

## **Stem cell therapies in neuroinflammatory and neuro-degenerative diseases: The hurdles, the existing evidence and the promise**

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Due to the limited capacity of CNS for regeneration, more effective treatment of chronic degenerative and inflammatory neurological conditions, may involve the use of stem cells which seem to carry the potential for regeneration and neuroprotection. Embryonic cells have strong pluripotent and self-renewal properties and represent the prototype of stem cells, but there are additional somatic stem cells that may be harvested from various tissues during adult life, such as the mesenchymal stem cells (MSC), which offer several practical advantages for clinical application. MSC can be obtained from every adult, are easily expanded to large numbers and carry less risks for malignancies.

Our pilot trial (Phase I/II, 2006-2009) with intrathecal(IT) and intravenous(IV) injection of autologous MSC included 19 patients with ALS and 15 with MS. No major side effects were reported. The mean disability score of ALS (ALSFRS) was stabilized during the 6 first months following the treatment in the ALS patients, indicating a halt of the progression of this severe paralytic disease. In MS patients, the mean disability score (EDSS) showed a clear trend of improvement.

A more recent phase I/II and IIa study in our Center, with IT or IM injections of modified MSCs (Brainstorm technology) in 26 ALS patients, revealed that 87 % of the patients treated IT showed an improvement in the rate of progression of either general disability or respiratory function.

Since the beginning of 2015 we have initiated a large double-blind crossover trial that enrolled 48 progressive MS-patients. The study started in February-2015 and completed in June 2018. During the 2-month run-in period, functional evaluations (EDSS, walking speed test, 9-hole peg test, neurocognitive evaluation, quantitative and functional MRI, OCT, VEP, and visual functions' assessment in the static and dynamic domains) were performed monthly before the transplantation and at 3 months intervals after the treatment, for a total of 12 months. Patients were randomized and treated with either autologous, bone marrow-derived MSC ( $1 \times 10^6$ /Kg) or placebo, IT or IV. At 6-months the patients were re-treated with a second injection of MSC or placebo and followed for safety and all the efficacy measures for additional 6 months. The study was approved by the local Ethics committee and MOH, registered to NIH (NCT02166021) and monitored by an external CRO and an external safety committee.

No serious treatment-related adverse events were observed during the whole period of the trial.

Only one patient withdrew his consent and stopped the trial, at one month after the first transplantation. Most of the (mild) side effects were related to the lumbar puncture (headaches and back pain).

Twenty-two, out of the 48 patients deteriorated in EDSS during the 2-3 months before the treatment (indicating that our group included patients with very active disease). A scheduled interim analysis of the 32 first patients was performed and showed a significant beneficial effect of the treatment in terms of EDSS progression and a positive trend in terms of the relapses frequency. The first analysis of the currently available data from all 48 patients is now running and will be presented upon completion.

Both our animal studies and our data from this study indicate that the clinical beneficial effects were more significant in patients receiving intrathecally the cells (a method advocated first by our group, so that the cells will reach easier the damaged CNS areas) than intravenously.

In my talk, I will summarize the clinical experience with stem cells in neurological diseases, the promise, the hurdles and the risks of such experimental therapeutic approaches.