

## **THE POTENTIAL USE OF STEM CELLS IN MULTIPLE SCLEROSIS: THE PROS**

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It is increasingly recognized that MS progression, in addition to demyelination, leads to substantial irreversible damage to, and loss of neurons, resulting in brain atrophy and cumulative disability. One of the most promising neuroprotective strategies involves the use of bone marrow derived stem cells. Both hematopoietic and non-hematopoietic (stromal) cells can, under certain circumstances, differentiate into cells of various neuronal and glial lineages. Neuronal stem cells have also been reported to suppress EAE by exerting direct in situ immunomodulating effects, in addition to their ability to provide a potential source for remyelination and neuroregeneration. Results from our laboratory indicate that intravenous or intracerebral/intraventricular injection of bone marrow derived stromal cells could differentiate in neuronal/glial cells and suppress the clinical signs of chronic EAE. Those bone marrow (BM) derived mesenchymal stem cells (MSC) possess strong neurotrophic and immunomodulatory properties. The ability to easily obtain MSC from the patient, expand them in culture and re-introduce them as an autologous graft, as well as the lack of risk for malignant transformation make these cells excellent candidates for cell therapy. We have performed a safety pilot study aimed to evaluate the feasibility and safety of intrathecal and intravenous administration of BM-MSC in patients with severe MS and with ALS. Fifteen MS patients with a mean EDSS of  $6.6 \pm 1.2$  and 19 ALS patients with a mean ALSFRS score of  $20.9 \pm 8.3$  were included in this trial. Following culture of the cells for 40-60 days in a Clean Room facility (GMP), BM-MSCs were cryopreserved until sterility was confirmed after additional 14 days. All MS patients received intrathecally a mean of  $63.2 \pm 2.5 \times 10^6$  and ALS patients a mean of  $54.7 \pm 17.4 \times 10^6$  cells. Fourteen patients (5 with MS and 9 with ALS) were also injected intravenously with MSC (mean:  $24.5 \pm 2.5 \times 10^6$  for MS and  $23.4 \pm 5.9 \times 10^6$  for ALS). MRI was performed in all patients within 4-48 hours from the infusion and thereafter every 3-6 months. Immunological analysis of lymphocyte populations and cytokine production was performed in 6 of the patients, at baseline and at 4 and 14 hours following MSC transplantation; the following tests were performed: a) FACS analysis for the expression of markers of regulatory cells (CD4/CD25/FoxP3), myeloid dendritic cells activation markers (CD86, CD 83 and HLA-DR), T-cell activation markers (CD69), b) lymphocyte proliferations assay and c) cytokine production. In 20 patients there were injection-related side effects of transient meningeal irritation and mild fever which lasted for 1-2 days. No major side effects were reported during a follow up period of up to 25 months. The mean ALSFRS remained stable during the 6 first months of observation (20.1-20.5), whereas the mean EDSS score improved to  $6.0 \pm 1.6$ ,  $5.8 \pm 1.6$  and  $5.8 \pm 1.7$  at 1, 3 and 6 months respectively. Immunological tests revealed a 30-50% increase in the proportion of CD4+CD25+ regulatory T cells and 30-60 % reduction of CD83 expression on myeloid dendritic cells, a significant decrease in the proliferative responses upon stimulation of lymphocytes with anti-CD3 or PHA as well as a significant decrease in IL-17 secretion. This is the first trial with intrathecal injection of MSC in MS and ALS and shows the safety and feasibility of the procedure and demonstrates the immediate strong immunomodulatory effects induced by these cells. Further controlled studies and longer observation periods are needed to evaluate possible efficacy and long term effects of such therapeutic approaches utilizing stem cells.