Research article

ISSN 2639-9512

Stem Cell & Regenerative Medicine

Stem Cell Therapy in Multiple Sclerosis: Regenerative Treatment for Neurological Repair

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Received: 10 Apr 2024; **Accepted:** 14 May 2024; **Published:** 21 May 2024

Citation: Faile T, Gallicchio VS. Stem Cell Therapy in Multiple Sclerosis: Regenerative Treatment for Neurological Repair. Stem Cells Regen Med. 2024; 8(1): 1-6.

ABSTRACT

Multiple sclerosis is a chronic autoimmune and neurodegenerative disease, which primarily affects the central nervous system. The purpose of this study was to collectively evaluate the efficiency and safety of a variety of stem cell therapies in clinical studies concerning multiple sclerosis. The findings of this research investigating the treatment options indicate that stem cell therapy of a variety of types hold promise as a treatment option of MS. The most frequently researched stem cells, MSCs and HSCs, primarily provide reduction in inflammation and uncontrollable immune response, with improvements in remyelination and motor function testing. Additionally, stem cell therapy has led to decreasing relapse rates and an overall improved quality of life in patients. Stem cell therapy provides a viable opportunity for MS patients and future treatments to control the disease. However, further research is needed to optimize treatment, confirm patient criteria, and determine the long-term safety and efficacy of these treatments through additional research and clinical testing.

Keywords

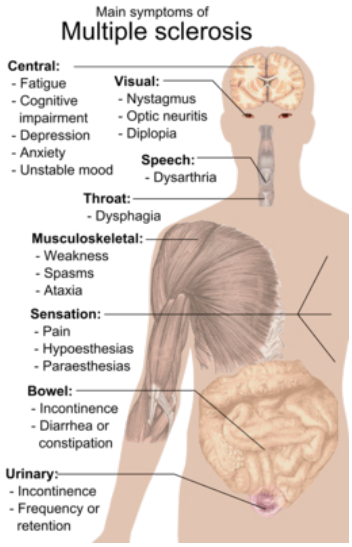
Multiple sclerosis, Stem cell, Regenerative medicine, Clinical trial, Regenerative medicine.

Abbreviations

AHSCT: Autologous hematopoietic stem cell transplantation, ASC: Adipose-derived stem cell, BDNF: Brain-derived neurotrophic factor, CCL2: Chemokine ligand 2, CNS: Central nervous system, CXCL12: Chemokine ligand 12, CXCL13: Chemokine ligand 13, DMT: disease-modifying therapy, EAE: Experimental autoimmune encephalomyelitis, EDSS: Expanded disability status scale, FGF: Fibroblast growth factor, GF: growth factor, hAEC: Human amniotic epithelial cells, hESC: Human embryonic stem cell, hiPSC: Human induced pluripotent stem cells, HSCT: hematopoietic stem cell transplantation, IL-8: Interleukin 8, IT: intrathecal, IV: intravenous, mL: milliliter, MRI: Magnetic resonance imaging, MS: Multiple sclerosis, MSC: Mesenchymal stem cell, MSC-NP: Mesenchymal stem cell-derived neural progenitors, NF-L: Neurofilament light chain, NPC: Neural progenitor cell, NSC: Neural stem cell, Pg: pictogram, PSC: Pluripotent stem cell, RRMS: Relapse-remitting multiple sclerosis, SC: Stem cell; SP: Secondary progressive, T25FW: Timed 25-foot walk, TMEV: Theiler's murine encephalomyelitis virus, UCMSC: Umbilical cord mesenchymal stem cell, UV: Ultraviolet.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory central nervous system (CNS) disease characterized by fatigue, pain, depression, anxiety, and neurologic dysfunction [1]. MS is caused by the destruction or demyelination of myelinated axons in the CNS [2]. Genes can increase disease susceptibility due to low Vitamin D, UV light exposure, Epstein Barr virus (EBV) infection, obesity, and smoking; these factors can accelerate the development of multiple sclerosis [3]. MS is T-cell mediated while B cells can contribute to the pathogenesis of multiple sclerosis, transitional B cells may predict the response to treatments for MS [4,5].



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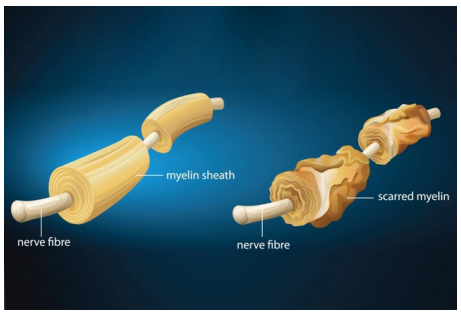

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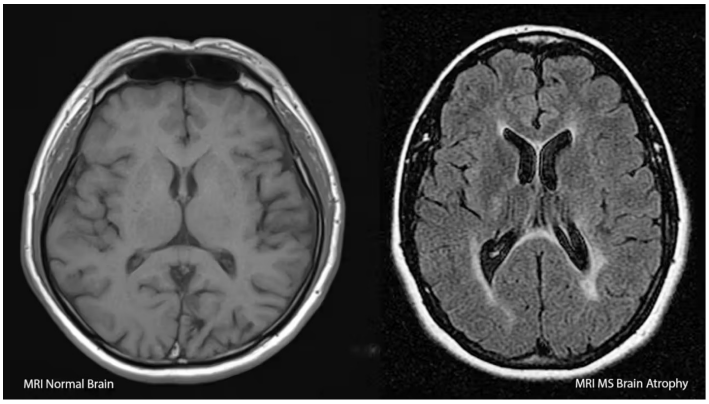

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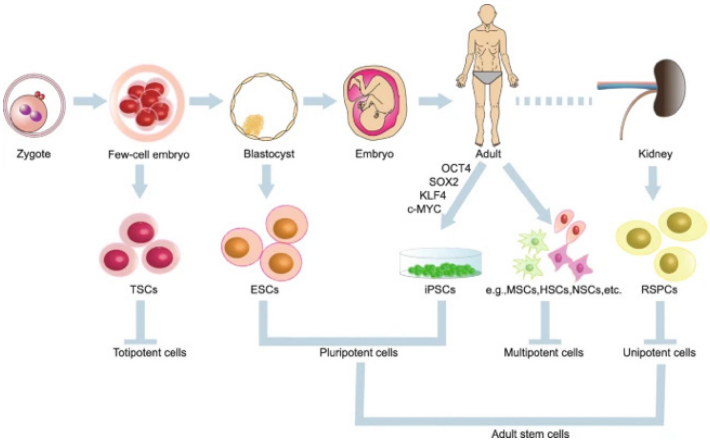
Stem cells (SCs) are unspecialized cells that develop/differentiate into the different tissues types in the human body and renew through mitosis [9]. SCs are classed as pluripotent, multipotent, and unipotent based on potential to generate varieties of cell lineages [10]. Pluripotent stem cells are the most potent and are only available during embryonic development. They can differentiate into tissues from all three germ layers - the endoderm, mesoderm, and ectoderm. Disease-specific cell lines have shown the ability to be specifically grown and used in further drug development for treatment in those diseases [11]. Embryonic stem cells, which are 3-5 days old, form a blastocyst made of approximately 150 cells and can become any type of cell in the body. Mesenchymal stem cells, which are in bone marrow or fat, have a limited function. Perinatal stem cells, which stem from the amniotic fluid and umbilical cord blood can also specialize [12]. In terms of neurological diseases like MS, over 200 clinical studies using multiple stem cell approaches have been registered in databases to date [13].



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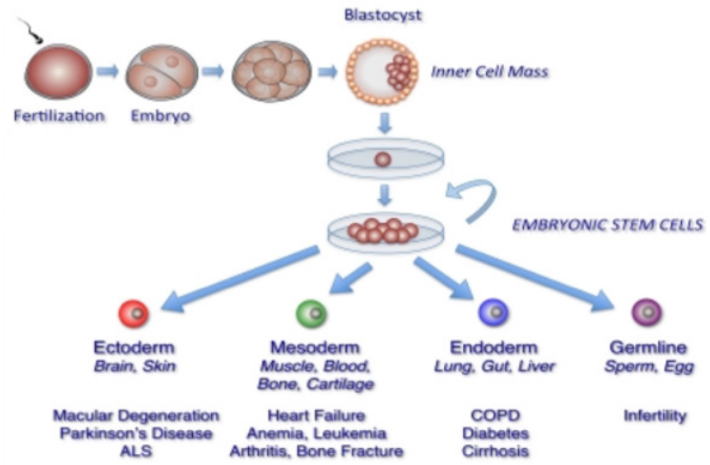

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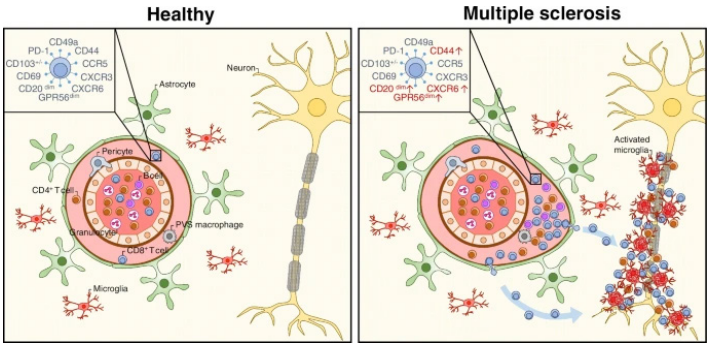
The low efficiency rates of current immunosuppression-based therapies of MS and emerging disease-modifying immunomodulatory agents fingolimod and dimethyl fumarate, cannot completely stop progressive neurodegenerative process. Because of this, cell replacement therapy has become increasingly popular and provides a range of treatment options that aim to increase the endogenous myelin repair capacity [16]. Multiple sclerosis is a spectrum, and aging increases the neural susceptibility to injury and decreases resilience, which leads to higher incidences of MS in older patients [17]. NSCs provide neurotrophic support and inhibit detrimental host immune responses *in vivo* following transplantation into the chronically inflamed CNS [18].



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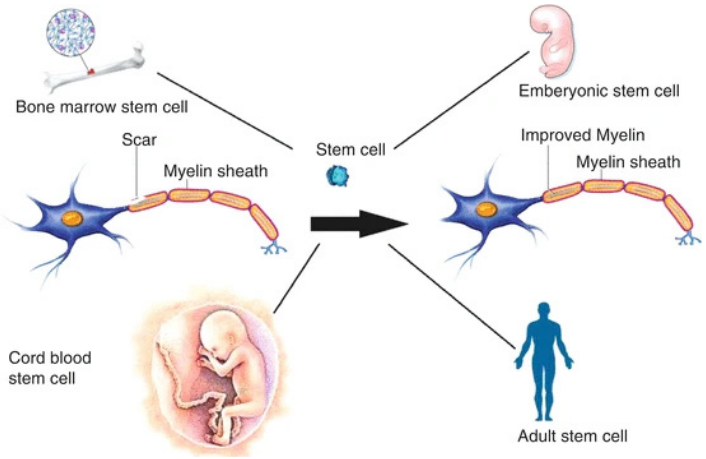
Discussion

In recent years, there has been increasing experimental use of all available stem cells for use in neurological therapies, specifically in MS. Human embryonic stem cells (hESC), which are derived early multipotent neural precursors, have been used in animal studies where the hESCs are transplanted into the brain ventricles of mice with induced experimental autoimmune encephalomyelitis (EAE). EAE is the animal version of MS and has been used comparatively to study the effects of MS in animals [20]. In additional animal studies, MSC-derived NSCs labeled with PKH26 were injected into the tail vein of EAE mice. These human primitive mesenchymal stem cells (MSCs) differentiated into neural stem cells (NSCs) provided significant myelination improvement tested through Luxol fast blue staining. The NSCs further differentiated into neural derivatives and promoted neurogenesis by possibly modulating BDNF and FGF signaling pathways [21]. EAE, TMEV, and toxin-induced demyelination are all used as models of MS in animals and provide opportunities for axonal repair and remyelination like that in MS [22].

Additional Stem Cell Derivations Used in Clinical Studies

- Autologous hematopoietic stem cells [23,24]
- Umbilical cord MSC (UCMSC) [25]
- Adipose-derived stem cells (ASCs) - Anti-inflammatory nature due to cytokine and growth factor production [26]
- Autologous MSC-derived neural progenitors (MSC-NPs) [27]
- Human amniotic epithelial cells (hAECs) [28]
- MSC isolation from umbilical cord tissue - exosome isolation via ultracentrifugation [29]
- Endogenous spinal cord stem cells [30]
- MSCs from bone marrow and human exfoliated deciduous teeth [31]
- Human induced pluripotent stem cells (hiPSCs) [32]

In recent years, human studies have become more popular among researchers, some of whom have conducted promising clinical studies including follow-ups. In this 2018 study, 20 subjects were given 7 intravenous infusions of 20×10^6 UCMSC over 7 days. Efficacy was assessed at baseline, 1 month, and 1 year after treatment using a wide variety of measurements (MRI, Kurtzke Expanded Disability Test, 25-Foot Walk Test, etc.) [25]. In 2015, 22 patients with progressive MS were assessed and given a single intrathecal dose of MSCs and followed for 1 year with no serious adverse events in that year post-clinical study. Despite not being placebo controlled, 70% of patients showed some signs of transient disease stabilization [27]. In a 2022 double-blind, phase II clinical study of 48 patients, all with progressive MS, the IT and IV transplantation of MSC were tested through NF-L and CXCL13 levels at baseline and 6 months prior [33]. Another 2020 clinical study with 20 subjects who were given 3 intrathecal injections of MSC-NPs 3 months apart while a 2 year follow up with EDSS test and timed 25-foot walk test was performed and results shown below [34]. One major clinical study consisting of 103 patients comparing hematopoietic stem cell transplantation (HSCT) vs. disease-modifying therapy (DMT) on disease progression where two follow-ups occurred - 98 patients were evaluated through 1 year and 23 were evaluated through 5 years [35]. Finally, a 50-study compilation with a 4831 patient total showed significant EDSS score decrease post treatment, a significantly reduced relapse rate, with 81% of patients relapse-free and new lesions in only 8% of patients. The overall survival percentage post-treatment was 94% [36].



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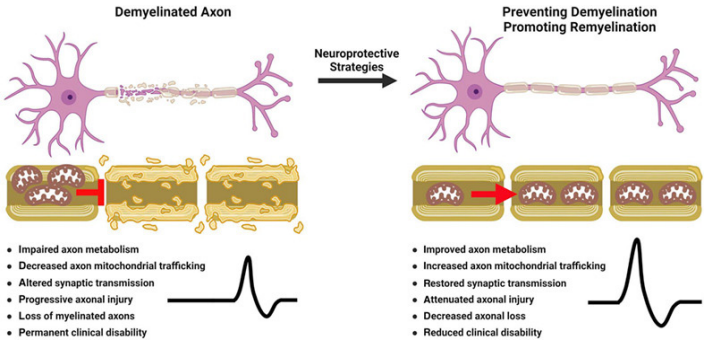

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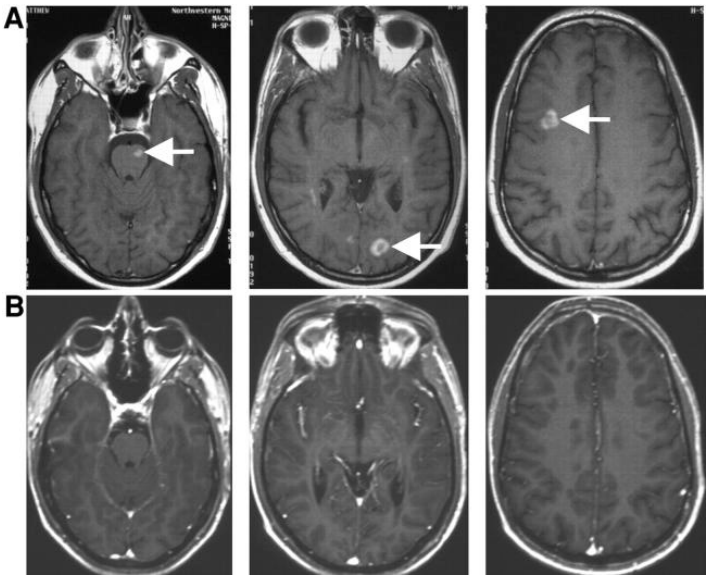
The previously discussed human studies have specifically had very positive results, including beneficial long-term results in follow-up studies. Nine out of 15 tested patients in the MSC-IT group of the 2022 study had a reduction in NF-L levels of more than 50% (median decrease: -4449 pg/mL) when compared with 5/15 in the MSC-IV group (median decrease: -151 pg/mL) and

1/15 in the placebo group (median increase: +2450 pg/mL) - p = 0.001. CXCL13 was also reduced for MSC-IT but was not labeled statistically significant [33]. In the 2020, 20-subject study 18 of 20 completed the follow up where 7 subjects sustained improvement of EDSS (degree of improvement not maintained in 5 of them) and 3 of 10 ambulatory patients showed sustained improvement in T25FW. There was an additional decrease in CCL2 and increase in IL-8, hepatocyte GF, and CXCL12 after treatment [34]. In the 2019 study of 103 patients comparing HSCT and DMT, the disease progression appeared in 3 patients in the HSCT group vs. 34 in the DMT group. In year one, the mean EDSS scores decreased (improved) from 3.38 to 2.36 in HSCT group vs. increased (worsened) from 3.31 to 3.98 in DMT group [35].



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Stem cell clinical study research has produced positive results from a wide variety of human studies using varying stem cell methods and tests. Studies have demonstrated that AHSCT can entirely suppress MS disease activity for 4–5 years in 70–80% of patients. The treatment-related mortality, which was 3.6% in studies before 2005, has decreased to 0.3% in studies from 2005-2017 when the resulting study was published [23]. That same year, AHSCT was found to have the ability to induce long-term suppression of inflammatory disease activity and can halt or reverse neurological deterioration even in progressive stages of the disease [40]. In another study, published in 2018, improvements were seen in EDSS scores ($p < 0.03$), as well as bladder, bowel, and sexual dysfunction ($p < 0.01$), non-dominant hand average scores ($p < 0.01$), walk times ($p < 0.02$) and a general perspective of a positive health change and improved quality of life. MRI scans of the brain and the cervical spinal cord showed inactive lesions in 15/18 (83.3%) subjects after 1 year [25]. In a study published in 2020, ASCs were found to inhibit the CD4+ T-cell activation and T-cell infiltration into the CNS, thus preventing further tissue damage of myelin sheath [26]. RRMS, an increasingly popular treatment method, has been shown superior effectiveness over alternative therapy methods in previous clinical studies. These studies have confirmed excellent outcomes, particularly with a benefit in early secondary progressive MS [41].

Stem cell research in humans has produced minimal negative effects in large sample sizes. In four of the fourteen studies researched, these side effects include headache and fatigue possibly due to treatment, a single meningeal irritation, an 18% worsening of condition, with headaches and fever reported as minor adverse MSC treatment effects, and a 4% death rate found related to treatment [25,27,36,42].

The potential that stem cell use has in the regulation and regenerative axon and myelin repair has massive repercussions in the future of medicine. However, this is a new concept and still has many unanswered questions. The primary pathway that must be taken is more research; the main concern in stem cell research is the safety profile, specifically of NPCs that are simply unknown due to a lack of clinical studies [43]. The promising aspect of stem cell research are the clinical studies that have been conducted with a high positive to negative result ratio, leading to the idea that stem cells have a future in regenerative medicine. There is a need to work on *in vivo* regulation of stem cell activity, but systemic injection of stem cells could lead to drug delivery to CNS. Further understanding of mechanisms such as immunomodulation and trophic factor-mediated remyelination has a high potential for success in future therapies [44]. More research is needed to determine the role of weight on stem cell proliferation. In ASCs of obese subjects, there was increased proliferation and tumorigenicity of breast cancer cells *in vitro* and *in vivo* through an estrogen-mediated leptin pathway, which has the potential to increase the potential of tumor development [26]. In addition to a lower initial treatment weight, younger patients, a relapsing form of MS, fewer prior immunotherapies, and lower baseline EDSS scores were all prominent factors in better outcomes [45]. With these uncertainties in human testing, it is possible that advances can come in the form of fully understanding stem cell mechanisms of function in animals, and possibly exploring a self-destruct option found in SCs [46]. Early-stage MS with a high incidence of inflammation is a particular concern and should be monitored by MRI to better determine efficacy of treatments [47]. A combination of a trophic or immunomodulatory approaches (MSCs or MSC-NPs) along with remyelinating agents e.g. anti-Lingo antibody, will need to be further studied to potentially promote more optimal axon repair in MS, as efficiency has been the most talked about concern with stem cell therapies [27]. Immunoablation followed by autologous hematopoietic stem cells (ASCT) have emerged as one of the most promising emerging treatments by providing this combination therapy approach [48,49]. Another promising treatment involves human amniotic epithelial cells (hAECs) which shows immune-regulatory effects, regenerative properties, and decreased antigenicity [28]. MSC-derived exosomes have been seen as possible alternatives to traditional stem cell treatments [29]. In terms of the future of stem cell research, the matter of ethical considerations of the human embryo debate must be solved before further research can be fully unlocked and more research is allowed to be done to come to conclusions about stem cell use in MS therapy [50,51].

Summary and Conclusions

Multiple sclerosis does not have a cure and treatment centers around the recovery from attacks and slowing the progression of the disease. As a neurological disease, MS has been studied previously by trying to attack the disease through immunosuppressive means, with little success. Studies have shown the increasingly positive results of stem cell research and the resulting clinical studies, particularly in AHSCT and the combination therapies of immunoablation followed by ASCT. While increasingly popular in recent years, ethical concerns surrounding stem cell harvesting have somewhat halted the full research capabilities of this otherwise promising research being done to slow down MS.

References

1. Nicholas R, Rashid W. Multiple sclerosis. Am fam physician. 2013; 87: 712.
2. Goldenberg M. M. Multiple sclerosis review. P & T: a peer-reviewed journal for formulary management. 2012; 37: 175-184.
3. Dobson R, Giovannoni G. Multiple sclerosis – a review. Eur J Neurol. 2019; 26: 27-40.
4. Karnell F. G, Lin D, Motley S, et al. Reconstitution of immune cell populations in multiple sclerosis patients after autologous stem cell transplantation. Clinical and experimental immunology. 2017; 189: 268-278.
5. Mimpen M, Damoiseaux J, van Doorn W, et al. Proportions of circulating transitional B cells associate with MRI activity in interferon beta-treated multiple sclerosis patients. J neuroimmunol. 2021; 358: 577664.
6. Häggström Mikael. Medical gallery of Mikael Häggström 2014. WikiJournal of Medicine 2014; 1.
7. https://today.uconn.edu/wp-content/uploads/2019/03/image-1024x683.jpg
8. https://www.healthline.com/health/multiple-sclerosis/how-ms-affects-your-brain
9. https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=a8da069a54f4bc7bf07559e0858875362c1cfda0
6. Singh V. K, Saini A, Kalsan M, et al. Describing the Stem Cell Potency: The Various Methods of Functional Assessment and In silico Diagnostics. Front cell Dev Biol. 2016; 4: 134.
7. Kolios G, Moodley Y. Introduction to stem cells and regenerative medicine. Respiration. 2013; 85: 3-10.
10. https://www.mayoclinic.org/tests-procedures/bone-marrow-transplant/in-depth/stem-cells/art-20048117
11. Alessandrini M, Preynat-Seauve O, De Bruin K, et al. Stem cell therapy for neurological disorders. S Afr med j. 2019; 109: 70-77.
12. Liu D, Cheng F, Pan S. et al. Stem cells: a potential treatment option for kidney diseases. Stem Cell Res Ther. 2020; 11: 249.
13. https://stemcells.nih.gov/sites/default/files/2024-01/figure1.png
14. Genc B, Bozan H.R, Genc S, et al. Stem Cell Therapy for Multiple Sclerosis. In: Pham, P. (eds) Tissue Engineering and Regenerative Medicine. Advances in Experimental Medicine and Biology. 2019; 1084: 145-174.
15. Kuhlmann T, Moccia M, Coetzee T, et al. International Advisory Committee on Clinical Trials in Multiple Sclerosis. Multiple sclerosis progression: time for a new mechanism-driven framework. The Lancet. Neurology. 2023; 22: 78-88.
16. Pluchino S, Smith J. A, Peruzzotti-Jametti L. et al. Promises and Limitations of Neural Stem Cell Therapies for Progressive Multiple Sclerosis. Trends mol med. 2020; 26: 898-912.
17. Smolders J, van Luijn M.M, Hsiao CC. et al. T-cell surveillance of the human brain in health and multiple sclerosis. Semin Immunopathol. 2022; 44: 855-867.
18. Aharonowiz M, Einstein O, Fainstein N, et al. Neuroprotective effect of transplanted human embryonic stem cell-derived neural precursors in an animal model of multiple sclerosis. PLoS One. 2008; 3: e3145.
19. Brown C, McKee C, Halassy S, et al. Neural stem cells derived from primitive mesenchymal stem cells reversed disease symptoms and promoted neurogenesis in an experimental autoimmune encephalomyelitis mouse model of multiple sclerosis. Stem Cell Res Ther. 2021; 12: 499.
20. Procaccini C, De Rosa V, Pucino V, et al. Animal models of Multiple Sclerosis. Eur J pharmacol. 2015; 759: 182-191.
21. Muraro P, Martin R, Mancardi G. et al. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. Nat Rev Neurol. 2017; 13: 391-405.
22. Das J, Sharrack B, Snowden J. A. et al. Autologous Haematopoietic Stem Cell Transplantation in Multiple Sclerosis: a Review of Current Literature and Future Directions for Transplant Haematologists and Oncologists. Curr hematol malig rep. 2019; 14: 127-135.
23. Riordan N. H, Morales I, Fernández G, et al. Clinical feasibility of umbilical cord tissue-derived mesenchymal stem cells in the treatment of multiple sclerosis. J transl med. 2018; 16: 57.
24. Al-Ghadban S, Bunnell B. A. Adipose Tissue-Derived Stem Cells: Immunomodulatory Effects and Therapeutic Potential. Physiology Bethesda. 2020; 35: 125-133.
25. Harris V. K, Sadiq S. A. Stem cell therapy in multiple sclerosis: a future perspective. Neurodegenerative disease management. 2015; 5: 167-170.
26. Zolfaghari Baghbadorani P, Rayati Damavandi A, Moradi S, et al. Current advances in stem cell therapy in the treatment of multiple sclerosis. Rev Neurosci. 2023; 34: 613-633.
27. Baharlooi H, Salehi Z, Minbashi Moeini M, et al. Immunomodulatory Potential of Human Mesenchymal Stem Cells and their Exosomes on Multiple Sclerosis. Adv pharm bull. 2022; 12: 389-397.
28. Covacu R, Brundin L. Endogenous spinal cord stem cells in multiple sclerosis and its animal model. J neuroimmunol. 2019; 331: 4-10.
29. Kråkenes T, Wergeland S, Al-Sharabi N, et al. The neuroprotective potential of mesenchymal stem cells from bone marrow and human exfoliated deciduous teeth in a murine model of demyelination. PloS one. 2023; 18: e0293908.

30. Kolagar T. A, Farzaneh M, Nikkar N, et al. Human Pluripotent Stem Cells in Neurodegenerative Diseases: Potentials, Advances and Limitations. Current stem cell research & therapy. 2020; 15: 102-110.
31. Petrou P, Kassis I, Ginzberg A, et al. Effects of Mesenchymal Stem Cell Transplantation on Cerebrospinal Fluid Biomarkers in Progressive Multiple Sclerosis. Stem cells transl med. 2022; 11: 55-58.
32. Harris V. K, Stark J. W, Yang S, et al. Mesenchymal stem cell-derived neural progenitors in progressive MS: Two-year follow-up of a phase I study. Neurol neuroimmunol neuroinflamm. 2020; 8: e928.
33. Burt R. K, Balabanov R, Burman J, et al. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. JAMA. 2019; 321: 165-174.
34. Nabizadeh F, Pirahesh K, Rafiei N, et al. Autologous Hematopoietic Stem-Cell Transplantation in Multiple Sclerosis: A Systematic Review and Meta-Analysis. Neurol ther. 2022; 11: 1553-1569.
35. Rahim F, Arjmand B. Stem Cell Clinical Trials for Multiple Sclerosis: The Past, Present and Future. In: Pham, P. (eds) Neurological Regeneration. Stem Cells in Clinical Applications. Springer, Cham. 2017.
36. Mey G. M, Mahajan K. R, DeSilva T. M, et al. Neurodegeneration in multiple sclerosis. WIREs mech dis. 2023; 15: e1583.
37. https://www.ncbi.nlm.nih.gov/pmc/articles/instance/2212822/bin/20041679f1.jpg
38. Collins F, Kazmi M, Muraro P. A, et al. Progress and prospects for the use and the understanding of the mode of action of autologous hematopoietic stem cell transplantation in the treatment of multiple sclerosis. Expert rev clin immunol. 2017; 13: 611-622.
39. Mariottini A, De Matteis E, Cencioni M. T, et al. Haematopoietic Stem Cell Transplantation for the Treatment of Multiple Sclerosis: Recent Advances. Curr neurol neurosci rep. 2023; 23: 507-520.
40. Islam M. A, Alam S. S, Kundu S, et al. Mesenchymal Stem Cell Therapy in Multiple Sclerosis: A Systematic Review and Meta-Analysis. J clin med. 2023; 12: 6311.
41. https://www.futuremedicine.com/doi/10.2217/17460751.2.1.7
42. Martino G, Franklin R, Van Evercooren A, et al. Stem cell transplantation in multiple sclerosis: current status and future prospects. Nat Rev Neurol. 2010; 6: 247-255.
43. Muraro PA, Pasquini M, Atkins HL, et al. Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. JAMA Neurol. 2017; 74: 459-469.
44. Zakrzewski W, Dobrzyński M, Szymonowicz M, et al. Stem cells: past, present, and future. Stem Cell Res Ther. 2019; 10: 68.
45. Muraro Paolo A, Ingoni Riccardo Cassiani, Martin Roland et al. Hematopoietic stem cell transplantation for multiple sclerosis: current status and future challenges. Curr Opin Neurol. 2003; 16: 299-305.
46. Alexander T, Arnold R, Hiepe F, et al. Resetting the immune system with immunoablation and autologous haematopoietic stem cell transplantation in autoimmune diseases. Clin Exp Rheumatol. 2016; 34: 53-7.
47. Scolding N. J, Pasquini M, Reingold S. C, et al. International Conference on Cell-Based Therapies for Multiple Sclerosis, International Conference on Cell-Based Therapies for Multiple Sclerosis, & International Conference on Cell-Based Therapies for Multiple Sclerosis. Cell-based therapeutic strategies for multiple sclerosis. Brain. 2017; 140: 2776-2796.
48. Hyun I. Stem cell ethics and policy: What's old is new again. Med. 2022; 3: 820-823.
49. Lo B, Parham L. Ethical issues in stem cell research. Endocrine reviews. 2009; 30: 204-213.