● LETTER TO THE EDITOR

Amyotrophic lateral sclerosis: promising therapeutic outcome–not far away?

Dear editors,

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease. It affects motor neurons in the brain and spinal cord resulting in bulbar palsy and respiratory failure. It also causes weakness of limbs. The disease usually progresses to fatal outcome within 2–4 years.

Neural stem cell research for diagnosis and treatment of neurodegenerative disorders is highly promising. But more data are required to prove their efficacy. There is evidence regarding stem cell application in traumatic brain injury and other neurological disorders (Mouhieddine et al., 2014).

Neurotrophic factors (NTFs) have been reported to increase the survival of motor neurons in ALS (Petrou et al., 2016). A culture-based method has been developed to promote the secretion of NTFs by mesenchymal stem cells (MSCs) (Petrou et al., 2016). NTFs have been shown to protect neurons in an animal model of neurodegenerative diseases (Chen et al., 2015). One phase I/II pilot trial (identifier NCT00781872) used intrathecal combined intravenous injections of bone marrow-derived MSCs in 34 patients with multiple sclerosis and ALS. Long-term (6–25 months) follow up observations did not show any severe adverse outcomes. MSCs transplantation was found to be a clinically feasible and relatively safe procedure (Karussis et al., 2010).

Recently, in open-label proof-of-concept studies (Petrou et al., 2016), all patients enrolled between June 2011 and October 2014 were followed up from 3 months prior to transplantation to 6 months after transplantation. In six patients with early-stage ALS, MSC-secreting NTF (MSC-NTF) cells were intramuscularly administered in the phase I/II of the trial. Another six patients with more advanced diseases received intrathecal administration of MSC-NTF cells. In a phase IIa study, 14 patients who had early-stage ALS received a combined intramuscular and intrathecal transplantation of autologous MSC-NTF cells. The primary endpoints of the studies were tolerability and safety of this treatment. The secondary endpoint was the impact of such intervention on various clinical parameters, including the ALS Functional Rating Scale-Revised score and the respiratory function. In the phase I/II trial, the treatment was well tolerated by all included 12 patients over the study follow up period. A similar effect was shown in 14 patients in the phase IIa trial. The rate of deterioration in lung function and the ALS Functional Rating Scale-Revised score in the intrathecal (or intrathecal + intramuscular) group was found to be reduced ($P < 0.04$) in comparison with the pre-treatment phase. The result suggests the safety of intrathecal and intramuscular transplantation of MSC-NTF cells in patients with ALS (identifier NCT01051882 and NCT01777646) (Petrou et al., 2016).

Bone marrow-derived MSCs have many advantages. For example, MSCs can be obtained safely from adult bone marrow; they can be cultured *in vitro*. Autologous MSCs can be administered safely without immunosuppressive therapy. Adult MSCs were shown to be associated with a low risk for induction of treatment-related malignant neoplasms (Karussis et al., 2010).

We can focus on some other studies regarding the safety profile of stem cell transplant in the treatment of ALS. Animal studies have shown no clinically significant alteration of cytokine levels (involved in cell-mediated and humoral immunity) after MSC-NTF cell transplantation. Repeated injections of human MSC-NTF cells are found to be well tolerated in the studied animals (mice) (Gothelf et al., 2014). Pre-clinical and clinical trials have suggested that MSCs are safe and feasible as a therapeutic option. They are not immunogenic and have immunosuppressive features (Thomsen et al., 2014). Genetic stability and opportunity for cryopreservation for future use of MSCs are still in the research stage. Cryopreservation can preserve the biological behavior of MSCs including differentiation potential, growth capacity, and surface marker. Therefore, cryopreserved MSCs can be used safely in future (Wang et al., 2012). A meta-analysis of randomized controlled trials did not reveal any adverse effects of MSC transplants like infusion toxicity, any disorder of organ systems, infection, malignant transformation or fatal outcome (Dulamea, 2015).

Another open-label phase I clinical trial showed the safety profile of two repeated intrathecal injections of autologous MSCs in ALS patients (Oh et al., 2015).

Safety and Efficiency of Umbilical Cord-derived Mesenchymal Stem Cells (UC-MSC) in Patients with Alzheimer's Disease (SEMAD) [identifier NCT01547689] is an ongoing study, and hopefully, it will provide more definite results (https://clinicaltrials.gov/ct2/show/NCT01547689, last accessed on 27/03/2016).

Before conclusion, we want to raise another issue about some biological markers of the efficacy of such therapy. The levels of vascular endothelial growth factor, angiogenin, and transforming growth factor-β were reported to be significantly higher in responders than in nonresponders after autologous MSC therapy in patients with ALS. The disease outcomes were evaluated by their scores on the revised ALS Functional Rating Scale (ALSFRS-R) (Kim et al., 2014).

So this new treatment modality is hoped to be successful in ALS patients. More study results will enlighten us about it.

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