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 experienced a second phase of activation, which ultimately leads to axonal demyelination and neurological disability. Recent advancements 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

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Introduction
Multiple Sclerosis is an inflammatory disease of the central nervous system in which T cells experienced 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 such as.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”,

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“Mesenchymal stem cell”, “hematopoietic or haematopoietic peripheral blood stem cell” and “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 (Figure 1). Finally 11 studies were subjected to title, abstract screening.

![Figure 1: Flowchart of eligible studies](image)

### Inclusion criteria
Study design: All trial studies were included in the evaluation, since these study designs is 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 where possible and the relevance of each study independently assessed by two reviewers according to the inclusion and exclusion criteria. Two authors (Fakher Rahimi and Najmaldin Saki) mined data and reached an agreement on all of the eligibility items, including author, journal and year of publication, location of study, selection.

### Results and Discussion
**Neural stem cells (NSCs) for the treatment of MS**
Overall 8 studies were selected through the search including different models of NSCs applications in MS (Table 1). NSCs can be isolated from the adult central nervous system (CNS). The sub-ventricular zone (SVZ) of lateral ventricle wall is major germinal region that use for isolation of NSCs. The migratory properties of NSCs are self-renewal, multipotency and long distance migration within the inflamed CNS. These properties make NSCs suitable for cellular therapy in brain. However, there is increasing evidence
that NSCs have neuroprotective and immunomodulatory effects. Moreover, multiple recent studies showed the beneficial effects of NSCs therapy in neurologic disorders, such as: Huntington disease, Parkinson disease (PD), MS, Stroke, Spinal cord injuries and amyotrophic lateral Sclerosis.

Thus, today NSCs therapy is a useful therapeutic, 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 dysmijelination and neurons cerebral degeneration. Recent studies reported therapeutic potential of adult neural stem cells (aNSCs) in MS. Another type of NSCs is bone marrow-derived NSCs (BM-NSCs), which have neurogenesis potential and immunomodulatory effects. BM-NSCs prefer ethically to the first type of NSCs. Neural progenitor cells (NPCs) are other type of NSCs that are capable to differentiate into oligodendrocytes. Furthermore, NPCs have anti-inflammatory properties by producing a variety of cytokines and neutrophils. Although these findings clearly confirmed tremendous potential of NSCs therapy for patients with MS (Table 1), but 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

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

Mesenchymal stem cells as a therapeutic strategy for MS

Overall 24 studies were selected through the search including different models of Mesenchymal stem cells (MSCs) applications in MS (Table 2). MSCs are capable transdifferentiation into cells of the endodermal and ectodermal origin. 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. Recently, numerous studies focused on MSCs for cell therapy in many neurodegenerative disorders such as MS. MSCs have a potential for migration into inflamed CNS tissue and differentiate into cells expressing neuronal and glial cell markers. Indeed, MSCs can differentiate into neuronal cells, which is confirmable with molecular, biomedical, anatomical and electrophysiological characteristics.
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 that improved neurological functions compared to controls, and suggest 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 disease.51 However, our literature survey about 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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Mesenchymal Stem cell</th>
<th>Model</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonab et al., 2012</td>
<td>Iran</td>
<td>Autologous bone marrow derived mesenchymal stem cell (BM-MSC)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Payne et al., 2012</td>
<td>Australia</td>
<td>bone marrow derived mesenchymal stem cell (BM-MSC)</td>
<td>Mouse</td>
<td>MSCs as a cell therapeutic that may be used to treat MS patients(110)</td>
</tr>
<tr>
<td>Cobo et al., 2012</td>
<td>Spain</td>
<td>allogenic mesenchymal stem cells (MSCs)</td>
<td>Mouse</td>
<td>Unmodified MSCs were not therapeutic when administer at the peak of disease(111)</td>
</tr>
<tr>
<td>Al Jumah et al., 2012</td>
<td>Saudi Arabia</td>
<td>Mesenchymal stem cells (MSCs)</td>
<td>Mouse</td>
<td>effectiveness of MSCs in modulating the immunopathogenic process and in providing neuroprotection in MS(112)</td>
</tr>
<tr>
<td>Fisher-Shoval et al., 2012</td>
<td>Israel</td>
<td>human placental MSCs (PL-MSCs)</td>
<td>Mouse</td>
<td>PL-MSCs have a therapeutic effect in the EAE mice model of MS(113)</td>
</tr>
<tr>
<td>Bai et al., 2012</td>
<td>USA</td>
<td>Mesenchymal stem cells (MSCs)</td>
<td>Mouse</td>
<td>MSC-stimulated functional recovery in animal models of MS(114)</td>
</tr>
<tr>
<td>Payne et al., 2012</td>
<td>Australia</td>
<td>human adipose-derived MSCs (Ad-MSCs)</td>
<td>Mouse</td>
<td>Ad-MSCs express anti-inflammatory cytokines may provide a rational approach to promote immunomodulation and tissue protection in MS(115)</td>
</tr>
<tr>
<td>Connick et al., 2012</td>
<td>UK</td>
<td>Autologous mesenchymal stem cells</td>
<td>Human</td>
<td>The evidence of structural, functional, and physiological improvement after treatment in some visual endpoints is suggestive of neuroprotection in MS(116)</td>
</tr>
<tr>
<td>Zhang et al., 2012</td>
<td>China</td>
<td>NT-3 gene-modified MSC</td>
<td>Rat</td>
<td>genetically modified MSCs could be a potential therapeutic avenue for improving the efficacy of stem cell treatment for neurodegenerative diseases such as MS(117)</td>
</tr>
<tr>
<td>Harris et al., 2012</td>
<td>USA</td>
<td>bone marrow mesenchymal stem cell-derived neural progenitors (MSC-NPs)</td>
<td>Human</td>
<td>MSC-NPs may influence the rate of repair through effects on endogenous progenitors in the spinal cord in MS(118)</td>
</tr>
<tr>
<td>Odinak et al., 2011</td>
<td>Russia</td>
<td>autologic multipotent mesenchymal stem cells (MSC)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Mohajeri et al., 2011</td>
<td>Iran</td>
<td>bone marrow derived mesenchymal stem cells</td>
<td>Human</td>
<td>support the potential of bone marrow derived MSC for treatment of MS patients(120)</td>
</tr>
</tbody>
</table>
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 mesenchymal stem 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)  

Total of 48 studies were selected through the search including different models of hematopoietic stem cells (HSCs) applications in MS (Table 3). HSCs are multipotent stem cells that give rise to all the blood cell types from the lymphoid to myeloid lineages. There are increasing use of HSCs transplantation over the last years for the treatment of hematological and non-hematological neoplasms and several autoimmune diseases, including MS. In MS, T cells experienced a second phase of activation, which ultimately leads to axonal demyelination and neurological disability. 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 HSCs transplantation, as a viable therapeutic option.55-57 Several studies in animal models of MS and human revealed that HSCs transplantation can induce MS remission.58-60 However, a few studies present that HSCs transplantation has no effect on MS improvement.

In experimental autoimmune Encephalomyelitis (EAE)-diseased mice shown that allogenic HSCs transplantation during acute phase of MS caused fully remission.61, 62 Moreover, autologous HSCs transplantation in EAE mice resulted in complete remission.63, 64

In this regards, 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 Even though macrophages play harmful or beneficial roles in CNS injury, but are able to remove the cellular debris in acute phase of injury.71-73

Juan et al. evaluated clinical and neurological outcomes after autologous HSCs 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 HSCs transplantation is immunity system alteration.75 Fassaset al. reported treatment of 15 patients with progressive MS and a median EDSS of 6.0 by HSCs transplantation after conditioning. During 6 months follow up no death and worsening in neurological symptoms were observed and EDSS was improved in 7 among the 15 patients.56

Saizet al. transplanted HSCs on 5 patients with progressive MS and median EDSS of 6.5 after BCNU, cyclophosphamide and ATG conditioning. They achieved improvement in 4 patients in MRI finding, but, neurological symptoms worsened in the fifth patient.76 Large series of MS patients including 85 cases were evaluated by the European Group for Blood and Marrow Transplantation (EBMT) Autoimmune Disease Working Party. 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), so the patients were subjected to HSCT after conditioning. During 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.77

Patients with both hematological neoplasms and autoimmune diseases inconsistently respond to HSCs transplantation.78 Mandalfinoet al. reported four patients with MS undergoing bone marrow transplantation with 6-48 months of follow-up. They observed that patients achieved neurological improvement following HSCs transplantation.79 Whereas, Lu et al. reported a case of MS associated with CML in 39-year-old woman, which showed continuation of MS activity after autologous HSCs transplantation.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 include heterogeneous patient numbers, follow up duration, status of MS symptoms, conditioning regimen. But results suggest that HSCs transplantation could improve MS symptoms in progressive phase.

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<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Mesenchymal Stem cell</th>
<th>Model</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Ho</td>
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<tr>
<td>Fassas</td>
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<tr>
<td>Mandal</td>
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</tr>
<tr>
<td>Lu</td>
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</tbody>
</table>

Table 3: Available studies related to use of Hematopoietic stem cell in MS
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Procedure</th>
<th>Human Use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shevchenko et al., 2012</td>
<td>Russia</td>
<td>autologous hematopoietic stem cell transplantation (AHSCT)</td>
<td>Human</td>
<td>support the feasibility of AHSCT with reduced-intensity conditioning in MS patient(131)</td>
</tr>
<tr>
<td>Saccardi et al., 2012</td>
<td>Italy</td>
<td>Haematopoietic stem cell transplantation (HSCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Lutterotti et al., 2012</td>
<td>Germany</td>
<td>Autologous hematopoietic stem cell transplantation (aHSCT)</td>
<td>Human</td>
<td>Support the use of aHSCT for treatment of MS(133)</td>
</tr>
<tr>
<td>Atkins et al., 2012</td>
<td>Canada</td>
<td>Autologous hematopoietic stem cell transplantation (HCT)</td>
<td>Human</td>
<td>The promising data that is emerging may establish these diseases as standard indications for HCT(134)</td>
</tr>
<tr>
<td>Chen et al., 2012</td>
<td>China</td>
<td>Autologous haematopoietic stem cell transplantation (AHSC)</td>
<td>Human</td>
<td>AHSCT is a feasible treatment for severe MS and its long-term efficacy is favorable(135)</td>
</tr>
<tr>
<td>Mancardi et al., 2012</td>
<td>Italy</td>
<td>Autologous haematopoietic stem cell transplantation (AHSCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Capobianco et al., 2012</td>
<td>Italy</td>
<td>autologous haematopoietic stem cell transplantation (HDC-AHSC)</td>
<td>Human</td>
<td>Use of HDC-AHSC could be effective and safe, but the very long-term risk of adverse events due to sequential aggressive immunosuppression has to be established(137)</td>
</tr>
<tr>
<td>Fassas et al., 2011</td>
<td>Greece</td>
<td>hemopoietic stem cell transplantation (HSCT)</td>
<td>Human</td>
<td>HSCT also resulted in a significant reduction in the number and volume of gadolinium-enhancing lesions on MRI of MS patient(138)</td>
</tr>
<tr>
<td>Reston et al., 2011</td>
<td>USA</td>
<td>autologous hematopoietic cell transplantation</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Xu et al., 2011</td>
<td>China</td>
<td>autologous peripheral blood stem cell transplantation (APBCST)</td>
<td>Human</td>
<td>Progressive OSMS has a higher relapse rate than CMS following APBSCST(140)</td>
</tr>
<tr>
<td>Guimarães et al., 2010</td>
<td>Brazil</td>
<td>autologous hematopoietic stem cell transplantation (autoHSCT)</td>
<td>Human</td>
<td>In spite of the high risk of complications of the procedure, the HSCT had positive impact in the health related quality of life(141)</td>
</tr>
<tr>
<td>Lu et al., 2010</td>
<td>Canada</td>
<td>allogeneic hematopoietic stem cell transplantation (allo-HSCT)</td>
<td>Human</td>
<td>Allo-HSCT fails to halt the demyelination and inflammation of MS(142)</td>
</tr>
<tr>
<td>Krasulová et al., 2010</td>
<td>Czech Republic</td>
<td>autologous haematopoietic stem cell transplantation (ASCT)</td>
<td>Human</td>
<td>ASCT represents a viable and effective treatment option for aggressive multiple sclerosis(143)</td>
</tr>
<tr>
<td>Tappenden et al., 2010</td>
<td>UK</td>
<td>autologous hematopoietic stem cell transplantation (HSCT)</td>
<td>Human</td>
<td>HSCT could potentially achieve an acceptable level of cost-effectiveness(144)</td>
</tr>
<tr>
<td>Rogojan et al., 2009</td>
<td>Denmark</td>
<td>haematopoietic stem cell transplantation (HSCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Burt et al., 2009</td>
<td>USA</td>
<td>Autologous non-myeloablative haemopoietic stem cell transplantation</td>
<td>Human</td>
<td>Non-myeloablative autologous haematopoietic stem cell transplantation in patients with relapsing-remitting MS reverses neurological deficits(146)</td>
</tr>
<tr>
<td>Lu et al., 2009</td>
<td>Canada</td>
<td>allogeneic hematopoietic cell transplantation (HCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Country</td>
<td>Procedure</td>
<td>Human</td>
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</tr>
<tr>
<td>Fassas et al., 2008</td>
<td>Greece</td>
<td>autologous transplantation of hematopoietic stem cells (ASCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Fagius et al., 2009</td>
<td>Sweden</td>
<td>autologous hematopoietic stem cell transplantation (HSCT)</td>
<td>Human</td>
<td>HSCT to be an effective treatment option for this relatively rare disease course in MS(148)</td>
</tr>
<tr>
<td>Saiz et al., 2008</td>
<td>Spain</td>
<td>Autologous hematopoietic stem cell transplantation (AH SCT)</td>
<td>Human</td>
<td>AHSCT cannot be deemed a curative treatment but may cause prolonged stabilisation or change the aggressive course of the disease(149)</td>
</tr>
<tr>
<td>Shevchenko et al., 2008</td>
<td>Russia</td>
<td>autologous hematopoietic stem cell transplantation (auto-HSCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Rocca et al., 2007</td>
<td>Italy</td>
<td>autologous hematopoietic stem cell transplantation (HSCT)</td>
<td>Human</td>
<td>After AHSC T, the rate of brain tissue loss in patients with MS declines dramatically after the first 2 years(151)</td>
</tr>
<tr>
<td>Portaccio et al., 2007</td>
<td>Italy</td>
<td>autologous hematopoietic stem cell transplantation (HSCT)</td>
<td>Human</td>
<td>Cases with very active, relapsing-remitting (RR) MS, who underwent AHSC T, and obtained a dramatic resolution to disease activity(152)</td>
</tr>
<tr>
<td>Roccatagliata et al., 2007</td>
<td>Genoa</td>
<td>autologous hematopoietic stem cell transplantation (AHSC T)</td>
<td>Human</td>
<td>AHSC T 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)</td>
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<tr>
<td>Metz et al., 2007</td>
<td>Germany</td>
<td>autologous hematopoietic stem cell transplantation (AHSC T)</td>
<td>Human</td>
<td>Continued clinical disease progression in multiple sclerosis patients with high expanded disability system scores despite autologous stem cell transplantation(154)</td>
</tr>
<tr>
<td>Xu et al., 2006</td>
<td>China</td>
<td>autologous haematopoietic stem cell transplantation (ASC T)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Loh et al., 2007</td>
<td>USA</td>
<td>autologous hematopoietic stem cell transplantation (auto-HSCT)</td>
<td>Human</td>
<td>Peripheral blood stem cells were not found to be significantly associated with development of a secondary autoimmune disorder(155)</td>
</tr>
<tr>
<td>Su et al., 2006</td>
<td>China</td>
<td>autologous hematopoietic stem cell transplantation (auto-HSCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Ni et al., 2006</td>
<td>China</td>
<td>autologous hematopoietic stem cell transplantation (auto-HSCT)</td>
<td>Human</td>
<td>Autologous HSCT seems beneficial to PMS. However, more patients and longer follow up would be required to assess the risk/benefit ratio(157)</td>
</tr>
<tr>
<td>Daumer et al., 2006</td>
<td>Germany</td>
<td>autologous hematopoietic stem cell transplantation (auto-HSCT)</td>
<td>Human</td>
<td>The estimated probability of MS progression, defined as an increase in EDSS score by &gt; 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 &gt;80% after 20 years of observation(158)</td>
</tr>
<tr>
<td>Papadaki et al., 2005</td>
<td>Greece</td>
<td>Bone marrow (BM) hematopoietic progenitors/stem cell</td>
<td>Human</td>
<td>provide support for the use of autologous stem cell transplantation in MS patients(159)</td>
</tr>
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<td>Blanco et al., 2005</td>
<td>Spain</td>
<td>peripheral blood mononuclear cells (PBMC)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Blanco et al., 2005</td>
<td>Spain</td>
<td>autologous hematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>The course of MS seems to be stabilized after autologous HSCT, especially in ambulatory patients with evidence of active disease like MS(161)</td>
</tr>
<tr>
<td>Saccardi et al., 2004</td>
<td>Italy</td>
<td>autologous hematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
</tbody>
</table>
### Embryonic stem cells application in MS treatment

Only three studies were reviewed in detail about 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 that celled blastocyst. 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 tried to differentiate mouse embryonic stem cells (mESCs) into oligodendrocyte with myelogenic properties. Moreover, studies revealed that hESCs can be directed into neural cell. Interestingly, recent studies discovered several systems such as small molecules and specific transcription factors that control ESCs fate to produce neurons and oligodendrocytes. HESCs derived oligodendrocytes are capable of remyelination. However, there are always risk of tumorigenesisin neural cells derived from ESCs limiting the potentialities of therapies might be give rise to specific specialty cells such as, dermatomes from undifferentiated

<table>
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<th>Authors</th>
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<tr>
<td>Blanco et al., 2004</td>
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<td>autologous haematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>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)</td>
</tr>
<tr>
<td>Healey et al., 2004</td>
<td>USA</td>
<td>autologous haematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>Inflammation parameters and functional disability findings raising questions about optimal future stem cell transplantation strategies for MS(164)</td>
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<tr>
<td>Inglese et al., 2004</td>
<td>Italy</td>
<td>autologous haematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>Findings have important implications in the understanding of the role of HSCT as a potential treatment for multiple sclerosis(166)</td>
</tr>
<tr>
<td>Sun et al., 2004</td>
<td>USA</td>
<td>autologous haematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>Findings have important implications in the understanding of the role of HSCT as a potential treatment for multiple sclerosis(167)</td>
</tr>
<tr>
<td>Saiz et al., 2004</td>
<td>Spain</td>
<td>autologous haematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>Allogeneic HSCT improved the clinical course of MS(168)</td>
</tr>
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<td>Saccardiet al., 2004</td>
<td>Italy</td>
<td>autologous haematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>The clinical role of autologous HSCT will require a comparison with conventional treatment of MS(170)</td>
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<td>Burt et al., 2003</td>
<td>USA</td>
<td>autologous haematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>The clinical role of autologous HSCT will require a comparison with conventional treatment of MS(170)</td>
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<tr>
<td>Nash et al., 2003</td>
<td>USA</td>
<td>autologous haematopoietic-stem-cell transplantation (HSCT)</td>
<td>Human</td>
<td>Conditioning regimen has an acceptable toxicity and clearly reduces the progression of MS(171)</td>
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<tr>
<td>Carreras et al., 2003</td>
<td>Spain</td>
<td>autologous peripheral blood stem cell</td>
<td>Human</td>
<td>Autologous HSCT suggest positive early results in the management of progressive MS and is feasible(77)</td>
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<td>Fassas et al., 2002</td>
<td>Greece</td>
<td>autologous peripheral blood stem cell</td>
<td>Human</td>
<td>Autologous HSCT suggest positive early results in the management of progressive MS and is feasible(172)</td>
</tr>
<tr>
<td>Rossiev et al., 2002</td>
<td>Russia</td>
<td>autologous peripheral blood stem cell</td>
<td>Human</td>
<td>Auto-PBSCT is effective and safety for PMS, hence the duration of remission remains to be decided in long-term follow up(173)</td>
</tr>
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<td>Ouyang et al., 2001</td>
<td>China</td>
<td>autologous peripheral blood stem cell transplantation (Auto-PBSCT)</td>
<td>Human</td>
<td>Stem cell transplantation has resulted in modest neurologic improvements for the first time since onset of progressive MS(57)</td>
</tr>
<tr>
<td>Burt et al., 1998</td>
<td>USA</td>
<td>hematopoietic stem cells (HSC)</td>
<td>Human</td>
<td>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)</td>
</tr>
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<td>Fassas et al., 1997</td>
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</table>
ESCs or incompletely differentiated neural cells. 98, 99
Aharonowiz et al. transplanted hESCs-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 host white matter. However, remyelination and production of mature oligodendrocytes were not clearly observed.

Besides, they conclude 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.

Conclusions
Now days, 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, is the use of synthesis and natural polymer that simulate extra cellular matrix for better response of body to grafted cells.

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Abdolreza Ardestiryaljami


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