Background

MSC-NTF cells (NurOwn®) are autologous bone-marrow derived mesenchymal stem cells (MSC) induced to secrete high levels of neurotrophic factors (NTFs). miRNAs are small non-coding RNAs that regulate a wide variety of biological processes via RNA-dependent post-transcriptional silencing mechanisms. MSC-NTF cells were administered by a single intrathecal injection to ALS patients in a US Phase 2 multicenter double-blind placebo-controlled trial to evaluate safety and efficacy (NCT02017912).

Objective

To relate CSF miRNA changes to CSF biomarkers of apoptosis and innate immunity pre- and 2 weeks post-intrathecal transplantation of NurOwn® in the Phase 2 placebo-controlled trial.

Design/Methods

CSF was collected prior to, and two weeks after intrathecal MSC-NTF cells transplantation. miRNAs were analyzed in CSF pools of three homogeneous groups: a) responders; b) non-responders as determined by the ALSFRS-R score and c) placebo patients. Levels of Caspase 3, MCP-1, SDF-1 and Chitotriosidase (CHIT)-1 in CSF from each patient was measured using the Exiqon platform.

Study Schematic

Results

Increased CSF miR-132 and miR-146a after treatment with MSC-NTF cells

Decreased CSF inflammatory markers and Caspase-3 after treatment with MSC-NTF cells

Decreased CSF CHIT-1 after treatment with MSC-NTF cells

Discussion

- miR-132 is known to positively modulate axon and dendrite development and maturation in response to various signals and may provide neuroprotection in tauropathies, through modulation of caspase 3 activation.
- miR-132 is downregulated in the CSF of sporadic, TARDBP, FUS and C9ORF72 ALS patients.
- miR-146 is known to modulate innate immunity under neuroinflammatory conditions through effects on microglia, astrocytes, and Tregs.
- miR-146 negatively regulates innate immunity and signal transduction linked to NF-kB activation.

Conclusions

- The biomarker data demonstrates increases in CSF miR-132 and miR-146a and statistically significant decreases in MCP-1, SDF-1, CHIT-1 and Caspase 3 in ALS phase 2 study participants 2 weeks following a single MSC-NTF cell transplantation.
- The observed miR modifications and corresponding CSF biomarker changes suggest that miR secreted by MSC-NTF cells may contribute to neuroprotection and immunomodulation.
- Additional miRNA and biomarker correlations will be examined in the ongoing NurOwn® Phase 3 ALS trial (NCT03280056).