Mesenchymal stem cell-derived neural progenitors in progressive MS
Two-year follow-up of a phase I study

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Abstract

Objective
To determine the long-term safety and efficacy of repeated intrathecal (IT) administration of autologous mesenchymal stem cell-derived neural progenitors (MSC-NPs) in patients with progressive MS by evaluating subjects 2 years after treatment.

Methods
Twenty subjects were enrolled as part of a phase I, open-label single-arm study of 3 IT injections of MSC-NPs spaced 3 months apart. Subjects were evaluated for adverse events and disability outcomes including the Expanded Disability Status Scale (EDSS) and the timed 25-foot walk (T25FW). Long-term evaluation was conducted 2 years after the third treatment. CSF was collected before and 3 months after treatment.

Results
Eighteen of the 20 study participants completed the full 2-year follow-up protocol. There were no long-term adverse events associated with repeated IT-MSC-NP treatment. Seven subjects showed sustained improvement in EDSS after 2 years, although the degree of improvement was not maintained in 5 of the subjects. Three of the 10 ambulatory subjects showed sustained improvement in the T25FW after 2 years. CSF biomarker analysis revealed a decrease in C-C motif chemokine ligand 2 (CCL2) and an increase in interleukin 8, hepatocyte growth factor, and C-X-C motif chemokine ligand 12 (CXCL12) after treatment.

Conclusions
Safety and efficacy of repeated IT-MSC-NP treatment was sustained for 2 years; however, the degree of disability reversal was not sustained in a subset of patients. CSF biomarkers altered in response to IT-MSC-NP treatment may reflect specific immunoregulatory and trophic mechanisms of therapeutic response in MS.

Classification of evidence
This study provides Class IV evidence that for patients with progressive MS, IT administration of MSC-NPs is safe and effective. The study is rated Class IV because of the absence of a non–IT-MSC-NP-treated control group.

Clinicaltrials.gov identifier
NCT01933802.
MS is an autoimmune CNS disease that is classified clinically into relapsing-remitting (RR), secondary progressive (SP) and primary progressive (PP) forms. In RRMS, the relapses are caused by inflammatory mechanisms that are highly responsive to an ever-increasing number of approved disease-modifying therapies (DMTs). However, the pathologic mechanisms driving progressive disease are poorly understood; fewer DMTs are approved, and these are generally less effective in comparison to RRMS. The accrual of neurologic disability in SPMS and PPMS represents a major unmet therapeutic challenge in neurology.

Mesenchymal stem cell-derived neural progenitors (MSC-NPs) are autologous bone marrow-derived cells currently under clinical investigation as a regenerative cell therapy for progressive MS. MSC-NPs represent a neural subpopulation of MSCs, characterized by high expression of neural markers including Nestin, down regulation of mesenchymal markers such as smooth muscle a-2 actin and CD90, and reduced multipotency. In vitro, MSC-NPs retain trophic and immunomodulatory functions associated with increased expression and secretion of growth factors including hepatocyte growth factor (HGF) and insulin-like growth factor. Based on the preclinical efficacy of intrathecal (IT) injection of MSC-NPs into mice with experimental autoimmune encephalomyelitis (EAE), we conducted a phase I open-label clinical trial testing the safety and tolerability of multiple IT injections of autologous MSC-NPs in 20 patients with MS. Short-term outcomes supported the overall safety of this therapeutic approach, in addition to revealing encouraging trends in efficacy, particularly in subjects who were ambulatory at the beginning of the study. This objective of the current study was to follow these patients for 2 years to better understand whether safety and efficacy trends were sustained long term.

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**Methods**

**Study design and patient selection criteria**

Twenty subjects with clinically definite SPMS or PPMS were recruited from the International MS Management Practice, which is affiliated with the Tisch MS Research Center of New York where the study was conducted. To be eligible, subjects had to have significant disability (Expanded Disability Status Scale [EDSS] ≥3.0) and stable disease. Disease stability was determined by less than a 1.0-point change in EDSS, lack of gadolinium-enhancing lesions on MRI, and stable MRI disease burden (number and size of T2 lesions) in the 12 months before the initiation of the experimental treatment. Subjects were excluded from the study if they had cognitive impairment or existing comorbidities that might complicate safety outcomes. As previously published, subjects who were already receiving DMTs on entering the study continued as a concomitant treatment through the course of the study and through the 2-year follow-up period. The exception was subject 9, who was untreated during the treatment phase of the study and started on rituximab 1 year after the third IT-MSC-NP dose.

**Standard protocol approvals, registrations, and patient consents**

The study was approved by Western Institutional Review Board and the Food and Drug Administration, and all subjects provided written informed consent before conducting any study-related procedures. The study was registered on clinicaltrials.gov (NCT01933802).

**Classification of evidence**

The study is an interventional phase I clinical trial with no controls and provides Class IV evidence that for patients with progressive MS, repeated IT administration of autologous MSC-NPs is safe and effective.

**Study procedures**

From 2014 to 2016, study subjects received 3 IT injections of autologous MSC-NPs at an average dose of 9.4 × 10⁶ cells (target dose was 1.0 × 10⁷ cells). Injections were spaced 3 months apart. MSC-NPs were manufactured from bone marrow-derived MSCs as previously described and resuspended in sterile saline before injection. For all IT-MSC-NP treatments, prophylactic IV infusion of antibiotics (80 mg of tobramycin and 500 mg of vancomycin) was coadministered to minimize any risk of meningitis.

Clinical evaluations were performed at baseline, 3 and 6 months after the third treatment (months 9 and 12, respectively), and 2 years after the third treatment (month 30) to determine long-term effects (figure 1). Assessment of neurologic disability included EDSS, timed 25-foot walk (T25FW), and 9-hole peg test (9HPT). Safety assessments included physical and neurologic examinations, headache pain scale, and brain MRI scans with and without gadolinium enhancement. Additional assessments, including bladder function and muscle strength, are reported elsewhere and were not performed as part of the 2-year follow-up.
CSF biomarker analysis
As part of the study protocol, the CSF was collected during each IT procedure and at the 3-month follow-up visit. Cell-free CSF was processed immediately and stored in aliquots at −80 °C as previously described.4 Levels of analytes C-C motif chemokine ligand 2 (CCL2)/monocyte chemotactic protein-1 (MCP-1), HGF, C-X-C motif chemokine ligand 12 (CXCL12)/stromal cell-derived factor (SDF) 1α, and interleukin (IL)-8/CXCL8 were measured in undiluted CSF by human magnetic luminex assay (R&D Systems, Minneapolis, MN). Transforming growth factor β2 (TGF-β2) was measured in undiluted CSF using the luminex TGF-β multiplex kit (R&D Systems). Neurofilament light (NfL) levels were measured in the CSF diluted 1:2 using NF-light® ELISA (UmanDiagnostics, Umeå, Sweden).

Statistics
Differences between biomarker levels before and after treatment were evaluated by the Wilcoxon matched-pairs signed rank test, and correlations were evaluated using linear regression analysis. A p value of <0.05 was considered to be statistically significant. Statistical analysis was performed using GraphPad Prism 8.

Data availability
Anonymized data presented in this article will be made available to any qualified investigator on request to the corresponding author.

Results
Long-term safety of IT-MSC-NP treatment
Of the 20 patients in the treatment cohort (table 1), only 2 (subjects 17 and 18) were unable to complete the 2-year post-third treatment follow-up visit in person and were assessed via telemedicine. Both subjects were severely disabled with an EDSS of 8.0 for the duration of the study up to the 30-month follow-up. In all subjects, there were no serious adverse events reported 2 years after receiving IT-MSC-NP treatment. One subject reported a minor headache during the 2-year follow-up visit and required no medication to resolve. Additional minor adverse events categorized as musculoskeletal (2 subjects) and dermatological (3 subjects) were deemed not related to the study treatment. These results confirm that multiple IT administration of MSC-NPs was associated with long-term safety.

Analysis of brain MRI scans did not show changes in any of the 20 patients in the trial and findings were typical of progressive MS (data not shown). Specifically, pretreatment scan T1 hypointense lesions, T2 hyperintense lesions, and atrophy measures were unchanged over the duration of the study. None of the patients had Gadolinium-enhancing lesions at any point during the study. There were also no discernible trends in any MRI parameters between patient “responders” and “nonresponders.”

Long-term EDSS and walking outcomes
EDSS changes for the duration of the 2.5-year study are shown in figure 2. EDSS values were predominantly derived from the pyramidal system and motor strength scores, with little-to-no contribution from cerebellar and other system values. We previously reported that 6 months after the third treatment, 8 of 20 subjects had demonstrated at least a 0.5 point improvement in EDSS, with 4 of the 8 subjects showing an improvement of 2.0 or greater positive change compared with baseline.1 At the 2-year follow-up assessment, 7 of the 8 subjects showed continued improvement. Two subjects demonstrated sustained improvement of 2.0 or greater (figure 2A) and 5 subjects demonstrated sustained EDSS

Table 1

<table>
<thead>
<tr>
<th>Study subject characteristics</th>
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<tbody>
<tr>
<td>MS subtype, n (%)</td>
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<tr>
<td>SPMS</td>
<td>16 (80)</td>
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<tr>
<td>PPMS</td>
<td>4 (20)</td>
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<tr>
<td>Sex, n (%)</td>
<td></td>
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<tr>
<td>Female</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>49 (27–65)</td>
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<tr>
<td>Disease duration, y (range)</td>
<td>19 (10–32)</td>
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<tr>
<td>Baseline EDSS (range)</td>
<td>6.8 (3.5–8.5)</td>
</tr>
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</table>

Abbreviations: EDSS = Expanded Disability Status Scale; PPMS = primary progressive MS; SPMS = secondary progressive MS. Age, disease duration, and baseline EDSS are expressed as mean values.
improvement of 0.5 points (figure 2B). One subject (12) who had previously demonstrated 1.0-point improvement between baseline and 6 months demonstrated a 0.5-point worsening from baseline at 2 years (figure 2D). In the remaining subjects, 6 showed continued stable EDSS throughout the course of the study (figure 2C), 2 subjects (10 and 13) continued to show

Table 2 T25FW results at baseline and at 3- and 24-month post-third IT-MSC-NP treatment

<table>
<thead>
<tr>
<th>Study subject ID</th>
<th>T25FW time at baseline (s)</th>
<th>T25FW time 3 mo post-treatment (s)</th>
<th>T25FW time 24 mo post-treatment (s)</th>
<th>% Improvement of T25FW 3 mo</th>
<th>% Improvement of T25FW 24 mo</th>
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<tr>
<td>1</td>
<td>6.0</td>
<td>5.0</td>
<td>5.9</td>
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<tr>
<td>2</td>
<td>10.8</td>
<td>5.9</td>
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<tr>
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<td>24.6</td>
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<td>54</td>
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<tr>
<td>9b</td>
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<td>28.8</td>
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Abbreviations: “—” = test not performed because subject not ambulatory; IT = intrathecal; MSC-NP = mesenchymal stem cell-derived neural progenitor; n/a = not applicable; T25FW = timed 25-foot walk. Nonambulatory study subjects not shown. Percentages in bold indicate sustained improvement of > 20% after 2 years.

*Pre- and post-walk times were determined using the same assistive device (if any) for each individual study subject.

b Subject 9 was untreated during the treatment phase of the study and started on rituximab 1 year after the third IT-MSC-NP dose. All other subjects had no change of disease-modifying therapy for the duration of the study.
disease worsening at all follow-up visits from baseline (figure 2D), and an additional 2 study subjects (14 and 15) showed disease worsening at 2 years compared with the 6-month visit (figure 2D).

Walking speed using the T25FW test was assessed in the 10 ambulatory patients within the cohort. We previously reported that 4 of the 10 ambulatory patients demonstrated a >20% improvement in walking speed 3 months post-treatment compared with baseline.1 At 2 years post-treatment, 3 of the subjects (2, 4, and 8) showed a sustained improvement in walking speed and the fourth subject (3) maintained a speed of just below 20% improvement from baseline (table 2). Subject 1 demonstrated a normal walking speed for the duration of the study. In addition, 1 subject (11) who was nonambulatory at baseline was capable of performing the walk test both 3 and 24 months after treatment. Regarding upper-limb function, there were no sustained differences in 9HPT in any of the patients (data not shown).

These results show that reversal of disability after 3 IT-MSC-NP treatments is sustained for 2 years after the treatment course; however, the degree of improvement is not sustained in a subset of patients. The remaining subjects in the trial experienced either sustained disease stability or disease worsening that is typical of progressive MS.

**CSF biomarker analysis**

A panel of potential biomarkers was measured in the CSF drawn before the first treatment and 3 months after the third treatment in 18 of the 20 study participants. To determine whether CSF biomarkers changed correlated with treatment-associated disease improvement, subjects were divided into 2 groups as “responders” (subjects in figure 2, A and B) and “nonresponders” (subjects in figure 2, C and D) based on EDSS improvement. CSF levels of the proinflammatory chemokine CCL2 were significantly decreased after IT-MSC-NP treatment in the entire treatment population (figure 3A) with no apparent difference between responders and nonresponders (not shown). In addition, TGF-β2 levels in the CSF increased post-treatment compared with baseline (figure 3B). Other TGF-β family members, TGF-β1 and TGF-β3, were not detectable in the CSF. Previous clinical studies found a correlation between decreased CCL2 and increased TGF-β in the CSF of amyotrophic lateral sclerosis (ALS) patients after IT MSC treatment.6,5 Similarly, we found that the overall levels of TGF-β2 and CCL2 were inversely correlated (figure 3C).

Additional biomarkers demonstrated some correlation with treatment response. CSF levels of HGF, CXCL12, and IL-8 (figure 4, A–C, respectively) were significantly increased in the CSF post-treatment in nonresponders compared with responders, possibly associating ongoing IT inflammation with lack of response to IT-MSC-NP. Overall CSF levels of NfL were unchanged after treatment (figure 4D). However, in the few patients with elevated CSF NfL (>1,000 pg/mL), responders showed a decrease in CSF NfL, whereas nonresponders exhibited an increase in CSF NfL (figure 4D). None of the candidate biomarkers correlated with age, disease duration, or EDSS, with the exception of HGF, which showed a positive correlation with subject age (p = 0.018) and disease duration (p = 0.0004). Overall, these findings identify a panel of CSF biomarkers altered in response to IT-MSC-NP treatment that may reflect specific immunoregulatory and trophic mechanisms of therapeutic response in MS.

**Discussion**

As cell therapy clinical trials in neurologic diseases such as MS become more common, a better understanding of the
long-term impact of these interventions is critical. Of the many early phase trials investigating autologous MSC-derived therapies administered intrathecally in MS,7–9 very few have reported on the long-term safety and efficacy of this approach.10,11 A recent dose-finding pilot study followed 6 patients with MS for an average of 7.4 years after IT MSC-NP treatment, suggesting long-term safety and tolerability.10 The long-term safety of IT MSC-NPs is further supported by the current Phase 1 clinical trial, demonstrating continued safety in the 2 years’ time period after 3 IT injections of autologous MSC-NPs in 20 patients with progressive MS.

Improvements in mobility and overall disability as measured by EDSS was sustained in a subset of patients and correlated with lower EDSS and ambulatory status at baseline. Study subjects were selected based on their long-standing disease, which was optimally managed by DMTs; thus, the observed sustained improvements in EDSS were unlikely because of a regression to the mean. However, a placebo effect cannot be ruled out.
because of the open-label, single-arm design of this study. Based on the observed sustained improvement in the 2 patients with the lowest EDSS at baseline, we hypothesize that additional IT MSC-NP injections might be required to maintain improvements in patients above a certain threshold of disability. Although all of the patients with sustained improvement were SPMS, there were too few PPMS patients included in the study to draw any conclusion regarding efficacy. Two of the 3 PPMS subjects demonstrated sustained lack of progression for 2 years after treatment (subjects 9 and 20). Taken together, these observations have informed the design of a phase II clinical trial which will test a total of 6 IT-MSC-NP injections spaced 2 months apart against a placebo (NCT 03355365) in a randomized double-blinded study in a total of 50 patients (40 SPMS and 10 PPMS).

CSF analysis demonstrated a shift in biomarkers associated with IT inflammation and tissue repair, highlighting potential therapeutic targets of IT-MSC-NP treatment in MS. Decreased CCL2 in the CSF was consistent with previous studies in ALS which similarly demonstrated reduced CSF CCL2 inversely correlating with increased TGF-β in ALS patients after IT MSC injections, suggesting a common target of MSC-based cell therapy in both diseases. CCL2 (MCP-1) in the brain is produced by astrocytes and resident microglia, where it plays a role in the progression of MS disease pathology and chronic neuroinflammation. The reported modulation of microglia activity by MSCs suggests that this may be a therapeutic target of MSC-NP-based therapy as well. TGF-β, which is expressed by MSC-NPs and MSCs and increases its anti-inflammatory function of MSCs on microglia.

Additional inflammatory biomarkers were found to be significantly increased in the CSF in subjects who did not show a clinical response to IT-MSC-NP treatment and included HGF, a potent immunoregulatory factor with pleiotropic effects on neurons and glial cells. HGF was previously implicated in mediating the efficacy of MSCs in EAE and although MSC-NP cells express high levels of HGF, the cellular source of HGF in the CSF remains unknown. Elevated levels of the chemokines IL-8 (CXCL8) and CXCL12 (SDF1) in the CSF were also observed in nonresponders after IT-MSC-NP treatment. Increased CSF IL-8 was previously associated with IT inflammation in active MS, although the role of IL-8 in progressive MS is unknown. Increased levels of IL-8 may reflect its role in neuroprotection and myelin repair. CXCR2, the receptor for IL-8, is expressed by microglia and oligodendroglia in active MS lesions and is required for tissue repair in EAE. Similarly, CXCL12 is a chemoattractant for MSCs and for OPCs and neural precursors where it can function to promote myelin repair. Increased IL-8 and CXCL12 may reflect upregulation in cells including astrocytes associated with a neuroprotective response.

Although the study was not designed to determine efficacy, the results suggest that nonambulatory subjects with more advanced disease and higher EDSS at baseline did not exhibit reduced EDSS after treatment. The preliminary evidence of increased inflammatory biomarkers in the nonresponder group suggests that modulation of neuroinflammation by MSC-NPs is not sufficient to overcome a threshold of disability associated with ongoing IT inflammation and long-standing disease burden. Although only a small number of subjects in the cohort exhibited elevated CSF NfL at baseline, decreased CSF NfL after treatment seemed to correlate with treatment response suggesting that acute neurodegeneration may be affected by IT-MSC-NP treatment. The predictive value of these candidate biomarkers is limited, however, because of the small number of subjects in the study and the lack of a placebo control.

In conclusion, in the long-term follow-up of 20 patients with progressive MS in the phase I clinical trial, we observed that most subjects who received repeated IT-MSC-NP injections exhibited either a reversal in disability or lack of disease progression that was sustained for 2 years after treatment. The impact of any efficacy conclusion, however, are severely limited by the very small number of patients in the study and the lack of blinding and placebo controls. Notably, the exceptional safety profile of repeated IT-MSC-NP treatment is in agreement with our previous long-term study and supports a favorable risk-benefit ratio associated with this therapeutic approach. A larger phase II placebo-controlled study is currently under way to determine efficacy of IT-MSC-NP treatment in MS.

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Disclosure
The authors report no disclosures. Go to Neurology.org/NN for full disclosures.

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<tr>
<td>Violaine K. Harris, PhD</td>
<td>Tisch MS Research</td>
<td>Design and conceptualized the study, analyzed the data, and drafted the manuscript for intellectual content</td>
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<td></td>
<td>Center of New York</td>
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<tr>
<td>James W. Stark, MD, FAAN</td>
<td>Tisch MS Research</td>
<td>Major role in the acquisition of data</td>
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<tr>
<td>Sophia Yang, BA</td>
<td>Tisch MS Research</td>
<td>Major role in the acquisition of data</td>
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<td>Tisch MS Research Center of New York</td>
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</table>

References

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