Analysis of 12 patients with amyotrophic lateral sclerosis (ALS) treated with autologous differentiated mesenchymal stem cells: a Phase I/II clinical trial

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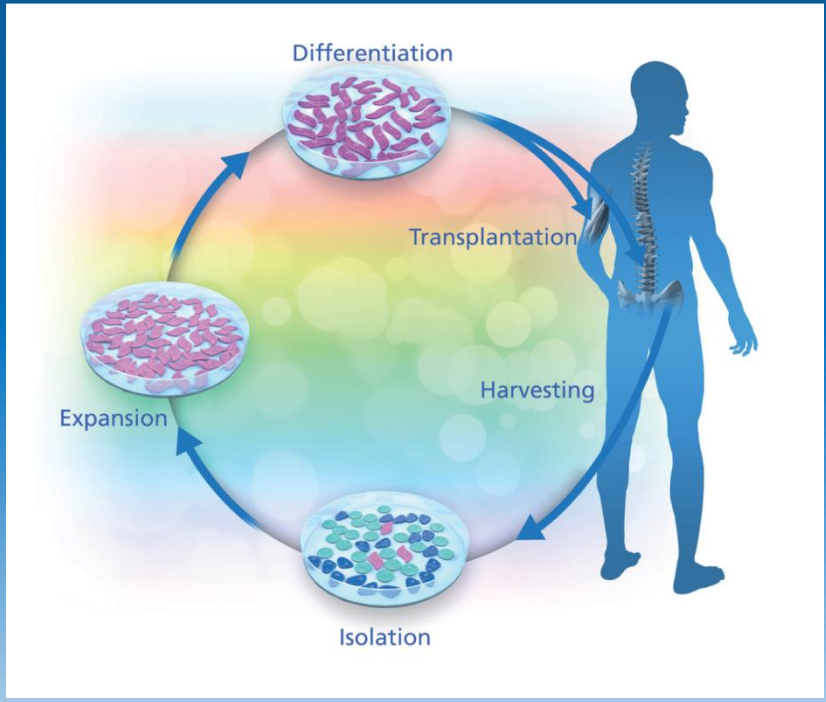
Objective

To evaluate the safety and tolerability of treatment with autologous mesenchymal stem cells (MSC) differentiated to secrete neurotrophic factors ("MSC-NTF" cells) in ALS patients utilizing the intramuscular (IM) and the intrathecal (IT) route of administration

Methods

This Phase I/II clinical study, completed in June 2012, included 12 ALS patients. MSC were isolated from the patients' own bone marrow, expanded ex-vivo and induced to differentiate into MSC-NTF cells.

Differentiation & Transplantation of Autologous MSC-NTF Cells



Methods

Autologous MSC-NTF cells were transplanted, by IM or IT injections to patients with early (ALSFRS-R score of >30; n=6) or advanced ALS (ALSFRS: 15-30; n=6), respectively. Clinical follow-up was performed monthly for 3 months pre-treatment and 6 months post-transplantation, including body weight, BMI, physical examination, muscle bulk and circumference, and vital signs.

Methods

In addition, ALSFRS-R score, respiratory function tests (Forced vital capacity (FVC)), computerized MRI volume analysis of the muscles, and compound muscle action potential amplitudes (CMAP) at 3 sites were used as additional surrogate markers of disease activity.

Clinical Monitoring of Study Participants

Assessment Parameters	Monthly	Bi-monthly
Body Weight	√	
BMI	√	
Physical Examination	√	
Vital signs	√	
ALSFRS-R Score	√	
Neurological Examination	√	
FVC	√	
Muscle Bulk (MVIC)	√	
Muscle Circumference	√	
Concomitant drugs	√	
EMG		√
Hematology CBC		√
Blood biochemistry		√
Coagulation tests		√
Urinalysis		√

Monthly 10X: 3 pre-, 6 post-treatment
Bi-Monthly 5X: 1 pre-, 3 post-treatment

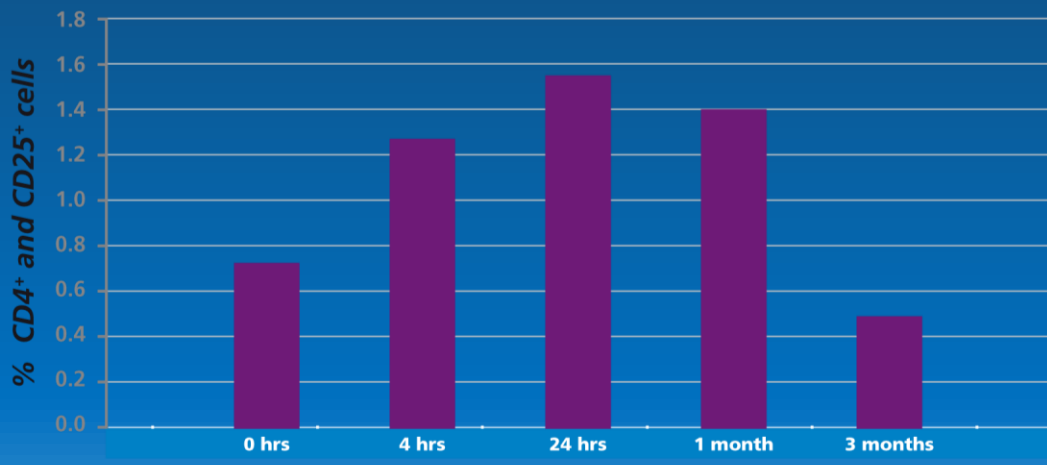
Safety Results

No significant adverse events were observed as a result of the treatment

Patient	Description
1	Headache for few hours on day of injection
2	Bruising at injection site
3	Mild fever post-injection
4	Headache, neck stiffness, fever 38.8 for 24 hours
5	None
6	None
7	Lost to follow up after 3 months*
8	None
9	None
10	None
11	Fever for 30 minutes 1-day post-injection
12	None

*Entered study with advanced stage disease.
Expired from pneumonia, unrelated to transplant.

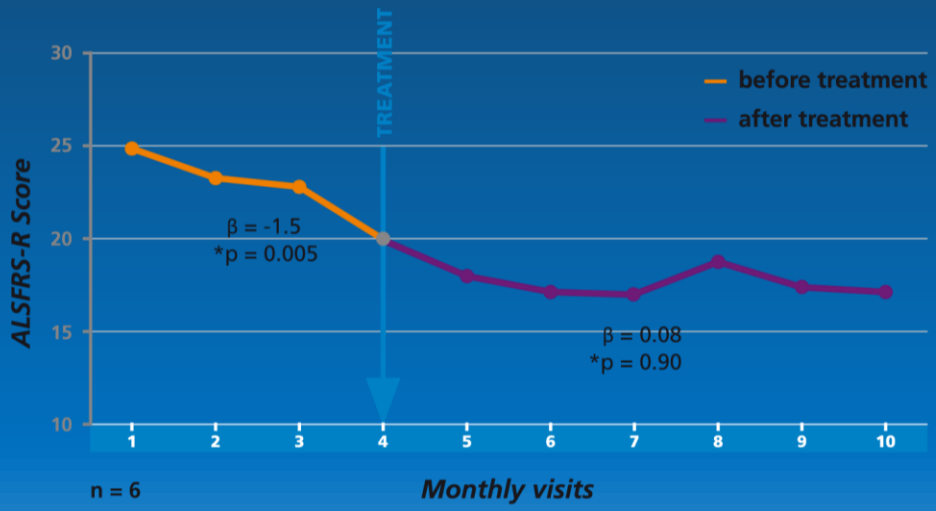
Upregulation of $CD4^+$ and $CD25^+$ regulatory cells following treatment with MSC-NTF cells



Mean values of all patients

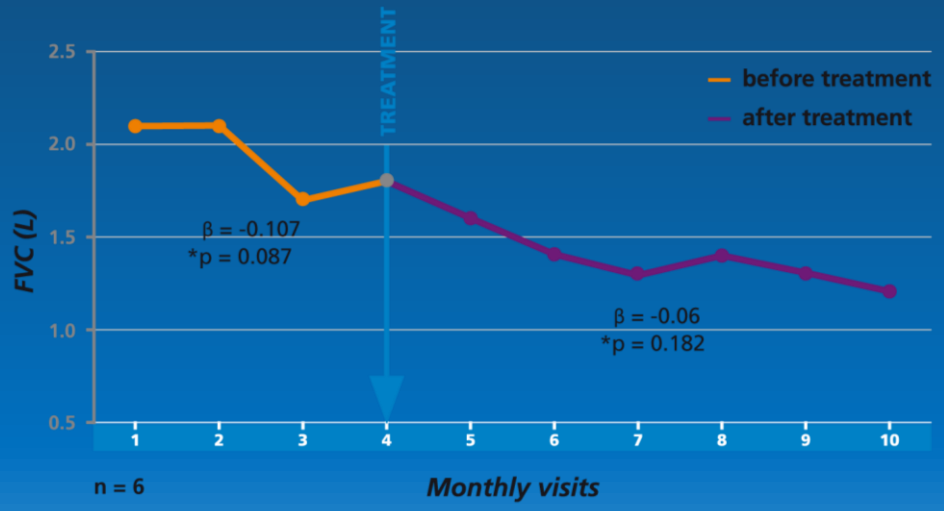
Clinical Results

Decreased mean rate of change in ALSFRS-R score following treatment with MSC-NTF cells in IT-transplanted patients



p value for differences between periods, p = 0.0013
*p value for differences within each period

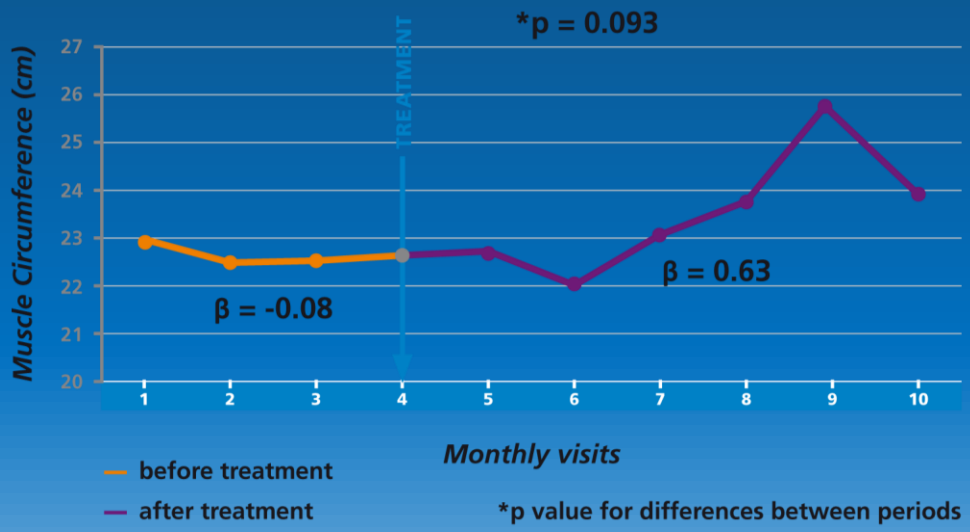
Decreased mean rate of change in FVC following treatment with MSC-NTF cells in IT-transplanted patients



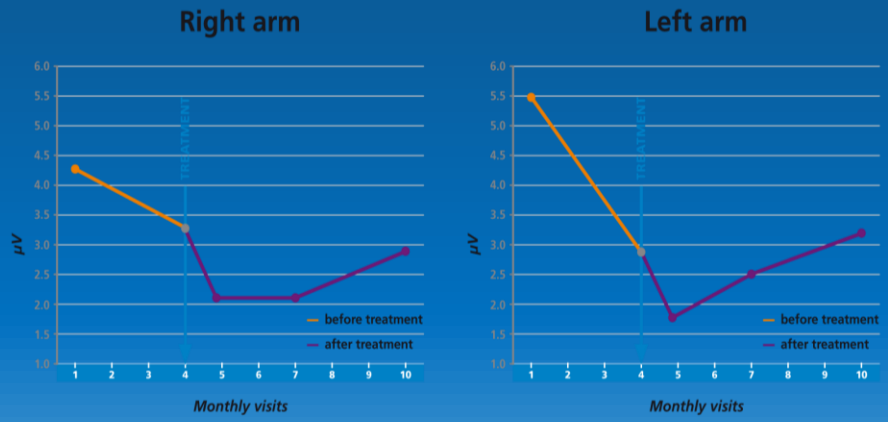
p value for differences between periods, p < 0.0001
*p value for differences within each period

Clinical Results

Mean arm muscle circumference increases following treatment with MSC-NTF cells in IT-transplanted patients



Mean Compound Muscle Action Potential (CMAP) in IT-transplanted patients following treatment with MSC-NTF cells



Conclusions

- IT and IM transplantation of autologous Neurotrophic Factor-Secreting Mesenchymal Stem Cells (MSC-NTF) in 12 ALS patients is safe.
- Preliminary indications of beneficial clinical effect - stabilization or slowing of progression - were evidenced in ALSFRS-R score & respiratory function (FVC) in the IT-transplanted patients.
- A beneficial trend was also observed in the changes in arm muscle circumference.
- Further clinical trials are needed to confirm these effects in ALS patients.