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Multiple sclerosis

Multiple sclerosis(MS) represents a chronic T-cell-mediated inflammatory autoimmune disease in which the immune system attacks the central nervous system(CNS). It is characterized by perivascular infiltrates of mononuclear cells, demyelination, axonal loss and gliosis with the formation of multiple plaques in the brain and spinal cord. It has progressive course leading to physical and cognitive disability. Usually the disease affects young adults at the age of 20–50 and is more common in women[1].

The cause of MS is still unknown. It is considered that genetic, environmental and immunological factors can play role in the etiology of the disease. There is assumption that exposure to the Epstein–Barr virus after early childhood and manifestations of infectious mononucleosis, reduced exposure to sunlight and ultraviolet radiation, vitamin D deficiency and cigarette smoking can represent triggers for development of MS[2].

The white matter in the brain and spinal cord is the target for multiple sclerosis. The disease destroys oligodendrocytes which represent special cells creating and maintaining the myelin sheaths which are necessary for transmit of electrical signals by neurons. Thinning or complete loss of myelin, sometimes transection of axons are the result of multiple sclerosis[3].

It is necessary to emphasize that none of the treatment for patients with multiple sclerosis available at present selectively inhibit the immune attack against the nervous system, nor promote regeneration of previously damaged tissue[4].

Mesenchymal stem cells in the treatment of multiple sclerosis

To date using of mesenchymal stem cells in the treatment of multiple sclerosis represents a promising alternative for conventional treatment. The therapeutic effects are based on the ability of mesenchymal stem cells to inhibit pathogenic T and B cell responses and to release the neuroprotective and pro-oligodendrogenic molecules favoring tissue protection and repair. Also, they differentiate into the injured cell types promoting tissue regeneration[5].
The first report of treating multiple sclerosis with autologous bone marrow derived mesenchymal stem cells(BMMSCs) was published in 2007 by Mohyeddin Bonab M. et al. This was pilot clinical trial in which ten patients with multiple sclerosis who failed to respond to conventional treatment were administered BMMSCs. The mean follow-up period was 19 months. Improvement in sensory, pyramidal and cerebellar functions was observed in the patients after stem cells therapy. Also, significant amelioration in the Expanded Disability Status Scale (EDSS) score occurred indicating augmentation of patients functional status[6].

In 2009 Riordan Ni.H. et al. reported about three clinical cases of successful using of adipose derived MSCs in patients with relapsing-remitting multiple sclerosis. There were three men with a very severe course of disease. All of them failed to respond to conventional treatment. They were received MSCs. No any significant side effects associated with injection of MSCs were observed. After the stem cell infusions over the period of several weeks the patients had reported a significant improvement of their cognitions, almost complete reduction of the spasticity in extremities, a considerable improvement of balance and coordination, an improved energy level and mood[7].
Encouraging results were obtained in clinical trial conducted by Karussis D. et al. in which the positive immunomodulatory effects of autologous BMMSCs in patients with multiple sclerosis were demonstrated. There were 15 patients with multiple sclerosis who received MSCs. The follow-up period was 25 months. Neurological disability was assessed by means of the Expanded Disability Status Scale (EDSS). It was showed that the mean EDSS score have declined gradually indicating functional improvement in patients. No major adverse effects were reported in any of the patients during a follow-up period[8].

In 2010 Yamout B. et al. demonstrated the results of the pilot clinical trial in which unresponsive to conventional treatment patients with advanced MS were treated by autologous BMMSCs. There were 7 patients who fulfilled the inclusion criteria and were enrolled in the trial. The follow-up period was 12 months. During the first 6 months patients showed improvement on different components of the Expanded Disability Status Scale and Multiple

Sclerosis Functional Composite. Also, improvement of the Paced Auditory Serial Addition Test (PASAT) score was observed. It is important that most patients reported subjective and functional improvement in their neurological status 3-6 months after the procedure. At 3 months during visual assessment amelioration in contrast visual testing was revealed. Early signs of clinical improvement maintained during all follow-up period[9].

Safety and feasibility of autologous bone marrow derived stem cells therapy(BMSCs) in relapsing progressive multiple sclerosis was also showed by Rice C.M. et al. in 2010. They conducted clinical trial which included six patients with advanced multiple sclerosis. All patients received intravenous infusion of autologous BMSCs. No serious adverse events were observed. The follow-up period was 12 months. During this period clinical disability scores improved or no changed. Also, multimodal evoked potential recordings showed neurophysiological enhancement[10].

In 2012 Bonab M.M. et al. published the results of uncontrolled open-label clinical study in which patients with progressive MS were treated by MSCs. Twenty two patients unresponsive to conventional treatments were recruited. The follow-up period was 12 months. It is important to point out that no major delayed adverse effects were reported. Stabilization and improvement of general progression of the disease according to the score of the Expanded Disability Status Scale were observed in almost all patients. Moreover, in almost all patients were found stabilization of MRI findings which indicated to halting the disease progression[11].

Successful application of autologous MSCs in the treatment of secondary progressive multiple sclerosis was showed in an open-label clinical trial conducted by Connick P. et al. in 2012. There were ten patients with multiple sclerosis involving the visual pathways. All of them received a single intravenous infusion of autologous BMMSCs. It is worth noting that any delayed serious adverse events weren't observed. The follow-up period was 10 months. In all patients was noticed improvement of the Expanded Disability Status Scale scores after treatment that indicated to reduction of general disability progression. Furthermore, in all patients were found stable MRI findings without any changes in the rate of lesion accumulation. Also, improvement in visual function, physiology and structure were demonstrated in all patients[12].

In 2014 Llufriu S. et al. reported the results of the first randomized placebo-controlled double-blind clinical trial in which autologous BMMSCs were used for the treatment of patients with relapsing-remitting multiple sclerosis. Nine patients unresponsive to conventional therapy were enrolled. All of them were randomly divided into two groups. Patients in first group were treated with BMMSCs which were injected intravenously. The second group was control in which all patients received placebo. The follow-up period was 6 months. After that the treatment was reversed(the first group became control and patients in the second group received stem cell therapy). Then patients were followed-up for another 6 months. Efficacy was evaluated in terms of cumulative number of gadolinium-enhancing lesions on magnetic resonance imaging(MRI) which showed the activity of the inflammatory process. At the end of follow-up period reduction of inflammatory MRI parameters were observed in all patients who received autologous MSCs. Moreover, reduced Th1 proinflammatory responses were also observed in all patients treated with autologous MSCs. It is important to emphasize that transplantation of mesenchymal stem cells wasn't accompanied by any serious adverse effect in all patients. The obtained results have demonstrated the positive immunomodulatory influence of mesenchymal stem cells which led to reduction of the activity of the inflammatory process in patients with multiple sclerosis. Also, it was showed that using of MSCs in the treatment of patients with multiple sclerosis is safe[13].

Thus, the results which have been observed in the clinical trials have demonstrated the feasibility, safety and efficacy of using stem cells as a treatment for patients with MS. Moreover, available data have showed that stem cell therapy leads to halting of disease progression.

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