Stem cell transplantation of neurotrophic factors shows promise in ALS

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Mesenchymal stem cells cultured to secrete neurotrophic factors (MSC-NTFs) can be administered to patients with amyotrophic lateral sclerosis (ALS) without lasting unwanted effects and may have clinical benefits, indicates a phase I/II safety analysis study.

"To our knowledge, this is the first human experience with stem cells that have been induced under culture conditions to produce NTFs, thus bearing the potential to support neuronal survival (neurotrophic/neuroprotective effect) and to modify the course of neurodegeneration in ALS", the researchers comment in *JAMA Neurology*.

Among 12 patients with the condition, aged 20 to 75 years, who received a single ($1x10^6$/kg cells) intrathecal or intramuscular injection of MSC-NTFs, as part of a first-in-man safety study, adverse events relating to the drug were mild (grades I and II) and transient, occurring close to the time of cell administration.

The most common of these over the 6-month follow-up period were headache and fever, affecting two and three patients, respectively. The same was true for a further 14 patients who participated in the second-stage dose-escalation study and received combined intrathecal and intramuscular MSC-NTF at low, mid and high doses. Eleven of these patients experienced headache and eight experienced fever. These patients also experienced back or leg pain and vomiting, seen in eight and three patients, respectively.

There were no significant changes in any laboratory parameters and no evidence of infection or tumour formation at the site of injection.

The researchers confirmed increased secretion of NTFs following transplantation compared with before, with transplanted MSC-NTFs secreting significantly more NTFs than the patients' own MSCs.

Although not sufficiently powered to determine efficacy, researcher Dimitrios Karussis (Hadassah-Hebrew University Medical Organisation, Jerusalem, Israel) and colleagues note that disease progression was slower in the 6 months following transplantation than during the 3-month run-in period.

Before transplantation, the decline in percentage predicted forced vital capacity (FVC) was 5.1% per month, on average, compared with 1.2% per month afterwards, a significant difference.

Similarly, scores on the ALS Functional Rating Scale–revised (ALS-FRS-R) declined more slowly after treatment, albeit not significantly so.

Over 80% of patients showed some degree of improvement at both 3 months and 6 months, and the rates of responders, based on a 25% improvement in either FVC or ALS-FRS-R, at these time points were 78% and 87%, respectively.

Further indication of clinical benefit was also seen in the slowing of muscle volume decline and of compound muscle action potentials, particularly in the injected arm and the intramuscularly treated patients, suggesting a localised neurotrophic effect at the site of administration.

"It is possible that the beneficial clinical trends observed in our study may be attributed to the improved capacity of the MSC-NTF cells to secrete NTFs compared with naïve MSCs, thus exerting—at least theoretically—a more potent neuroprotective effect", the researchers write.

They conclude: "[T]he importance of the observed modification of disease progression rate following MSC-NTF cell therapy in our pilot trials may represent an indication of a clinically meaningful effect, pending further confirmation from the ongoing, double-blind placebo-controlled multicentre phase 2 clinical trial."