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Multiple Sclerosis Under Attack; Shehata's Therapy

Multipl Skleroz Saldırı Altında: Shehata'nın Tedavisi

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Abstract

Multiple sclerosis is an autoimmune disease characterized by inflammatory demylination of the nerves in the central nervous system (brain and spinal cord). Depending on the attacked sites, the disease manifestations vary from limited sensory and/or motoric deficits to wide spread neurological and cognitive deficits. Similar to other autoimmune neurological and non-neurological diseases, the available therapeutic strategies rely on the pharmacological modulation of the immunity, which could be associated with significant side effects.

In this paper, the light will be shed on another innovative therapeutic strategy that rely on the biological modulation of the immune responses, together with the inhibition of the recruitment of the immune cells into the central nervous system after distortion of the blood brain barrier, as well as the enhancement of the regenerative ability towards the restoration of efficient blood brain barrier and the regenerative recovery of the neurological deficits.

Key words: Multiple sclerosis, autoimmunity, regenerative therapy, mesenchymal stem cells and fibrinogen

Öz

Multipl skleroz, merkezi sinir sistemindeki sinirlerin (beyin ve omurilikteki) inflamatuvar olarak demyelinizasyonu ile oluşan bir hastalıktır. Hastalarda, etkilenen bölgeye bağlı olarak, sınırlı motor ve duyusal ileti kusurundan, yaygın nörolojik ve bilişsel kısıtlılığa kadar farklı problemler görülebilmektedir. Diğer nörolojik olan ve olmayan otoimmün hastalıklarda olduğu gibi, tedavi, önemli istenmeyen yan etkileri de olan bağışıklık sisteminin farmakolojik olarak düzenlenmesi ile yapılmaktadır.

Bu makale, beyine kan beyin bariyeri bozulduktan sonra toplanan bağışıklık hücrelerinin baskılanmasını sağlayan bağışıklık yanıtının biyolojik olarak düzenlenmesi gibi yaratıcı tedavi yöntemleri ile, bu yöntemlerin zarar görmüş olan kan beyin bariyerini ve nörolojik problemleri düzeltebilme yetenekleri konusundaki bilgilere ışık tutacaktır.

Anahtar Kelimeler: Multipl skleroz, otoimmünite, yeniden üretici (rejeneratif) tedavi, mezenkimal kök hücreler, fibrinojen

Introduction

Multiple sclerosis (MS) is a neurological disease characterized by disseminated encephalomyelitis. Females are usually more frequently affected than males, where the usual age of onset (up to 80%) lies between 20–40 years. The clinical presentation can vary dramatically, however, sensory, motoric, visual, urinary bladder, sexual, and cognitive complaints are common in most of the cases. In addition, the natural history of the disease may take one of the following forms (Fig. 1)[1]:

- Relapsing-remitting multiple sclerosis (RRMS)
- Secondary progressive multiple sclerosis (SPMS)
- Primary progressive multiple sclerosis (PPMS)

The manifestations of MS can vary depending on the affected site of the central nervous system. Sensory deficits may appear in the form of positive Lhermitte sign, paresthesia

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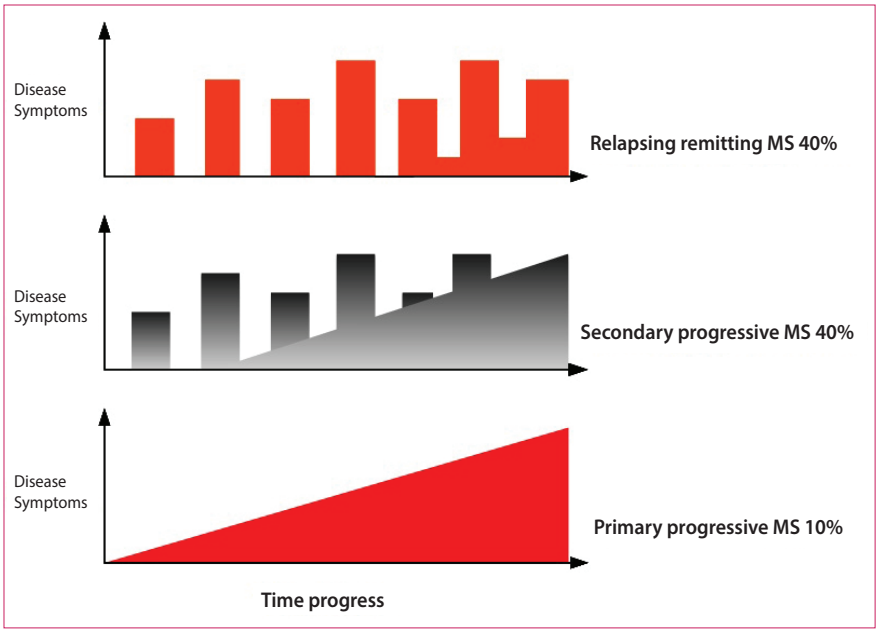

Figure 1. Diagrammatic representation of the common forms of MS. Relapsing remitting MS, where the disease symptoms occur in the form of attacks, in between the patient can be completely or partially free of symptoms. Secondary progressive MS, where the symptoms in between the attacks are progressively increasing. Primary progressive MS, where the symptoms progress from the disease onset without symptoms-free intervals.

and/or neuralgia. Motor deficits such as weakness, wasting, spasms, or paralysis could be manifested. Optic neuritis, double vision and other visual disturbances are also common manifestations. Ataxia, nystagmus, dysarthria and/or intention tremors represents the cerebellar involvement. Urinary bladder and intestinal disturbances could be frequently seen in MS, in the form of retention, urgency, incontinence and/or diarrhea versus constipation. Swallowing and/or respiratory complaints can indicate brain stem involvement. Erectile dysfunctions and/or epilepsy could also occur. Psychological manifestations, such as depression, fatigue, memory affection, concentration problems and/or emotional affection are also possible consequences of MS.[2]

Pathogenesis of MS

Multiple sclerosis disease manifestations are the result of CNS inflammation, where the exact trigger for those inflammatory reactions is not known. Genetic, environmental and infectious factors may play an important role in the disease development. The current available knowledge about the disease pathogenesis are mainly based on the studies applied on the animal model for human MS, known as the experimental autoimmune encephalomyelitis (EAE). The inflammatory reactions resulting in MS involve the activation of both innate and adaptive immune systems. The innate system is activated through the activation of toll-like receptors (TLRs), which prime intracellular macromolecules, called inflammasomes. The stimulated TLRs and inflammasomes result in increased cytokine production that activate various inflammatory cells and immune pathways, including regulatory and memory cells. Stimulated by the inflammatory cytokines, antigen presenting cells and macrophages, the adaptive immune system, composed mainly of the lymphocytic cells, comes in charge.[2,3]

In general, the immune reaction trigger, and accordingly the released cytokines, determine the immune cells in charge of the adaptive immune system. Extra-cellular antigens and certain cytokines give the B lymphocytes the upper hand, which is called humoral immune response. Intra-cellular processed antigens stimulate the release of special cytokines that mainly recruite T lymphocytes.[2,3]

In MS, evidence of the involvement of both B-and T-lymphocytes in the disease pathogenesis has been reported. The presence of immunoglobulins in the cerebrospinal fluid (CSF), proved by the oligoclonal bands, is a marker for MS diagnosis. Meanwhile, the intra-CNS migration and recruitment of various inflammatory cells and T lymphocytes that attack the neurons at the affected sites, leading to demyelination, is responsible for the various disease symptoms.[2,3]

As the risk of MS increases with the positive family history for the disease (40 fold increased risk among first degree relatives of patients), the genetic factors seem to play an important role in the disease pathogenesis, which could be summarized in localized damage of the blood brain barrier (resulting in the disseminated nature of the

disease) and the localized migration, and thus, activation of the inflammatory cells, mainly antigen presenting cells and both T and B lymphocytes. The HLA locus on chromosome 6p21, containing the DR antigens could be linked to an increased risk of MS. Environmental factors that play a role in most of the diseases of the autoimmune nature may also contribute to MS pathogenesis, such as viral infections and vitamin D deficiency.[2,3]

Treatment of MS

As the pathogenesis of MS involves immunological reactions, where the immune cells (lymphocytes) attack the blood brain barriers and the central nervous system, leading to demyelinating lesions that could be detected in magnetic resonance imaging (MRI), macrophages, T lymphocytes, and B lymphocytes have been reported to be the main mediators of the pathogenesis of MS. Thus, almost all the therapeutic strategies of the disease rely on the control of the functions of those cells (Table 1). However, the treatment of MS might be more effective and less side effects-associated, if the homing of the immune cells to the nervous system is blocked.[3]

The treatment of MS may be summarized as following:

Treatments for MS attacks

Corticosteroids, such as oral prednisone and intravenous methylprednisolone, are prescribed to reduce nerve inflammation. Plasmapheresis may be used if the symptoms are new, severe and haven't responded to steroids.

Treatments to modify the disease progression

For primary-progressive MS, ocrelizumab (Ocrevus) is the only FDA-approved disease-modifying therapy. It slows

Table 1. Currently approved anti-MS medications

Drug	Mechanism of action	Unfavorable effects
First line medications		
Interferon beta	Shifts the cytokine profile towards the anti-inflammatory side	The development of neutralizing antibodies No efficiency against progressive forms of the disease Elevated liver enzymes and depressed bone marrow function
Glatiramer acetate	Probably related to enhancing the activity of Th2 cells secreting anti-inflammatory cytokines	Skin reaction at the site of injection, systemic reaction Lymphadenopathy, dyspnea and lipoatrophy
Teriflunomide	May inhibit the proliferation of lymphocytes	Serious infections, elevated alanine transaminase, hypertension and decreased leukocyte count, up to pancytopenia
Dimethyl fumarate	Modulates the immune response towards the anti-inflammatory properties	Abdominal pain Diarrhea Leukopenia Lymphocytopenia Elevated liver transaminases
Second line medications		
Fingolimod	Reduces the mobilization of lymphocytes from the lymph nodes	Serious infections Transient bradycardia Atrioventricular block Elevated liver enzymes Macular edema
Natalizumab	Blockes the migration of the inflammatory cells into the CNS	Increased risk of progressive multifocal leukoencephalopathy Prolonged severe lymphopenia Development of neutralizing antibodies
Alemtuzumab	Mediates the cytolysis and the complement-mediated lysis of T and B lymphocytes	May induce secondary autoimmunity
Mitoxantrone	Functions as anti-proliferative and apoptosis-inducing in: T-lymphocytes B-lymphocytes Macrophages & other antigen-presenting cells	Urinary tract infections Elevated liver enzymes Leukopenia Amenorrhoea Acute promyelocytic leukaemia Cardiotoxicity with overdoses

worsening of disability in people with this type of MS. For relapsing-remitting MS, several disease-modifying therapies are available.

First-line medications against MS

Interferon beta (IFN-β), which is predominantly produced by fibroblasts have capacity to shift the cytokine profile towards the anti-inflammatory side. IFN-β also inhibits the proliferation and migration of lymphocytes into the CNS. For MS therapy, recombinant IFN-β-1b in a dose of 250 μg subcutaneously every other day or IFN-β-1a in a dose of 30 μg intramuscularly once weekly, or subcutaneously at doses of 22 or 44 μg three times a week, could be used. The application of IFN-β therapy has proved efficiency in decreasing the relapse rate by 30–34%. However, the use of IFN-β is associated with the development of neutralizing antibodies and has no efficiency against progressive forms of the disease. Up to 50–75% of the patients treated with IFN-β developed flu-like symptoms. In addition, IFN-β therapy has been associated with elevated liver enzymes and depressed bone marrow function, which may increase the risk of cancer and infections.[4–8]

Glatiramer acetate is a synthetic polypeptide, which resembles the myelin basic protein and is administered through subcutaneous injections at 20 mg per day. The mechanism of action of glatiramer acetate is not fully understood, but it is probably related to enhancing the activity of Th2 cells, which gives the anti-inflammatory cytokines the upper hand. Glatiramer acetate therapy has showed 29% reduction of the annual relapsing rate, however, no evidence of efficiency in secondary progressive or primary progressive was shown. The most frequent side effects reported with the use of glatiramer acetate are skin reaction at the site of injection in 65% of cases, systemic reaction in 15% of cases, lymphadenopathy, dyspnea and lipoatrophy, which is irreversible.[9–13]

Teriflunomide is an immunomodulatory agent that is selectively and reversibly able to inhibit the mitochondrial enzyme dihydroorotate dehydrogenase, which is required for *de novo* pyrimidine synthesis. In this way, it may inhibit the proliferation of lymphocytes. It is used as tablets, in a dose of 14 mg once daily. Teriflunomide therapy in MS has the ability to reduce the relapse rate by 31–36% and the rate of disability progression by 26–27%. While no data is currently available regarding the efficiency of teriflunomide with progressive MS forms, its major side effects include serious infections, elevated alanine transaminase, hypertension and decreased leucocyte count and pancytopenia.[14–16]

Dimethyl fumarate modulates the immune response towards the anti-inflammatory properties, mainly through the activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway. The drug is administered in a dose of 240 mg twice daily. The use of dimethyl fumarate can reduce the remission rate by 44–53%, the rate of disability progression by 22–32% and the MRI gadolinium-enhancing lesions by about 75–94%. The major side effects associated with the use of dimethyl fumarate are abdominal pain, diarrhea, leukopenia, lymphocytopenia and elevated liver transaminases.[17–21]

Second-line medications

Fingolimod 5 mg/day is a modulator of sphingosine 1-phosphate receptor (S1PR), reducing the mobilization of the lymphocytes from lymph nodes. Though fingolimod can reduce the relapsing rate by about 55%, it is not reported to be effective against the primary or the secondary progressive forms of the disease. Its main adverse effects are serious infections, transient bradycardia, atrioventricular block, elevated liver enzymes and macular edema.[22–24]

Natalizumab is a blocking monoclonal antibody against α4-integrin, thus, blocking the migration of the inflammatory cells into the CNS. The dose of natalizumab is 300 mg i.v. Infusion every 4 weeks. Natalizumab therapy has been associated with 68% reduction of the annual relapse rate and 54% reduction of the disability progression rate. However, its major side effect is the increased risk of progressive multifocal leukoencephalopathy, especially in anti-John Cunningham virus antibody positive patients, and prolonged severe lymphopenia. In addition, natalizumab is immunogenic in some patients, which leads to the development of neutralizing antibodies, decreasing the efficacy of the therapy.[25–28]

Alemtuzumab, an anti-CD52 recombinant monoclonal antibody, that mediates the cytolysis and the complement-mediated lysis of T and B lymphocytes. Thus, it reduces the relapse potential and disease progression in MS. Alemtuzumab is used as an intravenous infusion of 12 mg/day for five consecutive days followed by 12 months pause, before the infusion of another 12 mg/day for 3 successive days. Additional doses could be added, however, the drug

has the potential to induce secondary autoimmunity, which limits its usability as a first line therapy.[29–34]

Mitoxantrone is a synthetic anthracenedione derivative that functions as anti-proliferative and apoptosis-inducing in T lymphocytes, B lymphocytes, macrophages and other antigen-presenting cells. The treatment with mitoxantrone showed significant reduction in the relapsing rate (up to 60–70%). However, major side effects associated with its use include urinary tract infections, elevated liver enzymes, leucopenia, amenorrhea and acute promyelocytic leukemia. In addition, its maximum cumulative dose should not exceed 120–140 mg/m^2 of body surface, in order to avoid cardiotoxicity.[35–39]

An innovative thinking

The blood brain barrier (BBB) is a mechanical and functional barrier between the systemic circulation and the central nervous system that is composed of three cellular elements; the endothelial cells connected with their tight junctions, astrocyte end-feet, and pericytes. BBB allows the though regulation of the movement of molecules, ions, and cells between the blood and the CNS. This tightly regulates the CNS homeostasis, which is essential for the proper neuronal function, and the protection of the CNS from toxins, pathogens, inflammation, injury, and disease. The loss of some of the barrier properties of the BBB is a major component of the pathogenesis of many neurodegenerative and inflammatory diseases. A major step of the pathogenesis of MS and any other autoimmunity-based CNS inflammatory disease, is the recruitment of the inflammatory cells across the injured or activated BBB.[40]

Fibrinogen (FB) is a glycoprotein, which is a hexamer, containing two sets of three different chains (α, β, and γ), linked to each other by disulfide bonds. FB plays an important role in coagulation cascade, where it can form bridges between platelets, by binding to their GpIIb/IIIa surface membrane proteins, in addition to the major role, where prothrombin is converted into thrombin, which then converts the soluble FB (sFB) into insoluble fibrin strands that are then cross-linked by factor XIII to form the blood clot.[41]

Many studies have confirmed FB as a pro-inflammatory effector. In addition to its ability to stimulate the proliferation of B-lymphocytes, T-lymphocytes and monocytes[42], immobilized FB and fibrin have high affinity to macrophage antigen 1 (MAC-1) and can activate neutrophils and monocytes.[43–45] In neutrophils, FB/MAC-1 interaction activates the NF-κB pathway, which is an anti-apoptotic and inflammatory cytokine-inducing pathway.[43]

Role of Fibrinogen in Multiple Sclerosis

Deposition of fibrinogen (FB) in the CNS, after the disruption of the blood brain barriers, has been reported to induce immune reactions and increased recruitment of macrophages and lymphocytes into the CNS, which leads to demyelination. Fibrinogen has the ability to stimulate and recruit the CD11b$^+$ antigen-presenting cells, which enhances the recruitment and activation of myelin antigen-specific Th1 cells. In addition, the interaction between FB and αM βII-integrin receptor results in the activation of Talin-1, which interacts with Rap-1 and is essential for adhesion, migration and phagocytosis activity of antigen-presenting cells and lymphocytes.[46]

Although there is a strong evidence that fibrinogen plays an important pro-inflammatory role in the development of MS, this might be limited to the deposited FB (insoluble FB), which is out of doubt incorporated in the recruitment of lymphocytes and macrophages. Thus, the sequence of events in this regards might be simplified as disruption of the BBB → leakage of FB into CSF → perivascular deposition of FB → recruitment and chemotaxis of macrophages, T-and B-lymphocytes, which produce inflammatory cytokines and attack the myelin sheathes. This hypothesis might be supported by the finding that the fibrinogen leakage into CSF was not reported during the remission, but coincides with the fulminant MS.[47]

In contrast with the pro-inflammatory effects of immobilized FB/fibrin, sFB has the ability to inhibit lymphocytic antigen 1-dependent binding to the intracellular adhesion molecule 1 (ICAM-1) through a direct interaction with ICAM-1[48], and to reduce interleukin (IL) 8-activated neutrophils binding to ICAM-1-expressing cells, in addition to reducing the binding of neutrophils to TNFα-activated endothelium to 40%, under flow conditions.[46]

Accordingly, blocking the pro-inflammatory functions of FB would ideally protect against its role in the recruitment of the inflammatory cells into CNS, which coincidence with disease progression and or exacerbation, without affecting its other vital functions, such as its role in the

coagulation homeostasis. A monoclonal antibody, capable of binding the YC domain of FB, is able to inhibit the microglial adhesion and the Mac-1 binding to FB, which would significantly modify the symptoms of MS.[49]

Role of mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are multipotent stromal cells that could be derived from adult bone marrow, as well as other tissues. These cells have the ability to differentiate into many cell lines, including neurons, which gives a great hope that MSCs could be a magic regenerative therapy to restore and correct any neurological deficit that results from nervous system injury or degenerative diseases. MSCs can play an important role in neurogenesis, gliogenesis, remyelination and neural plasticity. The role of MSCs in MS and other autoimmune or inflammatory-based neurological diseases could be more significant and double faced. The disease manifestations and progression in MS are based on the neurological deficits that manifest (and stay after) with the inflammatory neurological injury. MSCs have the unique ability to restore the deficits through the regenerative differentiation ability, in addition to the control and or prevention of the autoimmune and inflammatory condition.[50,51]

Mesenchymal stem cells are very tolerated by the immune system, where they can attenuate the immunity through modulating T cell activation and proliferation, either by a direct cell-cell interaction or via soluble factors. In addition, this action is independent on the major histocompatibility (MHC) matching because MSCs are characterized by low expression level of MHC I and II, and lack the T cell co-stimulating molecules CD80 and CD86. Moreover, the transplantation of allograft MSCs is used for the attenuation of the graft versus host reaction.[52]

Recent studies have confirmed the principle that neurogenesis continues to take place during the adulthood as well. Neural stem cells (NSCs) take responsibility of this function, but lack the ability of self-renewal and multipotency. Although the neuronal stem cells develop originally from the ectodermal niche, while MSCs belong to the mesoderm, both cell types secrete many relevant growth factors, such as the nerve growth factor (NGF), the glial derived neurotrophic factor (GDNF), and the brain derived neurotrophic factor (BDNF). In addition, MSCs have shown great potential to differentiate into functional neurons. Moreover, MSCs secrete many immuno-modulatory factors that include IL10, transforming growth factor β (TGFβ), prostaglandin E2 (PGE2) and vascular endothelial growth factor (VEGF).[51,52]

IL10 is one of the major anti-inflammatory cytokine that down regulates the expression of cytokines in the T helper-1 cells, as well as the major histocompatibility class-II antigens and costimulatory molecules on the surface of macrophages. Moreover, IL10 antagonizes the activity of NF-κB and is capable of suppressing the production of IL8 in a dose dependent manner.[53,54] While the adhesiveness of the BBB-forming cells increases significantly upon IL1β, TNFα, IFNγ, and Lipopolysaccharide stimulation, which increases the leukocyte (macrophages and lymphocytes) migration into the CNS, TGFβ, secreted by MSCs, has the ability to block these effects in a dose dependent manner.[55] PGE2 functions towards the inhibition of the proliferation, differentiation and function of the antigen presenting, as well as the cytotoxic cells, including the dendritic cells, macrophages and natural killer (NK) cells.[56] Meanwhile VEGF has neuroprotective effects, where it enhances the survival of Schwann cells and cerebellar granule neurons, and protects against the degeneration of the motor neurons.[57] Thus, the use of MSCs in the cases of MS, and other autoimmune based CNS diseases, could work towards the attenuation of the aggressive immune reactions, together with the potential regenerative recovery of the deficits.

Connick et al from the university of Cambridge have conducted a clinical trial to assess the safety and efficiency of the intravenous administration of MSCs for the treatment of the secondary progressive MS. The use of $1.6x10^6$ cells per kg bodyweight via intravenous route was able to improve the visual manifestations of disease without any reported serious side effects.[58]

A phase II open-label clinical trial for MSC therapy in secondary progressive MS (SPMS) (ClinicalTrials.gov, NCT00395200) included 10 patients of about 14.4 years average duration of disease progression. The patients received an intravenous dose of $1–2x10^6$ cells/Kg body weight. The patients showed a statistically significant improvement of the visual acuity and visual evoked potentials, however without significant effects on color vision, visual field, macular volume, retinal nerve fiber layer thickness or optic nerve magnetization transfer ratio. The study confirmed the safety of MSCs therapy in MS.[59]

Another phase I open-label clinical trial in 2014, where autologous mesenchymal stem cell-neural progenitors

(MSC-NPs) were administrated intrathecal (IT) in 20 patients with progressive MS with an average EDSS of 6.0. The administration of MSC-NPs were performed in three doses of up to 10 million cells per injection, with three month-intervals. The therapy was reported to be safe and tolerable. A single IT injection of autologous MSCs was associated with short-term adverse events of transient low-grade fever, nausea, vomiting, weakness in the lower limbs and headache. No major adverse events were observed. The MSC therapy stabilized the disease progression safely. A randomized placebo-controlled phase II trial on 9 patients treated with 1–2x10^6 MSCs/Kg body weight intravenous infusion reported a reduction of the proinflammatory T cell profile, mainly IFN-c and IL17-producing $CD4^+$ T cells, thus, a reduced Th1/Th17 ratio.[59]

The therapeutic recommendation

The intravenous and intrathecal administration of the monoclonal FB-YC domain antibodies (which blocks the binding of FB to Mac-1 and the microglial cells, blocking the role of FB in the enhancement of CNS lymphocytic migration), together with MSCs (priorly cultured to 90% confluence), could have the potential not only to attenuate the disease progression, but also to recover the deficits.

The major concern of this therapeutic strategy might be the risk of the incorporation of MSCs in cancer development, which can not be completely excluded without the application of long-term clinical studies.

In a previous report, the proliferative potential of human umbilical cord perivascular MSCs (HUCPVMSCs) was compared to that of the BMMSCs. The results showed similar proliferation rates at the beginning, however, between days 7 and 14, the HUCPVMSCs had higher proliferation rate, and beyond 20 days, the BMMSCs responded to contact inhibition and stopped proliferation, while HUCPVMSCs continued to proliferate resulting in multilayering.[60] Similarly, HUCPVMSCs showed higher differentiation capacity.

Management of the acute MS exacerbations

The current trend for the therapy of acute MS exacerbations relies on the use of intravenous cortisone infusion in a dose of 500–1000 mg/day for 3–5 days, followed by a 21 day tapering oral steroid therapy. Though this therapy is usually able to shorten the duration of the acute MS exacerbation, it can't be applied for long term because of the side effects of the cortisone therapy. Nevertheless, the short term cortisone therapy during exacerbations is not free of side effects. The steroid therapy seems to decrease the oligodendrocyte-mediated repair of the demyelinated lesions, have a dramatic effects on the bone health, in addition to a group of systemic, metabolic and psychiatric complications.[61] In resistant cases, and based on the role of B lymphocytes in the pathogenesis of MS, the application of plasma exchange (PE) can improve symptoms in about 42.1% of the cases. However, serious side effects, such as myocardial infarction, arrhythmia and hemolysis, may occur in a rate of 2.8–6.5%.[62,63]

The use of the combined "MSCs-monoclonal FB-YC domain antibodies" during the acute MS exacerbations might have the potential to provide an effective therapeutic option, based on its rapid onset of action that is mediated by the monoclonal antibodies and the secreted mediators of MSCs. In the above recommended technique, the culture of the MSCs up to 90% confluence prior to administration will provide adequate mediators in the culture medium that will be potentiated by the further proliferation and the secretions of the cells *in vivo*. This innovative therapeutic strategy seems to worth further studying on the preclinical and clinical levels, in order to precisely assess its therapeutic value versus complications.

Conclusion

The currently available therapeutic options for MS rely on the modulation of the autoimmune reactivity, mainly the lymphocytic functions. The use of MSCs has proved safety, and is expected to provide immune-modulation and regenerative empowerment. In this paper, a combination of MSCs therapy and a specific blocker of the proinflammatory action of fibrinogen seems theoretically to provide a very powerful and targeted therapy against MS and its related disorders, where the side effects of the other therapeutic options could be avoided, and the neurological deficits could be restored. While the notions of MSCs and anti-fibrinogen therapies in MS were introduced before, this is the first paper ever to introduce the notion of their combination, establishing the Shehata's therapy. Experimental realization of this notion will provide more evidence based medical data regarding its safety and applicability, and might allow its broadcasting for the management of other autoimmune diseases.

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