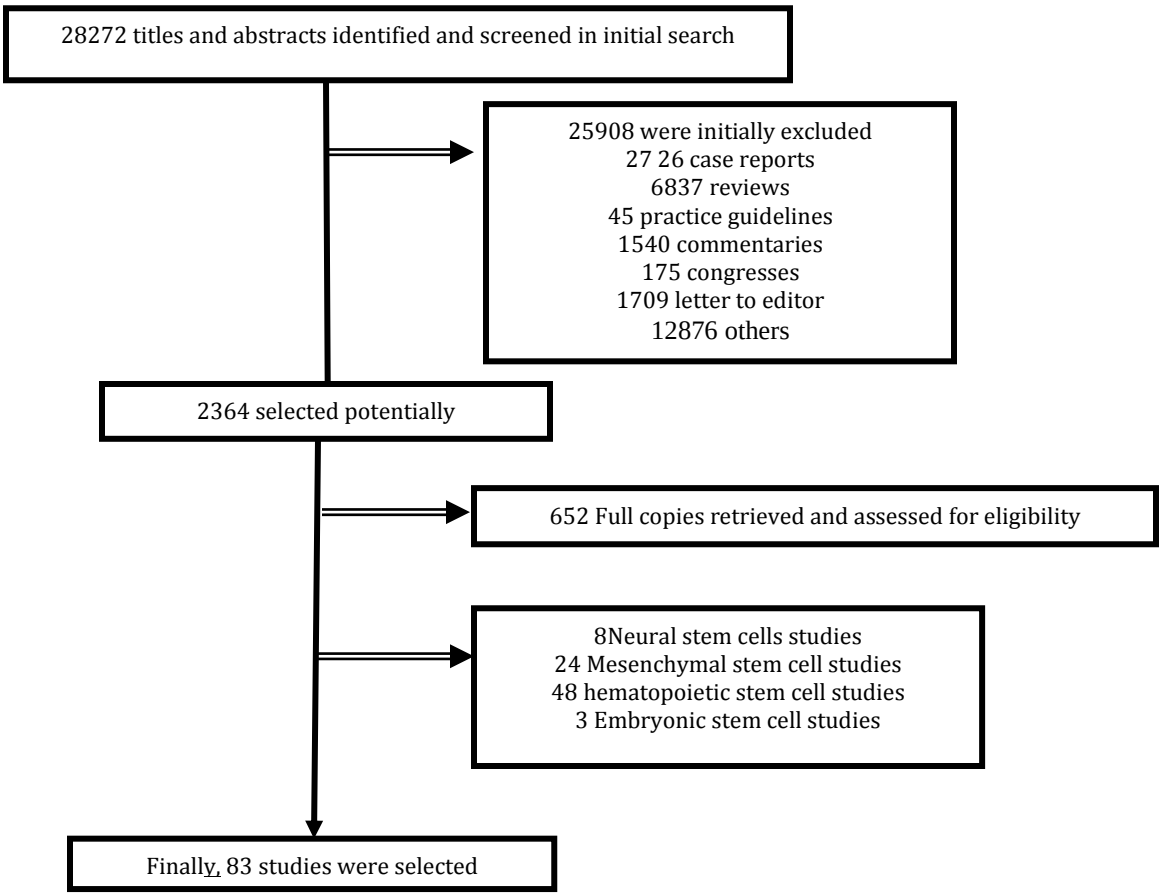

Figure 1: Flowchart of eligible studies

Inclusion Criteria

Study design: All trial studies were included in the evaluation since these study designs are essential for the systematic review.

Participants: Studies that included tissue therapy and Multiple Sclerosis conditions were included in the evaluation.

Exclusion criteria

The studies that showed not enough data for analysis were excluded after contacting corresponding author twice.

Data Extraction

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that appeared to be relevant were obtained and the relevance of each study was

independently assessed by two reviewers according to the inclusion and exclusion criteria. Two authors collected data and reached an agreement on all of the eligible items, including author, journal and year of publication, location of study and selection.

RESULTS AND DISCUSSION

Neural Stem Cells (NSCs) for the Treatment of MS

Overall, 8 studies included different models of NSCs applications in MS were selected through the search process (Table 1). NSCs can be isolated from the adult central nervous system (CNS). The sub-ventricular zone (SVZ) of lateral ventricle wall is a major germinal region that is used for isolation of NSCs.[8, 9] The migratory properties of NSCs are self-renewing, multipotent and long-distance migrants within the inflamed CNS.[10-15] These properties make NSCs suitable for cellular therapy in brain.[16] However, there is an increasing evidence that NSCs have neuroprotective and immunomodulatory effects.[17-21] Moreover, multiple recent studies showed the beneficial effects of NSCs therapy in neurologic disorders such as Huntington's disease, Parkinson's disease (PD), MS, Stroke, Spinal cord injuries and amyotrophic lateral sclerosis.[22]

Thus, today NSCs therapy is a useful therapeutic approach, which can be defined as the use of cells that need to differentiate into both oligodendrocytes and neurons to treat disease like MS. Several investigations have shown that NSCs can differentiate into mature oligodendrocytes in animal models of dysmiyelination.[18, 23-28] and neurons cerebral degeneration.[29] Recent studies reported therapeutic potential of adult neural stem cells (aNSCs) in MS.[14, 17, 18, 30]. Another type of NSCs is bone marrow-derived NSCs (BM-NSCs), which have neurogeneration potential and immunomodulatory effects.[31, 32] BM-NSCs are ethically preferred types of NSCs. Neural progenitor cells (NPCs) are other types of NSCs that are capable to differentiate into oligodendrocytes.[10] Furthermore, NPCs have anti-inflammatory properties by producing a variety of cytokines and neutrophils.[33, 34]

Although these findings clearly confirmed tremendous potential of NSCs therapy for patients with MS (Table 1), a lot of work still needs to be done to prove their clinical effectiveness and safety.

Table 1: Available Studies Related to Use of Neural Stem Cell in MS

Authors	Country	Neural Stem cell	Model	Findings
Heffernan et al., 2012	Australia	glial cells	Human	new therapeutic strategy for the treatment of as MS(101)
Payne et al., 2012	Australia	46C-NS cells	Mouse	Improving the efficiency at which NSCs home to inflammatory sites may enhance their therapeutic potential in MS(102)
Song et al., 2012	Australia	induced pluripotent stem (iPS) cells	Human	A novel approach for the study of MS pathophysiology and potential drug discovery(103)
Rasmussen et al., 2011	USA	Sub-ventricular zone cells	Mouse	treatments targeting chronic microglial activation have the potential for enhancing repair in MS(104)
Huang et al., 2011	UK	oligodendrocyte precursor cells (OPCs)	Human	might be useful pharmacological targets to overcoming remyelination failure in MS(105)
Giannakopoulou et al., 2011	Greece	neural precursor cell (NPC)	Mouse	NPC intraventricular transplantation should be accountable for their therapeutic effect in MS(106)
Carbajal et al., 2011	USA	oligodendrocyteprogentior cells (OPCs)	Mouse	highlight the importance of the CXCL12:CXCR4 pathway in regulating homing of engrafted stem cells to sites of tissue damage in the MS(107)
Yip et al., 2003	USA	oligodendrocyteprogentior cells (OPCs)	Human	Emerging knowledge of the molecules that may be involved in such responses may help in the design of future stem cell-based treatment of demyelinating diseases such as multiple sclerosis(108)

Mesenchymal Stem Cells as a Therapeutic Strategy for MS

Overall, 24 studies included applications of Mesenchymal stem cells (MSCs) in MS were selected through the search process (Table 2). MSCs are capable of transdifferentiation into cells of the endodermal and ectodermal origin.[35-38] These cells derived from various sources such as bone marrow, amniotic fluid, deciduous teeth, adipose tissue, umbilical cord, synovial membranes, peripheral blood and etc. However, the main source of MSCs is the bone marrow.[39-44] Recently, numerous studies have focused on MSCs for cell therapy in many neurodegenerative disorders such as MS.[45]

MSCs have a potential for migration into inflamed CNS tissue and differentiate into cells expressing neuronal and glial cell markers.[46] Indeed, MSCs can differentiate into neuronal cells, which is confirmable with molecular, biomedical, anatomical and electrophysiological characteristics.[47]

Harris et al., investigated potential role of MSCs on promotion of repair and recovery after intrathecal injection into mice with experimental autoimmune encephalomyelitis (EAE). They showed improvement in neurological functions compared with controls, and suggested that MSCs can influence the rate of repair through effects on endogenous progenitors in the spinal cords. Thus, MSCs can use in MS patient for promoting CNS repair.[48]

Reduction of expanded disability status scale (EDSS) were observed when Karussis et al., injected autologous MSCs intrathecally and intravenously in patients with MS.[49] They showed a clinical improvement in treated MS patients.[50] Neurotrophin-3 (NT-3)-modified MSCs via recombinant adenoviral vector[40] implanted into a region of ethidium bromide (EB)-induced demyelination in the rats with demyelinated spinal cord. Results were shown that AdvNT-3-MSC implants upgrade the endogenous remyelinating cells to participate directly in myelination. These data suggests that genetically modification of MSCs could be a potential therapeutic approach for elevating the efficacy of such treatment for MS and other neurodegenerative diseases.[51] However, our literature survey about the use of MSCs in MS patients has revealed the feasibility and safety of MSC therapy (Table 2).

Table 2: Available Studies Related to Use of Mesenchymal Stem Cell in MS

Authors	Country	Mesenchymal Stem cell	Model	Findings
Bonab et al., 2012	Iran	Autologous bone marrow derived mesenchymal stem cell (BM-MSC)	Human	MSC therapy can improve/stabilize the course of the disease in progressive MS in the first year after injection with no serious adverse effects(109)
Payne et al., 2012	Australia	bone marrow derived mesenchymal stem cell (BM-MSC)	Mouse	MSCs as a cell therapeutic that may be used to treat MS patients(110)
Cobo et al., 2012	Spain	allogenicmesenchymal stem cells (MSCs)	Mouse	Unmodified MSCs were not therapeutic when administer at the peak of disease(111)
Al Jumah et al., 2012	Saudi Arabia	Mesenchymal stem cells (MSCs	Mouse	effectiveness of MSCs in modulating the immunopathogenic process and in providing neuroprotection in MS(112)
Fisher-Shoval et al., 2012	Israel	human placental MSCs (PL-MSCs)	Mouse	PL-MSCs have a therapeutic effect in the EAE mice modelof MS(113)
Bai et al., 2012	USA	Mesenchymal stem cells (MSCs)	Mouse	MSC-stimulated functional recovery in animal models of MS(114)
Payne et al., 2012	Australia	human adipose-derived MSCs (Ad-MSCs)	Mouse	Ad-MSCs express anti-inflammatory cytokines may provide a rational approach to promote immunomodulation and tissue protection in MS(115)

Connick et al., 2012	UK	Autologous mesenchymal stem cells	Human	The evidence of structural, functional, and physiological improvement after treatment in some visual endpoints is suggestive of neuroprotection in MS(116)
Zhang et al., 2012	China	NT-3 gene-modified MSC	Rat	genetically modified MSCs could be a potential therapeutic avenue for improving the efficacy of stem cell treatment for neurodegenerative diseases such as MS(117)
Harris et al., 2012	USA	bone marrow mesenchymal stem cell-derived neural progenitors (MSC-NPs)	Human	MSC-NPs may influence the rate of repair through effects on endogenous progenitors in the spinal cord in MS(118)
Odinak et al., 2011	Russia	autologicmultipotentmesenchymal stem cells (MSC)	Human	safety of the elaborated protocol of treatment and the moderate clinical efficacy of treatment in MS patients or those with poor response to treatment(119)
Mohajeri et al., 2011	Iran	bone marrow derived mesenchymal stem cells	Human	support the potential of bone marrow derived MSC for treatment of MS patients(120)
Grigoriadis et al., 2011	Greece	Autologous bone marrow stromal cells (BMSCs)	Mouse	substantial relevance for clinical trials in MS, particularly regarding the possibility that transplanted BMSCs entering the inflamed central nervous system(121)
Cristofanilli et al., 2011	USA	embryonic-derived oligodendrocyte progenitor cells (OPCs)- Mesenchymal stem cells (MSCs)	Mouse	combining the immunomodulatory and trophic properties of MSCs with the myelinating ability of OPCs might be a suitable strategy for promoting neurological regeneration in MS(122)
Karussis et al., 2010	Israel	autologous mesenchymalstem cells (MSCs)	Human	Transplantation of MSCs in patients with MS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects(49)
Yamout et al., 2010	Lebanon	autologous bone marrow derived mesenchymal stem cells (BM-MSCs)	Human	clinical but not radiological efficacy and evidence of safety with no serious adverse events in MS(50)
Darlington et al., 2010	Canada	bone marrow-derived hMSCs	Human	importance of further preclinical work and immune-monitoring to define hMSC effects on disease-relevant immune responses under variable conditions in MS(123)
Rice et al., 2010	UK	autologous bone marrow-derived mesenchymal stem cells (MSCs)	Human	therapeutic potential of autologous MSCs which primarily utilize MSCs from individuals without MS, and relevance to clinical studies extrapolating from these scientific findings(124)
Mallam et al., 2010	UK	human MSCs (hMSC)	Human	implications for the development of new therapeutic interventions designed to mobilize endogenous cells to enhance repair in MS(125)
Barhum et al., 2010	Israel	Bone marrow mesenchymal stem cells (MSCs)	Mouse	NTFCs-transplanted ICV delay disease symptoms of EAE mice, possibly via neuroprotection and immunomodulation, and may serve as a possible treatment to MS(126)
Constantin et al., 2009	Italy	adipose-derived MSCs (ASCs)	Mouse	ASCs represent a valuable tool for stem cell-based therapy in chronic inflammatory diseases of the CNS such as MS(127)
Liang et al., 2009	China	mesenchymal stem cells	Human	mesenchymal stem cells have a potent immunosuppressive effect in MS(128)
Bai et al., 2009	USA	human bone marrow-derived MSCs (BM-hMSCs)	Mouse	BM-hMSCs represent a viable option for therapeutic approaches in MS(129)
Mohyeddin et al., 2007	Iran	Autologous Mesenchymal stem cells (MSCs)	Human	emphasizes on the feasibility of autologous MSC for treatment of MS patients(130)

Hematopoietic Stem Cell Transplantation in MS

A total of 48 studies including different models of hematopoietic stem cell (HSC) applications in MS were selected through the search (Table 3). HSCs are multipotent stem cells that give rise to all the blood cell types from the lymphoid to myeloid lineages. There is increasing use of HSC transplantation over the last years for the treatment of hematological and non-hematological neoplasms and several autoimmune diseases, including MS.[52] In MS, T cells experience a second phase of activation, which ultimately leads to axonal demyelination and neurological disability.[53]

Treatment of multiple sclerosis (MS) has 2 aspects: immunomodulatory therapy for the underlying immune disorder and therapies to relieve or modify symptoms. Hence, first-line immunomodulatory therapies for multiple sclerosis (MS) reduce the relapse rate and slow progression of disability, but are not successful for all patients. Some patients cannot tolerate these therapies or have a suboptimal response and therefore require changes in therapeutic management. Early recognition of suboptimal response and prompt intervention are necessary to limit future impairment.[54] Patients with relapse have good response to allogenic or autologous HSC transplantation, as a viable therapeutic option.[55-57] Several studies in animal models of MS and human revealed that HSC transplantation can induce MS remission.[58-60] However, a few studies present that HSC transplantation has no effect on MS improvement.

Experimental autoimmune encephalomyelitis (EAE)-diseased mice have shown that allogenic HSC transplantation during acute phase of MS lead to full remission.[61, 62] Moreover, autologous HSC transplantation in EAE mice resulted in complete remission.[63, 64]

In this regard, Takahashi et al., transduced TREM-2 (an innate immune receptor) in bone marrow-derived myeloid precursor cells and intravenously injected to mice with EAE. 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.[65]

Resident perivascular macrophage and microglia in central CNS physiologically derived from myeloid progenitors of hematopoietic cells not only during development, but also in life span.[66-68] Moreover, it has been presented that some hematopoietic cells are recruited to sites of neurological damage to become functional perivascular macrophage and microglia like dells.[69, 70] Although macrophages play harmful or beneficial roles in CNS injury, they are able to remove the cellular debris in acute phase of injury.[71-73]

Juan et al., evaluated clinical and neurological outcomes after autologous HSC transplantation in 22 patients with progressive MS. They showed that it can improve or stabilize neurological manifestations in most patients with progressive MS, following failure of conventional therapy.[74] Proposed mechanism for improvement of MS symptoms by autologous HSC transplantation is immunity system alteration.[75] Fassas et al., reported the outcomes of 15 patients with progressive MS and a median EDSS of 6.0 by HSC transplantation after conditioning. During 6 months of follow- up, no death and worsening of neurological symptoms were observed and EDSS was improved in 7 of 15 patients.[56]

In the study conducted by Saiz et al., 5 patients with progressive MS and median EDSS of 6.5 underwent HSCT after BCNU, cyclophosphamide and ATG conditioning. Based on MRI findings, 4 patients showed improvement, whereas neurological symptoms worsened in the fifth one. 76 Large series of MS patients including 85 cases were evaluated by the European Group for Blood and Marrow Transplantation (EBMT) Working Party on Autoimmune Diseases. The study included patients with secondary progressive MS (70%) and primary progressive MS (26%). The median EDSS of patients was 6.5 (ranging from 4.5 to 8.5), so the patients were subjected to HSCT after conditioning. At a median follow-up of 16 months, the chance of progression -free survival was 74% at 3 years. Five patients died of treatment-related complications including infection and cardiac failure.[77]

Patients with both hematological neoplasms and autoimmune diseases inconsistently respond to HSC transplantation.[78] Mandalfino et al., reported neurological improvement in 4 patients with MS,

following HSCT with follow-up of 6-48 months.[79] Whereas, Lu et al., reported that activities of MS persisted after allo-HSCT in a 39-year-old woman with CML affected by MS.[80] Another study on 5 autopsy cases in patients with MS that cured by autologous hematopoietic stem cell transplantation showed that MS activity continued in spite of high-dose cytotoxic/immunosuppressive therapy.[81] However, these studies included heterogeneous group of patients, follow-up duration, status of MS symptoms and conditioning regimen. But, results suggest that HSC transplantation could improve MS symptoms in progressive phase.

Table 3: Available Studies Related to Use of Hematopoietic Stem Cell in MS

Authors	Country	Mesenchymal Stem cell	Model	Findings
Shevchenko et al., 2012	Russia	autologous hematopoietic stem cell transplantation (AHSCT)	Human	support the feasibility of AHSCT with reduced-intensity conditioning in MS patient(131)
Saccardi et al., 2012	Italy	Haematopoietic stem cell transplantation (HSCT)	Human	HSCT indeed leads to extensive renewal of the T-cell repertoire provided crucial evidence to document that autologous HSCT goes beyond a profound and long-lasting immunosuppression, which can be achieved by conventional treatment in MS(132)
Lutterotti et al., 2012	Germany	Autologous hematopoietic stem cell transplantation (aHSCT)	Human	Support the use of aHSCT for treatment of MS(133)
Atkins et al., 2012	Canada	Autologous hematopoietic stem cell transplantation (HCT)	Human	The promising data that is emerging may establish these diseases as standard indications for HCT(134)
Chen et al., 2012	China	Autologous haematopoietic stem cell transplantation (AHSCT)	Human	AHSCT is a feasible treatment for severe MS and its long-term efficacy is favorable(135)
Mancardi et al., 2012	Italy	Autologous haematopoieticstem cell transplantation (AHSCT)	Human	This study shows that AHSCT with a BEAM/ATG conditioning regimen has a sustained effect in suppressing disease progression in aggressive MS cases unresponsive to conventional therapies(136)
Capobianco et al., 2012	Italy	autologous haematopoietic stem cell transplantation (HDC-AHSCT)	Human	Use of HDC-AHSCT could be effective and safe, but the very long-term risk of adverse events due to sequential aggressive immunosuppression has to be established(137)
Fassas et al., 2011	Greece	hemopoietic stem cell transplantation (HSCT)	Human	HSCT also resulted in a significant reduction in the number and volume of gadolinium-enhancing lesions on MRI of MS patient(138)
Reston et al., 2011	USA	autologous hematopoietic cell transplantation	Human	Patients with secondary progressive MS refractory to conventional medical treatment have longer progression-free survival following autologous stem cell transplantation with intermediate-intensity conditioning regimens than with high-intensity conditioning regimens(139)
Xu et al., 2011	China	autologous peripheral blood stem cell transplantation (APBCST)	Human	Progressive OSMS has a higher relapse rate than CMS following APBSCT(140)
Guimarães et al., 2010	Brazil	autologous hematopoetic stem cell transplantation (autoHSCT)	Human	In spite of the high risk of complications of the procedure, the HSCT had positive impact in the health related quality of life(141)
Lu et al., 2010	Canada	allogeneic hematopoietic stem cell transplantation (allo-HSCT)	Human	Allo-HSCT fails to halt the demyelination and inflammation of MS(142)
Krasulová et al., 2010	Czech Republic	autologous haematopoietic stem cell transplantation (ASCT)	Human	ASCT represents a viable and effective treatment option for aggressive multiple sclerosis(143)
Tappenden et al., 2010	UK	autologous haematopoietic stem cell transplantation (HSCT)	Human	HSCT could potentially achieve an acceptable level of cost-effectiveness(144)

Rogojan et al., 2009	Denmark	haematopoietic stem cell transplantation (HSCT)	Human	Relatively young patients with active inflammatory lesions of relatively short duration and rapidly progressive disease, but still low disability scores, unresponsive to conventional therapy seem the best candidates for transplantation(145)
Burt et al., 2009	USA	Autologous non-myeloablativehaemopoietic stem cell transplantation	Human	Non-myeloablative autologous haemopoietic stem cell transplantation in patients with relapsing-remitting MS reverses neurological deficits(146)
Lu et al., 2009	Canada	allogeneic hematopoietic cell transplantation (HCT)	Human	Despite high-dose, cytotoxic, immunosuppressive therapy and exchange of a presumed autoreactive immune system with a healthy immune system, MS in this patient continued to be active(80)
Fassas et al., 2008	Greece	autologous transplantation of hemopoietic stem cells (ASCT)	Human	ASCT does not only cause debulking of autoreactive clones but it also brings about qualitative immunological changes that might eventually establish immunologic self-tolerance; the progression of brain atrophy appears to slow down with time; with the implementation of proper patient-selection criteria, the risks of morbidity and mortality can be minimized(147)
Fagius et al., 2009	Sweden	autologous hematopoietic stem cell transplantation (HSCT)	Human	HSCT to be an effective treatment option for this relatively rare disease course in MS(148)
Saiz et al., 2008	Spain	Autologous hematopoietic stem cell transplantation (AHSCT)	Human	AHSCT cannot be deemed a curative treatment but may cause prolonged stabilisation or change the aggressive course of the disease(149)
Shevchenko et al., 2008	Russia	autologous hematopoietic stem cell transplantation (auto-HSCT)	Human	Auto-HSCT treatment strategies based on the level of disability, namely "early," "conventional," and "salvage/late" transplantation, appears to be feasible to improve treatment outcomes(150)
Rocca et al., 2007	Italy	autologous hematopoietic stem cell transplantation (AHSCT)	Human	After AHSCT, the rate of brain tissue loss in patients with MS declines dramatically after the first 2 years(151)
Portaccio et al., 2007	Italy	autologous hematopoietic stem cell transplantation (AHSCT)	Human	Cases with very active, relapsing-remitting (RR) MS, who underwent AHSCT, and obtained a dramatic resolution to disease activity(152)
Roccatagliata et al., 2007	Genoa	autologous hematopoietic stem cell transplantation (AHSCT)	Human	AHSCT is associated to a longlasting suppression of inflammation and to a marked decrease of the rate of brain atrophy after the second year following treatment(153)
Metz et al., 2007	Germany	autologous hematopoietic stem cell transplantation (AHSCT)	Human	Continued clinical disease progression in multiple sclerosis patients with high expanded disability system scores despite autologous stem cell transplantation(154)
Xu et al., 2006	China	autologous haematopoietic stem cell transplantation (ASCT)	Human	ASCT as a therapy is safe and available. It can improve or stabilize neurological manifestations in most patients with progressive MS following failure of conventional therapy(74)
Loh et al., 2007	USA	autologous hematopoietic stem cell transplantation (auto-HSCT)	Human	Peripheral blood stem cells were not found to be significantly associated with development of a secondary autoimmune disorder(155)
Su et al., 2006	China	autologous hematopoietic stem cell transplantation (auto-HSCT)	Human	Auto-HSCT proved to be safe and beneficial for some MS patients. Further studies are needed to establish the merit of this procedure for MS patients(156)
Ni et al., 2006	China	autologous hematopoietic stem cell transplantation (auto-HSCT)	Human	Autologous HSCT seems beneficial to PMS. However, more patients and longer follow up would be required to assess the risk/benefit ratio(157)
Daumer et al., 2006	Germany	autologous hematopoietic stem cell transplantation (auto-HSCT)	Human	The estimated probability of MS progression, defined as an increase in EDSS score by > or = 1.0 sustained for at least 180 days, was 5% after one year, 14% after two years, 22% after three years, 38% after five years, 57% after 10 years, and >80% after 20 years of observation(158)
Papadaki et al., 2005	Greece	Bone marrow (BM) hematopoietic progenitorsstem cell	Human	provide support for the use of autologous stem cell transplantation in MS patients(159)

Blanco et al., 2005	Spain	peripheral blood mononuclear cells (PBMC)	Human	Our study suggests that AHSCT can reduce BDNF levels to values associated with lower activity. This decrease does not seem to correlate with the brain atrophy measures observed in the MRI in MS(160)
Blanco et al., 2005	Spain	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	The course of MS seems to be stabilized after autologous HSCT, especially in ambulatory patients with evidence of active disease like MS(161)
Saccardi et al., 2004	Italy	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	Significant transplant-related morbidity and mortality have been observed. This is primarily due to complications related to either the stage of the disease at transplant or due to infections. The number of deaths related to cardiac toxicity is low(162)
Blanco et al., 2004	Spain	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	ASCT as a therapy is safe and available. It can improve or stabilize neurological manifestations in most patients with progressive MS following failure of conventional therapy(163)
Healey et al., 2004	USA	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	Inflammation parameters and functional disability findings raising questions about optimal future stem cell transplantation strategies for MS(164)
Inglese et al., 2004	Italy	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	In MS, progressive loss of tissue can occur independently of concomitant MRI-visible inflammation(165)
Sun et al., 2004	USA	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	Findings have important implications in the understanding of the role of HSCT as a potential treatment for multiple sclerosis(166)
Saiz et al., 2004	Spain	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	Findings have important implications in the understanding of the role of HSCT as a potential treatment for multiple sclerosis(167)
Saccardiet al., 2004	Italy	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	Allogeneic HSCT improved the clinical course of MS(168)
Burt et al., 2003	USA	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	a total body irradiation (TBI)-based regimen and hematopoietic stem cell transplantation (HSCT) are not effective for MS patients with progressive disease and high pretransplantation disability scores(169)
Nash et al., 2003	USA	autologous haematopoietic-stem-cell transplantation (HSCT)	Human	The clinical role of autologous HSCT will require a comparison with conventional treatment of MS(170)
Carreras et al., 2003	Spain	autologous peripheral blood stem cell	Human	conditioning regimen has an acceptable toxicity and clearly reduces the progression of MS(171)
Fassas et al., 2002	Greece	autologous peripheral blood stem cell	Human	Autologous HSCT suggest positive early results in the management of progressive MS and is feasible(77)
Rossiev et al., 2002	Russia	autologous peripheral blood stem cell	Human	Autologous HSCT suggest positive early results in the management of progressive MS and is feasible(172)
Ouyang et al., 2001	China	autologous peripheral blood stem cell transplantation (Auto-PBSCT)	Human	Auto-PBSCT is effective and safety for PMS, hence the duration of remission remains to be decided in long-term follow up(173)
Burt et al., 1998	USA	hematopoietic stem cells (HSC)	Human	Stem cell transplantation has resulted in modest neurologic improvements for the first time since onset of progressive MS(57)
Fassas et al., 1997	Greece	hematopoietic stem cells (HSC)	Human	Autologous HSCT appears feasible in MS; it does not aggravate disability and seems to offer a clinical benefit. However, these observations need confirmation and long-term outcomes will show if benefits counterbalance toxicity and cost(56)

Embryonic Stem Cell Application in MS Treatment

Only three studies were reviewed in detail on the use of Embryonic stem cells (ESCs) in MS. ESCs are pluripotent stem cells that derived from the inner cell mass of an early stage embryo called blastocyst.[82-84] They are able to develop into any type of cell in the body. The actual limitation in preparation of sufficient human oligodendrocyte precursor cells obligate research in getting tissue-specific progenitor cells from human embryonic stem cells (hESCs). Many studies have tried to differentiate mouse embryonic stem cells (mESCs) into oligodendrocyte with myelogenic properties.[85-87] Moreover, studies have revealed that hESCs can be directed into neural cells.[84, 88-90] Interestingly, recent studies discovered several systems such as small molecules and specific transcription factors that control ESC fate to produce neurons[91-94] and oligodendrocytes.[95,96] hESC-derived oligodendrocytes are capable of remyelination.[95, 97] However, there are always risk of tumorigenesisin neural cells derived from ESCs, limiting the potentialities of science and therapy in such studies.[55] hESC-based therapies can give rise to specific specialty cells such as, dermatomes from undifferentiated ESCs or incompletely differentiated neural cells.[98, 99]

Aharonowiz et al., transplanted hESC-derived neural progenitors into the mice with EAE.[100] They observed that clinical symptoms of EAE remarkably reduced after transplantation. Histological evaluation revealed that transplanted neural progenitors migrate to the mice brain, especially in the host white matter. However, remyelination and production of mature oligodendrocytes were not clearly observed.

Besides, 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 ESC-derived neural cell therapy in MS patients.

CONCLUSION

Nowadays, Stem cell therapy in axonal demyelination and neurological disability (Specially MS) had been accelerated growth in animal model as well as human patient clinical treatment. A new way that promotes this procedure is tissue engineering which uses synthesis of natural polymer that simulates extra cellular matrix for better response of body to grafted cells.

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