Review Article:

Immunomodulatory Effect of Mesenchymal Stem Cells in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis: A Review Study

Shaghayegh Pezeshki Naraghi[1], Seyed Mahmoud Hashemi[1*] (iD)

1. Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

ABSTRACT

Multiple Sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system that may lead to disability of the patient. Current MS treatment regimens are still insufficient and research is conducted for developing more effective therapies capable of targeting neurodegeneration, inflammation, and demyelination. Recent results of experimental and clinical studies in cell-based therapy suggest Mesenchymal Stem Cells (MSCs) as potential candidates in autoimmune disorders. Immunomodulatory and neuroprotective properties of mesenchymal stem cells might offer the valuable therapeutic potential to modulate inflammatory responses associated with MS and repairing damaged nervous tissue. This review summarizes the main experimental studies and clinical trials using MSCs in MS.

Introduction

Multiple Sclerosis (MS) is an autoimmune and common disease that affects central nervous system in humans [1]. It is a chronic disease more common in women and some parts of the world such as Northern Europe, America and Canada [2].

In MS, myelin that covers the nerves and is crucial for nerve transmission [3] is destroyed. Those parts of the nerve that lost their myelin cover due to MS is called plates. With the expansion of the plates, transmission of neural messages along the nerve slows down creating MS symptoms [4]. Symptoms usually start with unexplained and vague fatigue followed by general weakness. However, this weakness may occur only in one leg or one arm. Some patients experience blurred or double

* Corresponding Author:
Seyed Mahmoud Hashemi, PhD
Address: *Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
Phone: *+98 (935) 3717433*
E-mail: *smmhashemi@sbmu.ac.ir*

vision (diplopia). Moreover, symptoms like numbness and prickling of the face, arms, legs, and the whole body; balance disorder; chills; confusion; difficulty in swallowing or trouble speaking; and loss of bladder control can be seen in patients with MS [5].

From immunology perspective, because of an unknown factor myelin antigens are initially delivered to the T cells by the antigen-presenting dendritic cells in the lymphatic system, causing proliferation of reactive and active T cells in the lymph nodes [6]. Then the reactive T cells pass the blood brain barrier and enter into the central nervous system. Here they react with myelin antigens and produce inflammatory cytokines and chemokines, which in turn stimulate further migration of the immune cells to the site and progressive destruction of myelin in the central nervous system, causing sclerosis plaques in the brain and spinal cord [7, 8].

Various Methods for Classifying MS

According to the latest classification, four different courses are identified for the MS disease: 1. Relapsing Remitting MS (RRMS) [9]; 2. Secondary Progressive MS (SPMS) [10]; 3. Primary Progressive MS (PPMS) [11]; and 4. Progressive Relapsing MS (PR) [12].

Immunotherapy and Cell Therapy in MS

Intravenous immunoglobulin

In cases where the attack does not have an appropriate response to corticosteroid therapy, the doctor may use Intravenous Immunoglobulin (IVIG) [13, 14].

Plasmapheresis

Plasmapheresis is used in cases of disease attacks that do not give a favorable response to corticosteroids. In this type of treatment, a given volume of blood is replaced during 3 to 4 days [15]. Some medications are in this category that can reduce the number of attacks and slow down the course of the disease. The following drugs are in this group:

Interferons

Interferons proteins are produced naturally in the body and defend the body against viruses. There are three types of natural interferons: alpha, beta, and gamma; of which beta has a treatment role in MS. This type of interferon exists in the market in three injection forms [16]:

1. Interferon beta-1a including Avonex (Sinnovex) [17]; 2. Rebif (Resijen) [18]; and 3. Interferon beta-1b (Betaferon) [19].

Glatiramer acetate (brand Copaxone or Copamer and Isomer)

Glatiramer acetate is currently used only in MS. This drug is a chain of four molecules of amino acids called glutamic acid, lysine, alanine, and tyrosine. It is naturally found in myelin protein molecules (nerve sheath). Thus, the drug is similar to the myelin around the nerve in terms of chemical structure. The drug is used by the American Food and Drug Administration (FDA) since 1996 to reduce the number of attacks of MS, although the observations show its effectiveness in preventing the progression of disability. This medicine is used daily as a subcutaneous injection [20].

The mechanism of drugs action is not well understood, but it seems that it inhibits inflammatory reactions, and perhaps due to its similarity to the myelin sheath, it perverts the immune responses generated against this sheath [18]. In studies where the drug was compared with Rebif and Betaferon (BEYOND), no difference was found between this drug and others in terms of the effectiveness [21]. In addition to definite MS forms, the drug can be also used to cure Clinically Isolated Syndrome (CIS) (first attack of MS). However, it has no effect in progressive forms (primary and without attack) [22]. The drugs like interferon beta can be used for the disease attack forms with low failure rate.

Mitoxantrone

Mitoxantrone is usually among the chemotherapy drugs that, in certain cases of the disease, is injected once every three months. It usually does not continue more than two years. Until 2006, these drugs were the main treatment of MS [23, 24]. Since then, newer drugs were added to the treatment list. These include:

Natalizumab (Tysabri)

Natalizumab was confirmed by both American and Europe (EU), FDA in 2006. It has a very good effect in controlling MS and used once a month as intravenous injection. Unfortunately, due to its lethal complication called progressive multifocal leukoencephalopathy , the drug should be used with close monitoring and in the context of specific systems [25].

Fingolimod (Gilenya)

Fingolimod is the first oral medication for MS disease that has received approval from FDA in 2010, and has been licensed by the same organization in Europe in April 2011. The drug, taken by mouth daily, alleviates the number of attacks and slows down the disease progression [26, 27].

Here are two essential things. First, all of these drugs can control MS disease and do not have the ability to eradicate it, and second, a large group of medicines are now under investigation; some of them certainly will pass the tests successfully in the coming years [28].

Introduction of Mesenchymal Stem Cells

Mesenchymal Stem Cells (MSCs) have been identified as factors regulating the immune system [29], and the immunomodulatory role of these cells on a variety of immune system cells such as T and B lymphocytes [30][31], Natural Killer (NK) cells [32], macrophages [33]and Dendritic Cells (DCs) [34] has led to their use in the treatment of inflammatory diseases, particularly autoimmune diseases such as MS [35] and rheumatoid arthritis [36]. Bone marrow is the main source of mesenchymal stem cells [37], but they are isolated from other body tissues including adipose tissue [38]. Since T lymphocytes are considered as the most important cellular immune system cells, MSCs effect on the activity of these cells is of the utmost importance in directing the immune response [39].

T lymphocytes have different phenotypes and function in different conditions. According to prevailing conditions, they are distinct to certain subgroups with their special function and phenotype [40]. MSCs result in distinction of T cells from T regulatory cells that play an important role in maintaining tolerance and preventing autoimmune diseases [31]. Mesenchymal stem cells were first used to create the bone cells in the bone marrow in 1960. Later, researchers found that these cells, in addition to the ability to differentiate into the bone, cartilage and other connective tissues in laboratory conditions, can be isolated from a variety of sources including placenta, umbilical cord, adipose tissue and teeth [41].

Mesenchymal stem cell do not have the surface hematopoietic cell markers including cluster of differentiation (CD) 45, CD34, and CD14. But they express specific molecules such as SH2 (CD105), SH3, SH4 (CD73), CD44, CD22, intercellular adhesion protein (ICAM) -1 (CD54) and vascular cell adhesion protein (VCAM) -1 (CD106) as well as CD13, CD90, CD166 and STR-1. Also they are negative in terms of having CD40, CD80 and CD86 and express low levels of human leukocyte antigen (HLA) -I and LFA-3; however, They do not express HLA-III [42]. These stem cells have the immunomodulatory property; this property applies on B, T, NK and DC cells and reduces the immune response [31, 30].

MSCs Immunomodulatory Effects

MSCs have immunoregulatory role both in the innate and adaptive immune system. The unique properties of these cells suppress and modulate immune responses [43, 42]. MSCs reduce NKG2D, NKP44 and NKP30 on the surface of Natural Killer (NK) cells and lead to reduced production of interferon gamma (INFγ) in these cells [32]. As said previously, they have an inhibitory effect on neutrophil cells and prevent the production of hydrogen peroxide by activated neutrophils [44]. Many studies indicate that MSCs have an inhibitory effect on proliferation of T cell induced by polyclonal mitogens, allogeneic cells or specific antigens [45]. These cells do their inhibitory effect on the proliferation of lymphocytes by stopping the cells in the G1/G0 phase of cell cycle [46].

Due to the secretion of their cytokines, MSCs are capable of directing differentiation of T lymphocytes subsets to reduce the secretion of proinflammatory cytokines (IFNγ, Tumor Necrosis alpha [TNFα] and Interleukin [IL] -6 and IL-17) produced by activated T cells in the extracellular environment [47], and in contrast, secretion of anti-inflammatory cytokines (IL-4 and IL-10) increases [45]. T+CD4 lymphocytes have few main subgroups or subsets, each of which has its own specific phenotypic and performance characteristics; among these subsets, Th1 and Th17 are identified as inflammatory and directing inflammatory pathways subsets. On the other hand, Th2 and regulatory T cells (Treg) subsets are considered as a population of immune system suppressor or regulator cells [48, 49]. Th1 cells are the main cells in acute inflammatory reactions [50]. Abundant evidence has shown that MSCs reduce the production of INFγ by Th1 and lead to the inhabitation of this subset [51]. MSCs isolated from the bone marrow also inhibit allergic inflammation of the airways caused by Th2 cells by inducing IFNγ production [52].

Th17 cells produce IL-17A, IL17-F and IL-6, and are involved in autoimmunity and inflammation of the tissue [51]. Th17 cells as subsets of Th1 and have a central role in the process of acute graft rejection mediated by the cells, and with the production of inflammatory cytokines
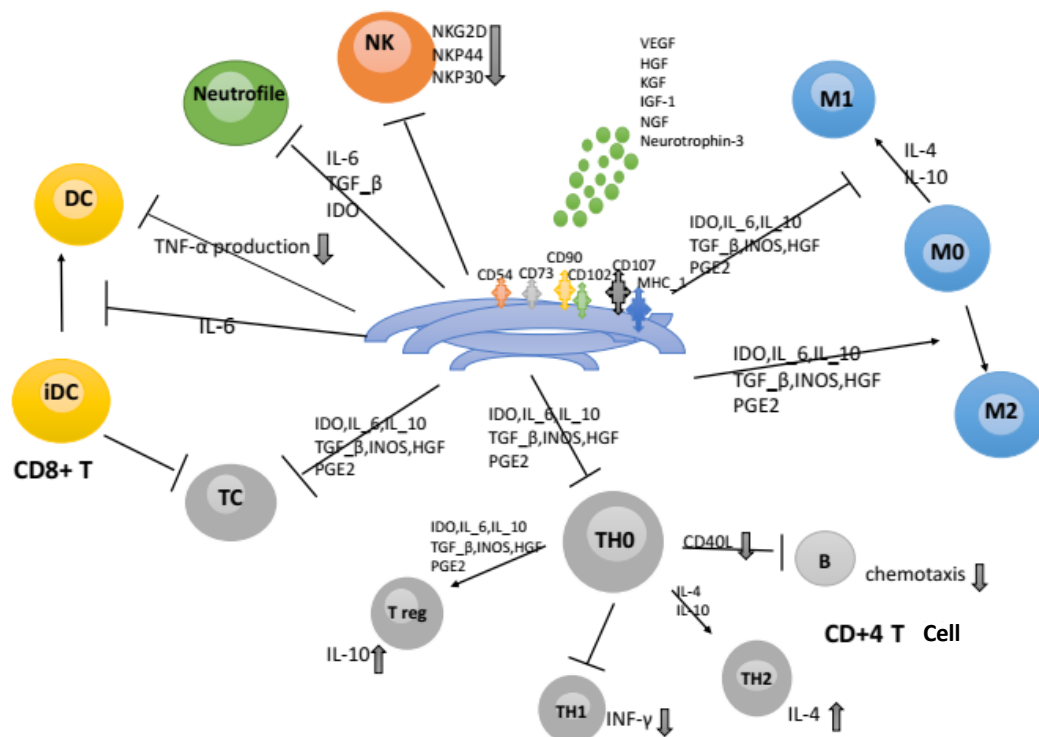
Pezeshki Naraghi Sh, et al. Immunomodulatory Effect of MSCs in MS and EAE. Immunoregulation. 2019; 1(2):67-80.

69

Figure 1. MSCs immunomodulatory effects

IMMUNOREGULATION

decreases the survival of the transplanted organ in the host body [53]. Various reports regarding the effect of MSCs on the Th17 cells have shown that MSCs inhibit Th17 response and inhibit inflammation caused by these cells, while other studies indicate that the MSCs induce and enhance Th17 response [54, 55].

Regulatory T cells (*T*reg) suppress and inhibit immune responses, and have an important role in maintaining tolerance and preventing autoimmune diseases [56]. *T*reg cells produce large amounts of IL-10 and Transforming Growth Factor (TGF)-β. MSCs lead to differentiation of T naive cells to *T*reg cells with high production capability of IL-10 and TGF-β [57]. On the other hand, with suppression of Th1 response and decreasing the production of INF-γ, the result is intense inhabitation of immune response [58]. Furthermore MSCs also cause adsorption and proliferation of *T*reg cells, and consequently, result in suppression of immune responses [59]. Therefore, the immunosuppressive characteristic of MSCs is currently used in the treatment of many autoimmune diseases such as MS [60], rheumatoid Arthritis [36], Type 1 diabetes [61], allergic diseases [62] and other hypersensitivities. It can also be used in organ transplantation as specific immunity suppressor to increase graft survival and coping T regulatory responses toward other lymphocyte subsets [63].

MSCs with secretion of indoleamine 2, 3-dioxygenase can catalyze an essential amino acid called tryptophan to kynurenine, and impair the synthesis of various cellular proteins leading to inhibition of cell proliferation [64]. They inhibit the differentiation and function of B cells, too. This effect plays its role by reducing the chemokine receptors CXCR4, CXCR5, and CCR7 [65].

Because of MSCs properties, especially their immunomodulatory function, they have been used as an immunomodulator for the treatment of diseases caused by the immune system. In recent years, the MSC therapy on the models of autoimmune diseases has been investigated [60].

MSCs Immunomodulatory Effect in Autoimmune and Inflammatory Diseases

Systemic injection of MSCs isolated from the bone marrow to a rat model (Experimental autoimmune encephalomyelitis, EAE) reduces the symptoms and severity of the disease (Table 1), suppresses demyelination in the brain and spinal cord, slows down the arrival of macrophages and T lymphocytes into the Central Nervous System (CNS) tissue, and reduces the antibody production against pathogenic protein-lipid proteins (one of the components of myelin) compared with the control group [66, 67]. In addition, the risk of a relapse and demyelination is reduced as compared with the control group. With the studies on the migration characteristics of MSCs in the rat model of EAE, it was found that MSCs remain in the lymph organs and the CNS inflamed areas

Table 1. Systemic injection of MSCs isolated from the bone marrow to a rat

Disease	Animal Model	Mesenchyme Type	Result	References
Myasthenia Gravis	Rat	Human bone marrow	Improved symptoms and reduced acetylcholine level	[70]
Rheumatoid arthritis	Rat	Human adipose tissue	Improved clinical symptoms,Reduced inflammatory cytokines,Increased anti-inflammatory cytokines in the joints	[36]
Diabetes	Rat	Human bone marrow	Increased number and size of the islets of Langerhans	[72]
Colitis	Rat	Rat bone marrow	Increased number and size of islets of Langerhans	[73]
Systemic lupus erythematosus	Rat	Rat bone marrow	Reduced rickets, and bone cell niche repair, and improved performance of damaged organisms	[71]
MS	Rat	Rat bone marrow	Improved symptomsreduced inflammatory cell infiltration and reduced demyelination	[46]
MS	Rat	Human bone marrow	Delayed the outbreak of disease, and improved symptoms	[73]

IMMUNOREGULATION

several weeks after systemic injection [68]. In addition to the immunomodulatory activity, MSCs have a protective effect on neurons by secreting nutritional factors and call for tissue precursor cells and their differentiation into different types of nerve cells [39, 69].

In connection with rheumatoid arthritis, the medical function of MSCs in the animal model of rheumatoid arthritis was studied and it was revealed that clinical symptoms and inflammatory cytokines decreases, but the anti-inflammatory cytokines in the lymph nodes and joints increases, and thus preventing severe damages to the tissues [36]. Studies on the MSCs therapeutic activity on the experimental models of muscle weakness (Myasthenia) showed that clinical signs and proliferation of specific lymphocytes of acetylcholine receptor (AchR) decreases, and the body weight in mice and rats with myasthenia is increases [70].

The rat model of Systemic Lupus Erythematosus (SLE) improved the illness in the models , and allogeneic MSC infusion reduces serum antibody, glomerular IgG level, and proteinuria, but increases bone formation and restores osteoblast niche [71].

MS and Mesenchymal Stem Cells

There are different types of stem cells: hematopoietic stem cells, mesenchymal cells, and neural cells that are used in the treatment of MS. Of which hematopoietic stem cells and mesenchymal cells are commonly used [75]. There are three ways to inject these cells: intravenous injection, spinal injection or tissue injection. Of course, the immunity of tissue injection has not yet been proved because a large amount of stem cells enter the body; it has also the risk of developing tumors in the tissues. For this reason, spinal and intravenous injections are done frequently [33, 76].

Stem Cell Injections

According to Figure 2, mesenchymal stem cells intravenously enter into the lungs. Many of these cells are destroyed by the macrophages of the lungs, and only a limited number of cells enter into the peripheral lymph nodules, heart, and brain [77].

Injecting Mesenchymal Stem Cells in EAE Rats

Experimental Autoimmune Encephalomyelitis (EAE) mouse is an animal model suitable for MS studies. In terms of clinical signs and tissue damages, it can well imitate MS because, in this model, the chronic neurologic disease is created along with the phases of attack and suppress, and like MS, hard sclerosis plaques are formed in the central nervous system [48, 49].
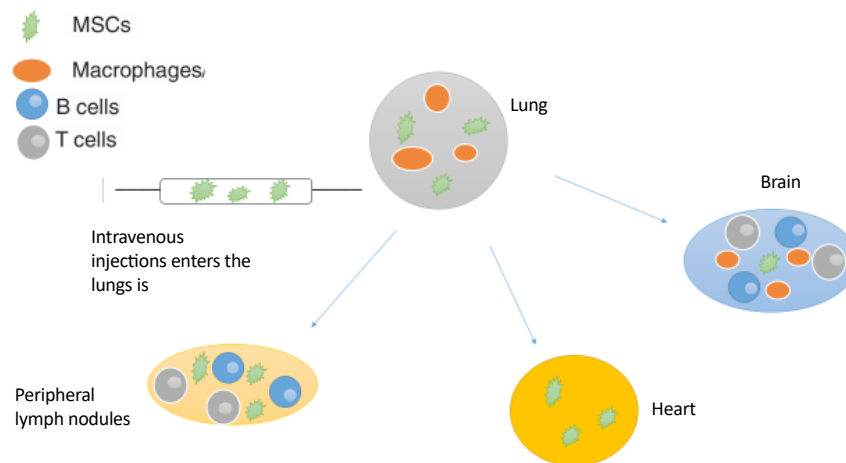
Pezeshki Naraghi Sh, et al. Immunomodulatory Effect of MSCs in MS and EAE. Immunoregulation. 2019; 1(2):67-80.

71

Figure 2. Stem cell injections

IMMUNOREGULATION

Measurement of IL4, IL10 and IL17 CytoKines in EAE Rat With MSC Injection

In this study, the rate of important cytokines IL-4 (TH2 response), IL-17FA (inflammatory response) and IL-10 (anti-inflammatory response) has been studied.Production of IL-4 and IL-10 cytokines from mouse spleen cells has increased while the production of inflammatory cytokines IL-17AF decreased [66, 78].

In fact, these findings indicate that mesenchymal stem cells migrate from the immune cells into the CNS tissue and thus prevent further destruction of myelin and suppress the inflammatory response by increasing anti-inflammatory IL-10 and IL-4 cytokines [79, 80]. Furthermore, mesenchymal stem cells, by increasing IDO1 (Indoleamine 2, 3-dioxygenase 1), ADP (antioxidant enzymes), ribose polymerase-1 and P53, oligodendrocyte progenitor cells, reduce the migration of inflammatory cells into the CNS and also induces remyelination [64, 81, 82]. Also the pathologist examination on stained samples shows the reduced number of immune cells infiltrating into the nerve tissue [39, 83].

Because of their immunomodulatory and neuroprotective properties, mesenchymal cells hold great promises in the treatment of autoimmune diseases such as MS. Studies on animals show the positive impact of MSCs in reducing the symptoms of EAE (Table 2) [84, 85]. Transplanting human adipose-derived MSCs (Ad-MSCs) expressing the anti-inflammatory cytokine Interleukin (IL)-4 in EAE causes reduction in peripheral MOG-specific T-cell responses and a shift from a pro- to anti-inflammatory cytokine response [86].

In another study using human bone marrow-derived mesenchymal stem cells (hBM-MSCs) to secret IFN-β (MSCs-IFNβ), the MSCs-IFNβ treatment enhanced the immunomodulatory effects. This, in turn, suppresses proinflammatory cytokines (IFN-ϒ and TNF-α) and conversely increases anti-inflammatory cytokines (IL-4 and IL-10). Importantly, the injected MSCs-IFNβ migrates into the inflamed CNS and significantly reduces further injury of the Blood-Brain Barrier (BBB) permeability in EAE mice [87]. Moreover, Payne, N. L. et al. engineered the expression of IL-10 in human adipose-derived mesenchymal stem cells (Adi-IL-10-MSCs) and transplanted these cells early in the disease course to mice with EAE. They showed that when administered at the time of CD4+T-cell priming, Adi-MSCs overexpressing human IL-10 significantly attenuates EAE by modulating APC function and inhibiting Th17-mediated neuro-inflammation [88].

In a recent study, a comparative analysis of the immunomodulatory properties of Adipose Tissue Mesenchymal stem cells (AT-MSCs) and their Conditioned Media (CM), derived from C57/BL6 mice, was done for mitigating the adverse clinical course of EAE. There was no significant difference in the clinical scores and the body weight of EAE mice treated with AT-MSCs and CM. The reduction in proliferative responses and brain cell infiltration was more pronounced in the mice injected with CM than in other groups. It was found that the percentage of splenic CD4+CD25+FOXP3+population and the level of IL4 production in the mice administrated with AT-MSCs more increased compared to other animals [89].

In another study, they compared the immune regulatory properties of adipose tissue MSCs (AT-MSCs) in two independent routes of injection; namely Intraperitoneal

Table 2. EAE and the positive impact of MSCs

Disease	Injection Way	Cell Source	Result	Cause	Reference
EAE	Intravenous	Syngeneic (C57BL6)	Syngeneic (C57BL6) Environmental toleranceReduce inflammation CNS	Decreased INFγDecreased TNFα	[84]
EAE	Intravenous	Xenogenic (Human)	Environmental toleranceReduce inflammation CNS	Induced oligodendrocyte progenitor cells (NG2)	[85]
EAE	Intravenous	Xenogenic (Human)	Neuroprotection	Production of NGF	[85]
EAE	Intravenous	Allogeneic (C57BL6 SJL)	Neuroprotection Environmental tolerance	Inhibition of Th17, Th1 and NK cells production	[78]
EAE	IntravenousIntraventricular	Syngeneic (C57Bl6)	Immunomodulatory (reduced inflammation) and neuroprotection	Immunomodulatory and reducing inflammatory cytokine	[39]
EAE	Intraperitoneal	Syngeneic (C57Bl6)	Immunomodulatory	Reduced inflammatory cytokines Th17	[67]
EAE	Intravenous	Syngeneic adipose derived MSC (C57Bl6)	Immunomodulatory and neuroprotection	Increased cytokines type TH2Decreased Th17	[79]
EAE	Intravenous	Xenogenic (Human)	Immunomodulatory and neuroprotection	Decreased Th17Increased IL4	[80]
EAE	Intraperitoneal	Syngeneic (C57Bl6)	Immunomodulatory	Increased IDO1Indoleamine 2, 3-dioxygenase 1	[64]
EAE	Intravenous	Syngeneic (C57Bl)	Neuroprotection	Activities of ADP antioxidant enzymes, Ribose polymerase-1 and P53	[82]
EAE	Intraperitoneal	AllogeneicBALB (C57Bl)	Immunomodulatory	Increase INFγ Reduced IL-17	[92]
EAE	Intraperitoneal	Immunomodulation and neuroprotection	Xenogenic (Human)	Decreased inflammation	[83]
EAE	Intravenous	Adipose-derived MSCs (Ad-MSCs) engineered to overexpress the anti-inflammatory cytokine interleukin (IL-4)	Immunomodulation and neuroprotection	Reduction in peripheral MOG-specific T-cell responses and a shift from a pro- to anti-inflammatory cytokine response	[86]
EAE	Intravenous	Interferon β-secreting human bone marrowmesenchymal stem cells	Suppressing demyelination and immunomodulatory effects	Promoting a shift from the Th1 to the Th2 cytokine balance	[87]

Pezeshki Naraghi Sh, et al. Immunomodulatory Effect of MSCs in MS and EAE. Immunoregulation. 2019; 1(2):67-80.

73

Disease	Injection Way	Cell Source	Result	Cause	Reference
EAE	Intravenous	Human adipose-derived mesenchymal stem cells engineered to secrete IL-10	Immunomodulation and neuroprotection	Inhibit APC function and limit CNS autoimmunity	[88]
EAE	Intravenous	Autologous adipose tissue mesenchymal stem cells (AT-MSCs) and their conditioned media (CM)	Reduction in proliferative responses and brain cell infiltration was more pronounced in mice injected with CM	Induced CD4 + CD25 + FOXP3 + regulatory T cells after in vitro co-culture with naïve T cells	[89]
EAE	Intravenous	Adipose-derived mesenchymal stem cells (AD-MSCs) expressing murine interferon beta (MSCs-VP/IFN-β)	Immunomodulationreduces the migration of inflammatory cells into the CNS	Induction of Tregs and IL-10 and reduction of IL-17	[91]

(IP) and Intravenous (IV), and reported that the IP route has a more pronounced effect in maintaining the splenic CD4+CD25+FOXP3+T cell population and increase of IL-4 secretion. They also showed that IP injection of cells resulted in lower IFN-γ secretion and reduced cell infiltration in brain more effectively as compared to the IV route. The effects of AT-MSCs on down-regulation of splenocyte proliferation, IL-17 secretion and alleviating the severity of clinical scores were similar in IP and IV routes [90]. Furthermore, it was reported that Adipose-Derived Mesenchymal Stem Cells (AD-MSCs) expressed murine interferon beta (MSCs-VP/IFN-β) in the animal model of MS (EAE) to induce Tregs and IL-10 and reduce IL-17 [91].

Treatment of Patients With MS Using Mesenchymal Stem Cells (MSCs) (Table 3)

In early human studies, Bonab et al. injected progressive MCS to 10 patients with MS. Although they did not achieve successful results, they were hopeful that given the immunomodulatory effects of MSCs, this treatment would improve the condition of the patients [92]. Another group of researchers injected endometrial cells that contained a population of stem cells such as mesenchymal stem cells to four patients with MS intravenously and intrathecally, and reported healing effects with no adverse effects in these cells [93].

In another study, stem cells derived from umbilical cord were used in patients with MS that was associated with immunosuppression and attenuation of disease [58]. Yamout et al. reported that intrathecal injection of MSC derived from autologous bone marrow expanded in vitro to 10 patients with MS was associated with healing effects [94].

Karussis et al. conducted studies on 15 patients with MS using intrathecal and intravenous injection of autologous stem cells and showed the MSCs immunomodulatory effect as well as the safety of the treatment of MS by injecting stem cells [96]. Another study done in the phase IIA of clinical studies, confirmed the safety and efficacy of autologous stem cells in 10 patients with MS [96]. In addition, treatment of 50 patients with MS in Iraq with intrathecal injection of purified peripheral blood cells through aphaeresis with Granulocyte Colony Stimulating Factor (G-CSF) yielded promising results [97].

Connick et al. in a clinical trial study injected autologous stem cells intravenously to 10 patients with MS who had disorders in optic nerves and monitored them for 10 months. They observed that the patients had achieved relative improvement in their optical nerves, and no side effects were observed during the use of stem cells [97]. In another study, autologous stem cells were intravenously injected to 8 patients with MS. The outcome was promising together with some positive effects without significant side effects [98].

Bonab et al. reported that intrathecal injection of stem cells that was expanded in vitro, have reduced the disease symptoms without the side effects [99]. Furthermore intrathecal treatment of MS patients with MSC resulted in increased expression of FoxP3 [100]. On the other hand, intrathecal injection of stem cells to 25 patients with MS had no significant effect on the cytokines such as IFN-γ, TGF-B, IL-4, IL-10, and IL-6, as well as FoxP3 in peripheral blood cells [101]. In addition, in a study over four years of treatment, a patient with progressive MS with both allogeneic MSCs derived from human umbilical cord and cells derived from autologous bone marrow, no significant side effects were observed [102]. Several clinical trials are underway around the world that exam-

Table 3. Treatment of patients with MS using mesenchymal stem cells (MSCs)

Disease Type	Number of Patients	Cells Injected into the Patient	Injection Route	Clinical Results	Reference
Progressive MS	10	MSCs expanded in vitro	Intrathecal injection	Improvement of symptoms	[93]
MS	4	MSCs derived from endometrial cells	Intravenous andintra-thecal injection	Improved symptoms,no side effects	[94]
MS	32	MSCs derived from umbilical cord	Intrathecal injection	Suppression of neuro-inflammation	[58]
MS	10	MSCs derived from autologous bone marrow	Intrathecal injection	Improved symptoms	[95]
MS	15	MSCs derived from autologous bone marrow	Intravenous injection-Intrathecal injection	Improved symptoms, no side effects	[96]
Secondary progres-sive MS	10	MSC derived from autologous bone marrow	Intravenous injection	Improved symptoms, no side effects	[97]
MS in Iraq	50	The peripheral blood cells purified through aphaeresis with G-CSF	Intrathecal injection	Improvement of clinical symptoms, no adverse-clinical effects	[98]
MS with optic nerve disorders	10	Autologous MSCs	Intravenous injection	Relative improvement in optic nerve, no clinical side effects	[99]
MS	8	Autologous MSCs	Intravenous injection	Improved clinical symp-toms, no clinical side effects	[100]
Progressive MS	25	Autologous MSC	Intrathecal injection	MSC therapy can improve/stabilize the course of the disease in progressive MS in the first year after injection with no serious adverse effects.	[101]
MS	7	Autologous MSC	Intrathecal injection	Increased expression of FoxP3, and thus increasing $Treg$	[102]
MS	25	Autologous MSC	Intrathecal injection	It has no effect on the cyto-kines such as IFN-γ, TGF-B, IL-4, Il-10, Il-6 as well as Foxp3 in the peripheral blood	[102]
Progressive MS	1	1) Allogeneic MSCs derived from hu-man umbilical cord2) MSCs derived from autologous bone marrow	Intrathecal injection	The use of both types of MSCs improves clinical symptoms with no clinical side effects	[103]
3 SPMS 3 RRMS 2 PPMS	8	Autologous MSC	Intravenously	MRI lesion relapse andim-proved clinical symptoms	[98]

ImmunoRegulation

Pezeshki Naraghi Sh, et al. Immunomodulatory Effect of MSCs in MS and EAE. Immunoregulation. 2019; 1(2):67-80.

75

ImmunoRegulation

ine the effectiveness and side effects of treatment of MS patients using stem cells [33]. However, despite some studies in phase I/II, no significant positive result indicating complete remission of the disease using stem cells is available and more research is needed.

The use of stem cells and MSCs for the treatment of autoimmune diseases has been much considered in the past decade. Now MSCs are widely used in clinical trials, and initial promising results are obtained with regard to the control and prevention of MS. Several studies have shown that these cells are in close contact with various immune cells. Therefore, they can be considered a valuable tool for the treatment of various inflammatory diseases such as MS. However, clarification of the exact mechanisms of these cells in the treatment of patients with MS is required. The identification of these mechanisms in future could be useful in selecting the appropriate dose and injection time. It is also valuable in the selection of cells derived from different tissues and sources for the treatment of MS.

Ethical Considerations

Compliance with ethical guidelines

There is no ethical principal to be considered doing this research.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Joseph FG, Hirst CL, Pickersgill TP, Ben-Shlomo Y, Robertson NP, Scolding NJ. CSF oligoclonal band status informs prognosis in multiple sclerosis: A case control study of 100 patients. Journal of Neurology, Neurosurgery, and Psychiatry. 2009; 80(3):292–6. [DOI:10.1136/jnnp.2008.150896] [PMID]

[2] Hanken K, Eling P, Hildebrandt H. The representation of inflammatory signals in the brain - a model for subjective fatigue in multiple sclerosis. Frontiers in Neurology. 2014; 5:264. [DOI:10.3389/fneur.2014.00264] [PMID] [PMCID]

[3] Laule C, Leung E, Li DK, Traboulsee AL, Paty DW, MacKay AL, et al. Myelin water imaging in multiple sclerosis: quantitative correlations with histopathology. Multiple Sclerosis Journal. 2006; 12(6):747–53. [DOI:10.1177/1352458506070928] [PMID]

[4] Ponichtera-Mulcare J. Exercise and multiple sclerosis. Medicine & Science in Sports & Exercise. 1993; 25(4):451–65. [PMID]

[5] Goldenberg MM. Multiple sclerosis review. Physical Therapy. 2012; 37(3):175–84. [PMID] [PMCID]

[6] Fletcher JM, Lalor SJ, Sweeney CM, Tubridy N, Mills KHG. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clinical & Experimental Immunology. 2010; 162(1):1–11. [DOI:10.1111/j.1365-2249.2010.04143.x] [PMID] [PMCID]

[7] Trapp BD, Nave KA. Multiple sclerosis: An immune or neurodegenerative disorder? Annual Review of Neuroscience. 2008; 31:247–69. [DOI:10.1146/annurev.neuro.30.051606.094313] [PMID]

[8] McFarland HF, Martin R. Multiple sclerosis: A complicated picture of autoimmunity. Nature Immunology. 2007; 8(9):913–9. [DOI:10.1038/ni1507] [PMID]

[9] Barnett MH, Prineas JW. Relapsing and remitting Multiple Sclerosis: Pathology of the newly forming lesion. Annals of Neurology. 2004; 55(4):458–68. [DOI:10.1002/ana.20016] [PMID]

[10] Rovaris M, Confavreux C, Furlan R, Kappos L, Comi G, Filippi M. Secondary progressive multiple sclerosis: current knowledge and future challenges. The Lancet Neurology. 2006; 5(4):343–54. [DOI:10.1016/S1474-4422(06)70410-0]

[11] Thompson A. Primary progressive multiple sclerosis. Brain. 1997; 120(6):1085–96. [DOI:10.1093/brain/120.6.1085] [PMID]

[12] Dutta R, Trapp BD. Relapsing and progressive forms of multiple sclerosis: Insights from pathology. Current Opinion in Neurology. 2014; 27(3):271–8. [DOI:10.1097/WCO.0000000000000094] [PMID] [PMCID]

[13] Río J, Comabella M, Montalban X. Multiple sclerosis: current treatment algorithms. Current Opinion in Neurology. 2011; 24(3):230–7. [DOI:10.1097/WCO.0b013e328346bf66] [PMID]

[14] Loma I, Heyman R. Multiple sclerosis: Pathogenesis and treatment. Current Neuropharmacology. 2011; 9(3):409–16. [DOI:10.2174/157015911796557911] [PMID] [PMCID]

[15] Stefoski D, Schauf CL, McLeod BC, Davis FA. Plasmapheresis decreases neuroelectric blocking activity in multiple sclerosis. Neurology. 1982; 32(8):907. [DOI:10.1212/WNL.32.8.904]

[16] Comabella M, Lünemann JD, Río J, Sánchez a, López C, Julià E, et al. A type I interferon signature in monocytes is associated with poor response to interferon-beta in multiple sclerosis. Brain. 2009; 132(Pt 12):3353–65. [DOI:10.1093/brain/awp228] [PMID]

[17] Rudick RA, Goelz SE. Beta-interferon for multiple sclerosis. Experimental Cell Research. 2011; 317(9):1301–11. [DOI:10.1016/j.yexcr.2011.03.002] [PMID]

[18] Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurologica Scandinavica. 2006; 113(5):283–7. [DOI:10.1111/j.1600-0404.2006.00585.x] [PMID]

[19] Mokhber N, Azarpazhooh A, Orouji E, Khorram B, Modares Gharavi M, Kakhi S, et al. Therapeutic effect of Avonex, Rebif and Betaferon on quality of life in multiple sclerosis. Psychiatry and Clinical Neurosciences. 2015; 69(10):649–57. [DOI:10.1111/pcn.12308] [PMID]

[20] Comi G, Cohen JA, Arnold DL, Wynn D, Filippi M. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. Annals of Neurology. 2011; 69(1):75–82. [DOI:10.1002/ana.22316] [PMID]

[21] Twork S, Nippert I, Scherer P, Haas J, Pöhlau D, Kugler J. Immunomodulating drugs in multiple sclerosis: Compliance, satisfaction and adverse effects evaluation in a German multiple sclerosis population. Current Medical Research and Opinion. 2007; 23(6):1209–15. [DOI:10.1185/030079907X188125] [PMID]

[22] Rice CM, Cottrell D, Wilkins A, Scolding NJ. Primary progressive multiple sclerosis: Progress and challenges. Journal of Neurology, Neurosurgery, and Psychiatry. 2013; 84(10):1100–6. [DOI:10.1136/jnnp-2012-304140] [PMID]

[23] Neuhaus O, Kieseier BC, Hartung H-P. Therapeutic role of mitoxantrone in multiple sclerosis. Pharmacology & Therapeutics. 2006; 109(1-2):198–209. [DOI:10.1016/j.pharmthera.2005.07.002] [PMID]

[24] Esposito F, Radaelli M, Martinelli V, Sormani MP, Martinelli Boneschi F, Moiola L, et al. Comparative study of mitoxantrone efficacy profile in patients with relapsing-remitting and secondary progressive multiple sclerosis. Multiple Sclerosis Journal. 2010; 16(12):1490–9. [DOI:10.1177/1352458510379613] [PMID]

[25] Chataway J, Miller DH. Natalizumab therapy for multiple sclerosis. Neurotherapeutics. 2013; 10(1):19–28. [DOI:10.1007/s13311-012-0171-4] [PMID] [PMCID]

[26] Pelletier D, Hafler DA. Fingolimod for Multiple Sclerosis. The New England Journal of Medicine. 2012; 366:339–47. [DOI:10.1056/NEJMct1101691] [PMID]

[27] Brown BA, Kantesaria PP, McDevitt LM. Fingolimod: A novel immunosuppressant for Multiple Sclerosis. Annals of Pharmacotherapy. 2007; 41(10):1660–8. [DOI:10.1345/aph.1G424] [PMID]

[28] Morris K, Yiannikas C. Treatment update in multiple sclerosis. Current Allergy and Asthma Reports. 2012; 12(3):246–54. [DOI:10.1007/s11882-012-0256-5] [PMID]

[29] Gebler A, Zabel O, Seliger B. The immunomodulatory capacity of mesenchymal stem cells. Trends in Molecular Medicine. 2012; 18(2):128–34. [DOI:10.1016/j.molmed.2011.10.004] [PMID]

[30] Corcione A, Benvenuto F, Ferretti E, Giunti D, Cappiello V, Cazzanti F, et al. Human mesenchymal stem cells modulate B-cell functions. Blood. 2006; 107(1):367–72. [DOI:10.1182/blood-2005-07-2657] [PMID]

[31] Duffy MM, Ritter T, Ceredig R, Griffin MD. Mesenchymal stem cell effects on T-cell effector pathways. Stem Cell Research & Therapy. 2011; 2(4):34–43. [DOI:10.1186/scrt75] [PMID] [PMCID]

[32] Spaggiari GM, Capobianco A, Becchetti S, Mingari MC, Moretta L. Mesenchymal stem cell – natural killer cell interactions: evidence that activated NK cells are capable of killing MSCs , whereas MSCs can inhibit IL-2 – induced NK-cell proliferation. Blood. 2015; 107(4):1484–91. [DOI:10.1182/blood-2005-07-2775] [PMID]

[33] Wei X, Yang X, Han Z, Qu F, Shao L, Shi Y. Mesenchymal stem cells: A new trend for cell therapy. Acta Pharmacologica Sinica. 2013; 34(6):747–54. [DOI:10.1038/aps.2013.50] [PMID] [PMCID]

[34] Ramasamy R, Fazekasova H, Lam EW-F, Soeiro I, Lombardi G, Dazzi F. Mesenchymal stem cells inhibit dendritic cell differentiation and function by preventing entry into the cell cycle. Transplantation. 2007; 83(1):71–6. [DOI:10.1097/01.tp.0000244572.24780.54] [PMID]

[35] Davila C, Dulamea A. Mesenchymal stem cells in multiple sclerosis-translation to clinical trials. Journal of Medicine and Life. 2015; 8(1):24-7. [PMID] [PMCID]

[36] El-Jawhari JJ, El-Sherbiny YM, Jones EA, McGonagle D. Mesenchymal stem cells, autoimmunity and rheumatoid arthritis. International Journal of Medicine. 2014; 107(7):505-14. [DOI:10.1093/qjmed/hcu033] [PMID] [PMCID]

[37] Ehninger A, Trumpp A. The bone marrow stem cell niche grows up: Mesenchymal stem cells and macrophages move in. Journal of Experimental Medicine. 2011; 208(3):421–8. [DOI:10.1084/jem.20110132] [PMID] [PMCID]

[38] Isern J, García-García A, Martín AM, Arranz L, Martín-Pérez D, Torroja C, et al. The neural crest is a source of mesenchymal stem cells with specialized hematopoietic stem cell niche function. eLife. 2014; 3:e03696. [DOI:10.7554/eLife.03696] [PMID] [PMCID]

[39] Gerdoni E, Gallo B, Casazza S, Musio S, Bonanni I, Pedemonte E, et al. Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis. Annals of Neurology. 2007; 61:219–27. [DOI:10.1002/ana.21076] [PMID]

[40] Chang JT, Palanivel VR, Kinjyo I, Schambach F, Intlekofer AM, Banerjee A, et al. Asymmetric T lymphocyte division in the initiation of adaptive immune responses. Science. 2007; 315(5819):1687–91. [DOI:10.1126/science.1139393] [PMID]

[41] MacQueen L, Sun Y, Simmons CA. Mesenchymal stem cell mechanobiology and emerging experimental platforms. Journal of the Royal Society Interface. 2013; 10(84):20130179. [DOI:10.1098/rsif.2013.0179] [PMID] [PMCID]

[42] Shi Y, Hu G, Su J, Li W, Chen Q, Shou P, et al. Mesenchymal stem cells: A new strategy for immunosuppression and tissue repair. Cell Research. 2010; 20(5):510–8. [DOI:10.1038/cr.2010.44] [PMID]

[43] Tokoyoda K, Hauser AE, Nakayama T, Radbruch A. Organization of immunological memory by bone marrow stroma. Nature Reviews Immunology. 2010; 10(3):193–200. [DOI:10.1038/nri2727] [PMID]

[44] Raffaghello L, Bianchi G, Bertolotto M, Montecucco F, Busca A, Dallegri F, et al. Human mesenchymal stem cells inhibit neutrophil apoptosis: A model for neutrophil preservation in the bone marrow niche. Stem Cells Journals. 2008; 26(1):151–62. [DOI:10.1634/stemcells.2007-0416] [PMID]

[45] Wang Y, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. Nature Immunology. 2014; 15(11):1009–16. [DOI:10.1038/ni.3002] [PMID]

Pezeshki Naraghi Sh, et al. Immunomodulatory Effect of MSCs in MS and EAE. Immunoregulation. 2019; 1(2):67-80.

77

[46] Al Jumah M a, Abumaree MH. The Immunomodulatory and Neuroprotective Effects of Mesenchymal Stem Cells (MSCs) in Experimental Autoimmune Encephalomyelitis (EAE): A Model of Multiple Sclerosis (MS). International Journal of Molecular Sciences. 2012; 13(7):9298–331. [DOI:10.3390/ijms13079298] [PMID] [PMCID]

[47] Ben-Ami E, Berrih-Aknin S, Miller A. Mesenchymal stem cells as an immunomodulatory therapeutic strategy for autoimmune diseases. Autoimmunity Reviews. 2011; 10(7):410–5. [DOI:10.1016/j.autrev.2011.01.005]

[48] Arsenio J, Kakaradov B, Metz PJ, Kim SH, Yeo GW, Chang JT. Early specification of CD8+ T lymphocyte fates during adaptive immunity revealed by single-cell gene-expression analyses. Nat Immunol. 2014; 15(4):365–72. [DOI:10.1038/ni.2842] [PMID] [PMCID]

[49] Steinman L. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. Nature Medicine. 2007; 13(2):139–45. [DOI:10.1038/nm1551]

[50] Goto H, Matsuo H, Nakane S, Izumoto H, Fukudome T, Kambara C, et al. Plasmapheresis affects T helper type-1/T helper type-2 balance of circulating peripheral lymphocytes. Therapeutic Apheresis and Dialysis. 2001; 5(6):494–6. [DOI:10.1046/j.1526-0968.2001.00386.x] [PMID]

[51] Duffy MM, Pindjakova J, Hanley SA, McCarthy C, Weidhofer GA, Sweeney EM, et al. Mesenchymal stem cell inhibition of T-helper 17 cell- differentiation is triggered by cell-cell contact and mediated by prostaglandin E2 via the EP4 receptor. European Journal of Immunology. 2011; 41(10):2840–51. [DOI:10.1002/eji.201141499] [PMID]

[52] Favaro E, Carpanetto A, Lamorte S, Fusco A, Caorsi C, Deregibus MC, et al. Human mesenchymal stem cell-derived microvesicles modulate T cell response to islet antigen glutamic acid decarboxylase in patients with type 1 diabetes. Diabetologia. 2014; 57(8):1664–73. [DOI:10.1007/s00125-014-3262-4] [PMID]

[53] Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. The New England Journal of Medicine. 2009; 361(9):888–98. [DOI:10.1056/NEJMra0707449] [PMID]

[54] Ghannam S, Pène J, Moquet-Torcy G, Torcy-Moquet G, Jorgensen C, Yssel H. Mesenchymal stem cells inhibit human Th17 cell differentiation and function and induce a T regulatory cell phenotype. The Journal of Immunology. 2010; 185(1):302–12. [DOI:10.4049/jimmunol.0902007] [PMID]

[55] Ghoreschi K, Laurence A, Yang XP, Hirahara K, O'Shea JJ. T helper 17 cell heterogeneity and pathogenicity in autoimmune disease. Trends in Immunology. 2011; 32(9):395–401. [DOI:10.1016/j.it.2011.06.007]

[56] Chang JT, Wherry EJ, Goldrath AW. Molecular regulation of effector and memory T cell differentiation. Nature Immunology. 2014; 15(12):1104–15. [DOI:10.1038/ni.3031] [PMID] [PMCID]

[57] Tang Q, Bluestone JA. The Foxp3+regulatory T cell: A jack of all trades, master of regulation. Nature Immunology. 2008; 9(3):239–44. [DOI:10.1038/ni1572] [PMID] [PMCID]

[58] Zhao Z, Wu Y, Cheng M, Ji Y, Yang X, Liu P, et al. Activation of Th17/Th1 and Th1, but not Th17, is associated with the acute cardiac event in patients with acute coronary syndrome. Atherosclerosis. 2011; 217(2):518–24. [DOI:10.1016/j.atherosclerosis.2011.03.043] [PMID]

[59] Benvenuto F, Ferrari S, Gerdoni E, Gualandi F, Frassoni F, Pistoia V, et al. Human mesenchymal stem cells promote survival of T cells in a quiescent state. Stem Cells. 2007; 25(7):1753–60. [DOI:10.1634/stemcells.2007-0068] [PMID]

[60] Dazzi F, Krampera M. Mesenchymal stem cells and autoimmune diseases. Best Practice & Research Clinical Haematology. 2011; 24(1):49–57. [DOI:10.1016/j.beha.2011.01.002] [PMID]

[61] Zhou H, Gao Y, Tian HM. [Bone marrow mesenchymal stem cell therapy on diabetic nephropathy in rats (Chinese)]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2009; 40(6):1024–8. [PMID]

[62] Dazzi F, Horwood NJ. Potential of mesenchymal stem cell therapy. Current Opinion in Oncology. 2007; 19(6):650–5. [DOI:10.1097/CCO.0b013e3282f0e116] [PMID]

[63] Ghannam S, Pene J, Torcy-Moquet G, Jorgensen C, Yssel H. Mesenchymal stem cells inhibit human Th17 cell differentiation and function and induce a T regulatory cell phenotype. The Journal of Immunology. 2010; 185(1):302–12. [DOI:10.4049/jimmunol.0902007] [PMID]

[64] Lanz TV, Opitz CA, Ho PP, Agrawal A, Lutz C, Weller M, et al. Mouse mesenchymal stem cells suppress antigen-specific TH cell immunity independent of indoleamine 2,3-dioxygenase 1 (IDO1). Stem Cells and Development. 2010; 19(5):657–68. [DOI:10.1089/scd.2009.0385] [PMID] [PMCID]

[65] Abumaree M, Al Jumah M, Pace RA, Kalionis B. Immunosuppressive Properties of Mesenchymal Stem Cells. Stem Cell Reviews and Reports. 2011; 8(2):375–92. [DOI:10.1007/s12015-011-9312-0]

[66] Rafei M, Campeau PM, Aguilar-Mahecha A, Buchanan M, Williams P, Birman E, et al. Mesenchymal stromal cells ameliorate experimental autoimmune encephalomyelitis by inhibiting CD4 Th17 T cells in a CC chemokine ligand 2-dependent manner. The Journal of Immunology. 2009; 182(21):5994–6002. [DOI:10.4049/jimmunol.0803962] [PMID]

[67] Rafei M, Birman E, Forner K, Galipeau J. Allogeneic mesenchymal stem cells for treatment of experimental autoimmune encephalomyelitis. Molecular Therapy. 2009; 17(10):1799–803. [DOI:10.1038/mt.2009.157] [PMID] [PMCID]

[68] Fisher-Shoval Y, Barhum Y, Sadan O, Yust-Katz S, Ben-Zur T, Lev N, et al. Transplantation of placenta-derived mesenchymal stem cells in the EAE mouse model of MS. Journal of Molecular Neuroscience. 2012; 48(1):176–84. [DOI:10.1007/s12031-012-9805-6] [PMID]

[69] Yang SH, Park MJ, Yoon IH, Kim SY, Hong SH, Shin JY, et al. Soluble mediators from mesenchymal stem cells suppress T cell proliferation by inducing IL-10. Experimental & Molecular Medicine. 2009; 41(5):315–24. [DOI:10.3858/emm.2009.41.5.035] [PMID] [PMCID]

[70] Yu J, Zheng C, Ren X, Li J, Liu M, Zhang L, et al. Intravenous administration of bone marrow mesenchymal stem cells benefits experimental autoimmune myasthenia gravis mice through an immunomodulatory action. Scandinavian Journal of Immunology. 2010; 72(3):242–9. [DOI:10.1111/j.1365-3083.2010.02445.x] [PMID]

[71] Sui W, Hou X, Che W, Chen J, Ou M, Xue W, et al. Hematopoietic and mesenchymal stem cell transplantation for severe and refractory systemic lupus erythematosus. Clinical Immunology. 2013; 148(2):186–97. [DOI:10.1016/j.clim.2013.05.014] [PMID]

[72] Domínguez-Bendala J, Lanzoni G, Inverardi L, Ricordi C. Concise review: Mesenchymal stem cells for diabetes. Stem Cells Translational Medicine. 2012; 1(1):59–63. [DOI:10.5966/sctm.2011-0017] [PMID] [PMCID]

[73] Flores AI, Gómez-Gómez GJ, Masedo-González Á, Martínez-Montiel MP. Stem cell therapy in inflammatory bowel disease: A promising therapeutic strategy? World Journal of Stem Cells. 2015; 7(2):343–51. [DOI:10.4252/wjsc.v7.i2.343] [PMID] [PMCID]

[74] Wang X, Kimbrel EA, Ijichi K, Paul D, Lazorchak AS, Chu J, et al. Human ESC-derived MSCs outperform bone marrow MSCs in the treatment of an EAE model of multiple sclerosis. Stem Cell Reports. 2014; 3(1):115–30. [DOI:10.1016/j.stemcr.2014.04.020] [PMID] [PMCID]

[75] Meamar R, Nematollahi S, Dehghani L, Mirmosayyeb O, Shayegannejad V, Basiri K, et al. The role of stem cell therapy in multiple sclerosis: An overview of the current status of the clinical studies. Advanced Biomedical Research. 2016; 5:46. [DOI:10.4103/2277-9175.178791] [PMID] [PMCID]

[76] Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: Mesenchymal stem cells: Their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells. 2007; 25(11):2739–49. [DOI:10.1634/stemcells.2007-0197] [PMID]

[77] Harris VK, Yan QJ, Vyshkina T, Sahabi S, Liu X, Sadiq SA. Clinical and pathological effects of intrathecal injection of mesenchymal stem cell-derived neural progenitors in an experimental model of Multiple Sclerosis. Journal of the Neurological Sciences. 2012; 313(1-2):167–77. [DOI:10.1016/j.jns.2011.08.036] [PMID]

[78] Kassis I, Grigoriadis N, Gowda-Kurkalli B, Mizrachi-Kol R, Ben-Hur T, Slavin S, et al. Neuroprotection and immunomodulation with mesenchymal stem cells in chronic experimental autoimmune encephalomyelitis. JAMA Neurology. 2008; 65(6):753–61. [DOI:10.1001/archneur.65.6.753] [PMID]

[79] Constantin G, Marconi S, Rossi B, Angiari S, Calderan L, Anghileri E, et al. Adipose-derived mesenchymal stem cells ameliorate chronic experimental autoimmune encephalomyelitis. Stem Cells. 2009; 27(10):2624–35. [DOI:10.1002/stem.194] [PMID]

[80] Bai L, Lennon DP, Eaton V, Maier K, Caplan AI, Miller SD, et al. Human bone marrow-derived mesenchymal stem cells induce Th2-polarized immune response and promote endogenous repair in animal models of multiple sclerosis. Glia. 2009; 57(11):1192–203. [DOI:10.1002/glia.20841] [PMID] [PMCID]

[81] Zhang J, Li Y, Chen J, Cui Y, Lu M, Elias SB, et al. Human bone marrow stromal cell treatment improves neurological functional recovery in EAE mice. Experimental Neurology. 2005; 195(1):16–26. [DOI:10.1016/j.expneurol.2005.03.018] [PMID]

[82] Lanza C, Morando S, Voci A, Canesi L, Principato MC, Serpero LD, et al. Neuroprotective mesenchymal stem cells are endowed with a potent antioxidant effect in vivo. Journal of Neurochemistry. 2009; 110:1674–84. [DOI:10.1111/j.1471-4159.2009.06268.x] [PMID]

[83] Gordon D, Pavlovska G, Glover CP, Uney JB, Wraith D, Scolding NJ. Human mesenchymal stem cells abrogate experimental allergic encephalomyelitis after intraperitoneal injection, and with sparse CNS infiltration. Neuroscience Letters. 2008; 448(1):71–3. [DOI:10.1016/j.neulet.2008.10.040] [PMID] [PMCID]

[84] Zappia E, Casazza S, Pedemonte E, Benvenuto F, Bonanni I, Gerdoni E, et al. Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T cell anergy. Blood. 2005; 106(5):1755–61. [DOI:10.1182/blood-2005-04-1496] [PMID]

[85] Zhang J, Li Y, Lu M, Cui Y, Chen J, Noffsinger L, et al. Bone marrow stromal cells reduce axonal loss in experimental autoimmune encephalomyelitis mice. Journal of Neuroscience Research. 2006; 84(3):587–95. [DOI:10.1002/jnr.20962] [PMID]

[86] Payne NL, Dantanarayana A, Sun G, Moussa L, Caine S, McDonald C, et al. Early intervention with gene-modified mesenchymal stem cells overexpressing interleukin-4 enhances anti-inflammatory responses and functional recovery in experimental autoimmune demyelination. Cell Adhesion & Migration. 2012; 6(3):179–89. [DOI:10.4161/cam.20341] [PMID] [PMCID]

[87] Ryu CH, Park KY, Hou Y, Jeong CH, Kim SM, Jeun SS. Gene therapy of Multiple Sclerosis using interferonβ-secreting human bone marrow mesenchymal stem cells. BioMed Research International. 2013; 2013:1–9. [DOI:10.1155/2013/696738]

[88] Payne NL, Sun G, McDonald C, Moussa L, Emerson-Webber A, Loisel-Meyer S, et al. Human adipose-derived mesenchymal stem cells engineered to secrete IL-10 inhibit APC function and limit CNS autoimmunity. Brain, Behavior, and Immunity. 2013; 30:103–14. [DOI:10.1016/j.bbi.2013.01.079]

[89] Yousefi F, Ebtekar M, Soudi S, Soleimani M, Hashemi SM. In vivo immunomodulatory effects of adipose-derived mesenchymal stem cells conditioned medium in experimental autoimmune encephalomyelitis. Immunology Letters. 2016; 172:94-105. [DOI:10.1016/j.imlet.2016.02.016]

[90] Yousefi F, Ebtekar M, Soleimani M, Soudi S, Hashemi SM. Comparison of in vivo immunomodulatory effects of intravenous and intraperitoneal administration of adipose-tissue mesenchymal stem cells in Experimental Autoimmune Encephalomyelitis (EAE). International Immunopharmacology. 2013; 17(3):608–16. [DOI:10.1016/j.intimp.2013.07.016] [PMID]

[91] Mohammadzadeh A, Pourfathollah AA, Shahrokhi S, Fallah A, Tahoori MT, Amari A, et al. Evaluation of AD-MSC (Adipose derived -Mesenchymal stem cells) as a vehicle for IFN-β delivery in Experimental Autoimmune Encephalomyelitis. Clinical Immunology. 2016; 169:98–106. [DOI:10.1016/j.clim.2016.06.015]

[92] Mohyeddin Bonab M, Yazdanbakhsh S, Lotfi J, Alimoghaddom K, Talebian F, Hooshmand F, et al. Does mesenchymal stem cell therapy help multiple sclerosis patients? Report of a pilot study. Iranian Journal of Immunology. 2007; 4(1):50-7. [DOI:IJIv4i1A7] [PMID]

[93] Gharibi T, Ahmadi M, Seyfizadeh N, Jadidi-Niaragh F, Yousefi M. Immunomodulatory characteristics of mesenchymal stem cells and their role in the treatment of Multiple Sclerosis. Cellular Immunology. 2015; 293(2):113–21. [DOI:10.1016/j.cellimm.2015.01.002]

[94] Yamout B, Hourani R, Salti H, Barada W, El-Hajj T, Al-Kutoubi A, et al. Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: A pilot

Pezeshki Naraghi Sh, et al. Immunomodulatory Effect of MSCs in MS and EAE. Immunoregulation. 2019; 1(2):67-80.

79

ImmunoRegulation

study. Journal of Neuroimmunology. 2010; 227(1-2):185–9. [DOI:10.1016/j.jneuroim.2010.07.013] [PMID]

[95] Karussis D, Karageorgiou C, Vaknin-Dembinsky A, Gowda-Kurkalli B, Gomori JM, Kassis I, et al. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. JAMA Neurology. 2010; 67(10):1187–94. [DOI:10.1001/archneurol.2010.248] [PMID] [PMCID]

[96] Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, et al. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: An open-label phase 2a proof-of-concept study. The Lancet Neurology. 2012; 11(2):150–6. [DOI:10.1016/S1474-4422(11)70305-2]

[97] Hammadi AMA, Marino A, Farhan S. Clinical outcome of 50 progressive multiple sclerosis patients treated with cellular therapy in Iraq. International Journal of Stem Cells. 2011; 4(2):113–5. [PMCID] [PMID]

[98] Odinak MM, Bisaga GN, Novitskiĭ A V, Tyrenko V V, Fominykh MS, Bilibina AA, et al. [Transplantation of mesenchymal stem cells in multiple sclerosis (Russian)]. Zh Nevrol Psikhiatr Im S S Korsakova. 2011; 111(2 Pt 2):72–6. [PMID]

[99] Mohyeddin Bonab M, Ali Sahraian M, Aghsaie A, Ahmadi Karvigh S, Massoud Hosseinian S, Nikbin B, et al. Autologous mesenchymal stem cell therapy in progressive Multiple Sclerosis: An open label study. Current Stem Cell Research & Therapy. 2012; 7(6):407–14. [DOI:10.2174/157488812804484648]

[100] Mohajeri M, Farazmand A, Mohyeddin Bonab M, Nikbin B, Minagar A. FOXP3 gene expression in multiple sclerosis patients pre- and post mesenchymal stem cell therapy. Iranian Journal of Allergy, Asthma and Immunology. 2011; 10(3):155–61. [DOI:010.03/ijaai.155161] [PMID]

[101] Mohyeddin Bonab M, Mohajeri M, Sahraian MA, Yazdanifar M, Aghsaie A, Farazmand A, et al. Evaluation of cytokines in multiple sclerosis patients treated with mesenchymal stem cells. Archives of Medical Research. 2013; 44(4):266–72. [DOI:10.1016/j.arcmed.2013.03.007]

[102] Hou ZL, Liu Y, Mao XH, Wei CY, Meng MY, Liu YH, et al. Transplantation of umbilical cord and bone marrow-derived mesenchymal stem cells in a patient with relapsing-remitting multiple sclerosis. Cell Adhesion & Migration. 2013; 7(5):404-7. [DOI:10.4161/cam.26941] [PMID] [PMCID]