

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.

MORE ONLINE

→ Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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From the Tisch Multiple Sclerosis Research Center of New York.

Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

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Glossary

9HPT = 9-hole peg test; **ALS** = amyotrophic lateral sclerosis; **DMT** = disease-modifying therapy; **EAE** = experimental autoimmune encephalomyelitis; **EDSS** = Expanded Disability Status Scale; **HGF** = hepatocyte growth factor; **IL** = interleukin; **IT** = intrathecal; **MCP-1** = monocyte chemoattractant protein-1; **MSC-NP** = mesenchymal stem cell-derived neural progenitor; **NfL** = neurofilament light; **PPMS** = primary progressive MS; **RRMS** = relapsing-remitting MS; **SDF** = stromal cell-derived factor; **SPMS** = secondary progressive MS; **T25FW** = timed 25-foot walk; **TGF** = transforming growth factor.

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.¹ 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 α -2 actin and CD90, and reduced multipotency.² 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.² 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.^{1,3} 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.¹ 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.

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.¹ 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

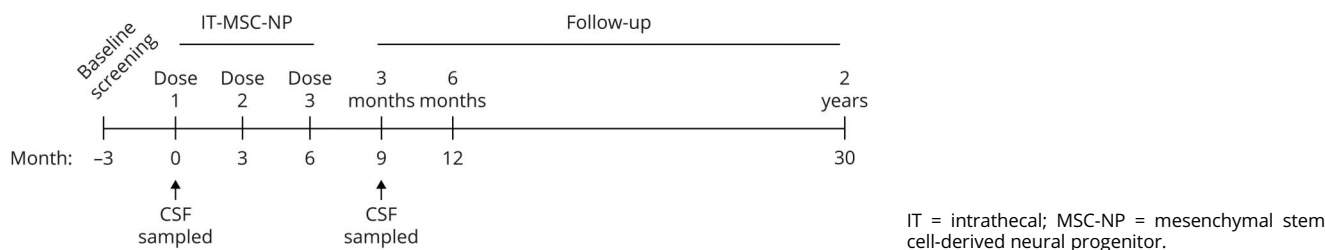
The study is an interventional phase I clinical trial with no controls and provides Class IV evidence that for patients with progressive MS, repeated IT administration of autologous MSC-NPs is safe and effective.

Study procedures

From 2014 to 2016, study subjects received 3 IT injections of autologous MSC-NPs at an average dose of 9.4×10^6 cells (target dose was 1.0×10^7 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.¹ 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.¹

Figure 1 Schematic of phase I trial design testing 3 IT injections of autologous MSC-NPs



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 chemoattractant protein-1 (MCP-1), HGF, C-X-C motif chemokine ligand 12 (CXCL12)/stromal cell-derived factor (SDF) 1 α , and interleukin (IL)-8/CXCL8 were measured in undiluted CSF by human magnetic luminex assay (R&D Systems, Minneapolis, MN). Transforming growth factor β 2 (TGF- β 2) 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

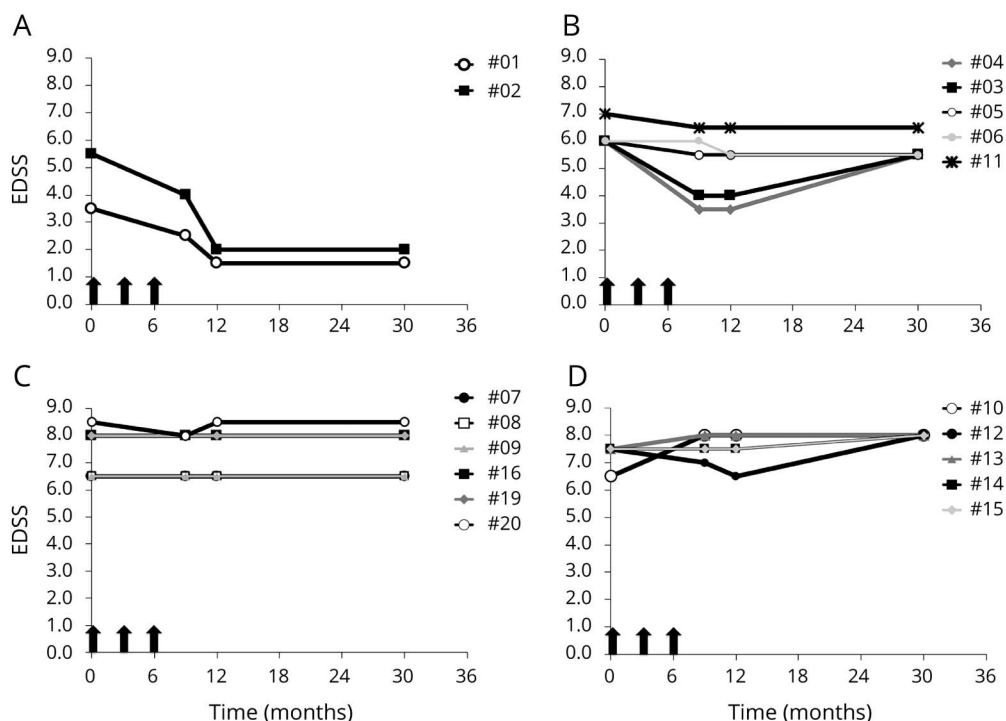
EDSS changes for the duration of the 2.5-year study are shown in figure 2. EDSS values were predominantly derived from the pyramidal system and motor strength scores, with little-to-no contribution from cerebellar and other system values. We previously reported that 6 months after the third treatment, 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 Study subject characteristics

Study subjects, n	20
MS subtype, n (%)	
SPMS	16 (80)
PPMS	4 (20)
Sex, n (%)	
Female	14 (70)
Age, y (range)	49 (27–65)
Disease duration, y (range)	19 (10–32)
Baseline EDSS (range)	6.8 (3.5–8.5)

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.

Figure 2 Changes in EDSS scores up to 2 years after IT-MSC-NP treatment



(A) EDSS scores of 2 study subjects with sustained improvement of 2.0 or greater. (B) EDSS scores of 5 study subjects with sustained improvement of 0.5 points. (C) EDSS scores of 6 study subjects with stable disease throughout the course of the study. (D) EDSS scores of 5 subjects who showed disease worsening between baseline and long-term follow-up. Arrows in each graph represent each IT-MSC-NP treatment. EDSS = Expanded Disability Status Scale; IT = intrathecal; MSC-NP = mesenchymal stem cell-derived neural progenitor.

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

Study subject ID	T25FW time at baseline (s)	T25FW time 3 mo post-treatment (s) ^a	T25FW time 24 mo post-treatment (s) ^a	% Improvement of T25FW 3 mo	% Improvement of T25FW 24 mo
1	6.0	5.0	5.9	17	2
2	10.8	5.9	6.9	46	36
3	12.7	9.6	10.4	24	18
4	8.4	6.1	6.4	26	24
5	12.2	12.6	12.7	-3	-4
6	18.3	18.6	20.7	-2	-13
7	28.1	27.0	34.0	4	-21
8	53.4	23.9	24.6	55	54
9 ^b	25.3	22.0	28.8	13	-14
10	97.4	—	—	n/a	n/a

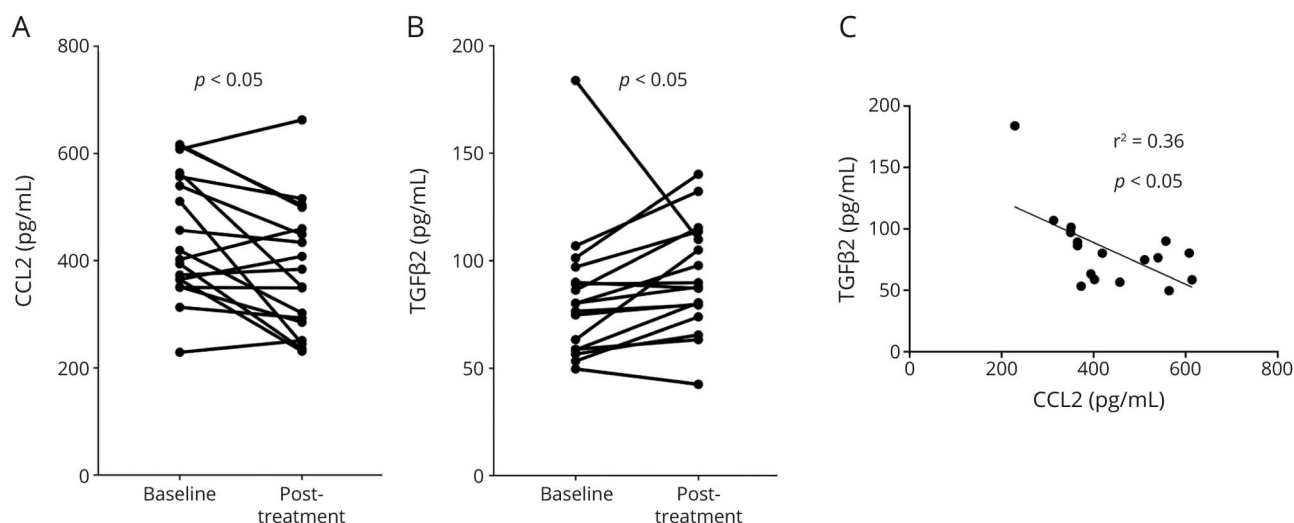
Abbreviations: “—” = test not performed because subject not ambulatory; IT = intrathecal; MSC-NP = mesenchymal stem cell-derived neural progenitor; n/a = not applicable; T25FW = timed 25-foot walk.

Nonambulatory study subjects not shown. Percentages in bold indicate sustained improvement of > 20% after 2 years.

^a 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.

Figure 3 Decreased CCL2 and increased TGF- β 2 in CSF following IT-MSC-NP treatment



Individual values at baseline and post-treatment for all study subjects are shown. Levels of (A) CCL2 were significantly decreased and (B) TGF- β 2 significantly increased in CSF sampled 3 months after the third IT-MSC-NP treatment compared with baseline. (C) CSF levels of CCL2 and TGF- β 2 were inversely correlated. IT = intrathecal; MSC-NP = mesenchymal stem cell-derived neural progenitor; TGF = transforming growth factor.

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 biomarker changes 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

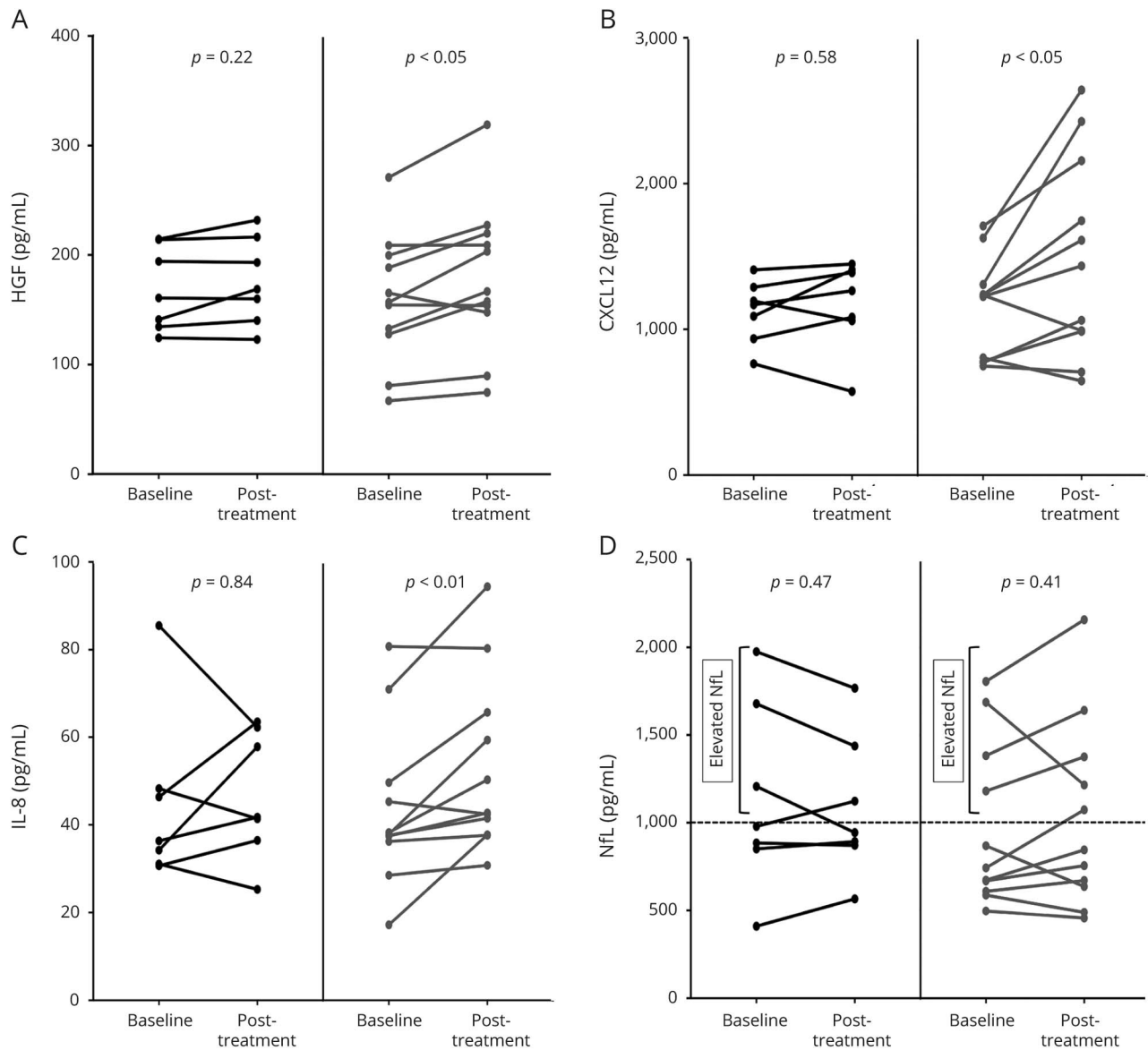
after IT-MSC-NP treatment in the entire treatment population (figure 3A) with no apparent difference between responders and nonresponders (not shown). In addition, TGF- β 2 levels in the CSF increased post-treatment compared with baseline (figure 3B). Other TGF- β family members, TGF- β 1 and TGF- β 3, 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.^{5,6} Similarly, we found that the overall levels of TGF- β 2 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

Figure 4 Increased inflammatory biomarkers in CSF of subjects who lacked EDSS improvement following IT-MSC-NP treatment



Individual values at baseline and post-treatment for subjects who showed improved EDSS (black lines) and subjects who lacked EDSS improvement (gray lines) are shown separately in left and right panels, respectively. Levels of (A) HGF, (B) CXCL12, and (C) IL-8 were significantly increased post-treatment in the CSF from nonresponders compared with responders. (D) Overall levels of CSF NFL were not significantly altered post-treatment in either group. In subjects with elevated CSF NfL (>1,000 pg/mL), responders exhibited decreased CSF NfL, whereas nonresponders exhibited increased CSF NfL after treatment. EDSS = Expanded Disability Status Scale; HGF = hepatocyte growth factor; IT = intrathecal; MSC-NP = mesenchymal stem cell-derived neural progenitor; NfL = neurofilament light.

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 I 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,^{5,6} 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.^{12,13} The reported modulation of microglia activity by MSCs suggests that this may be a therapeutic target of MSC-NP-based therapy as well.^{14,15} TGF- β , which is expressed by MSC-NPs and MSCs and increases its anti-inflammatory function of MSCs on microglia.¹⁶

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.¹⁷ HGF was previously implicated in mediating the efficacy of MSCs in EAE,¹⁸ and although MSC-NP cells express high levels of HGF,² 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,^{19,20} 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.^{13,21} CXCR2, the receptor for IL-8, is expressed by microglia and oligodendroglia in active MS lesions^{22,23} and is required for tissue repair in EAE.²⁴ Similarly, CXCL12 is a chemoattractant for MSCs and for OPCs and neural precursors where it can function to promote myelin repair.^{25–27} Increased IL-8 and CXCL12 may reflect upregulation in cells including astrocytes associated with a neuroprotective response.²⁸

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 longstanding 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.¹⁰ A larger phase II placebo-controlled study is currently under way to determine efficacy of IT-MSC-NP treatment in MS.

Study funding

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Disclosure

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

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Appendix Authors

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

Continued

Appendix (continued)

Name	Location	Contribution
Shayna Zanker, BS	Tisch MS Research Center of New York	Major role in the acquisition of data
John Tuddenham, BA	Tisch MS Research Center of New York	Major role in the acquisition of data
Saud A. Sadiq, MD	Tisch MS Research Center of New York	Design and conceptualized study, interpreted the data, and revised the manuscript for intellectual content

References

- Harris VK, Stark J, Vyshkina T, et al. Phase I trial of intrathecal mesenchymal stem cell-derived neural progenitors in progressive multiple sclerosis. *EBioMedicine* 2018; 29:23–30.
- Harris VK, Farouqi R, Vyshkina T, Sadiq SA. Characterization of autologous mesenchymal stem cell-derived neural progenitors as a feasible source of stem cells for central nervous system applications in multiple sclerosis. *Stem Cells Transl Med* 2012;1:536–547.
- Harris VK, Yan QJ, Vyshkina T, Sahabi S, Liu X, Sadiq SA. Clinical and pathological effects of intrathecal injection of mesenchymal stem cell-derived neural progenitors in an experimental model of multiple sclerosis. *J Neurol Sci* 2012;313:167–177.
- Harris VK, Donelan N, Yan QJ, et al. Cerebrospinal fluid Fetuin-A is a biomarker of active multiple sclerosis. *Mult Scler* 2013;19:1462–1472.
- Oh KW, Moon C, Kim HY, et al. Phase I trial of repeated intrathecal autologous bone marrow-derived mesenchymal stem cells in amyotrophic lateral sclerosis. *Stem Cells Transl Med* 2015;4:590–597.
- Oh KW, Noh MY, Kwon MS, et al. Repeated intrathecal mesenchymal stem cells for amyotrophic lateral sclerosis. *Ann Neurol* 2018;84:361–373.
- Bonab MM, Sahraian MA, Aghsaie A, et al. Autologous mesenchymal stem cell therapy in progressive multiple sclerosis: an open label study. *Curr Stem Cell Res Ther* 2012;7:407–414.
- Karussis D, Karageorgiou C, Vaknin-Dembinsky A, et al. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. *Arch Neurol* 2010;67:1187–1194.
- Yamout B, Hourani R, Salti H, et al. Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: a pilot study. *J Neuroimmunol* 2010;227:185–189.
- Harris VK, Vyshkina T, Sadiq SA. Clinical safety of intrathecal administration of mesenchymal stromal cell-derived neural progenitors in multiple sclerosis. *Cytotherapy* 2016;18:1476–1482.
- Sahraian MA, Mohyeddin Bonab M, Baghbanian SM, Owji M, Naser Moghadasi A. Therapeutic use of intrathecal mesenchymal stem cells in patients with multiple sclerosis: a pilot study with booster injection. *Immunol Invest* 2019;48:160–168.
- Bose S, Cho J. Role of chemokine CCL2 and its receptor CCR2 in neurodegenerative diseases. *Arch Pharm Res* 2013;36:1039–1050.
- Semple BD, Kossmann T, Morganti-Kossmann MC. Role of chemokines in CNS health and pathology: a focus on the CCL2/CCR2 and CXCL8/CXCR2 networks. *J Cereb Blood Flow Metab* 2010;30:459–473.
- Giunti D, Parodi B, Usai C, et al. Mesenchymal stem cells shape microglia effector functions through the release of CX3CL1. *Stem Cells* 2012;30:2044–2053.
- Yan K, Zhang R, Sun C, et al. Bone marrow-derived mesenchymal stem cells maintain the resting phenotype of microglia and inhibit microglial activation. *PLoS One* 2013; 8:e84116.
- Noh MY, Lim SM, Oh KW, et al. Mesenchymal stem cells modulate the functional properties of microglia via TGF-beta secretion. *Stem Cells Transl Med* 2016;5: 1538–1549.
- Molnarfi N, Benkhoucha M, Funakoshi H, Nakamura T, Lalive PH. Hepatocyte growth factor: a regulator of inflammation and autoimmunity. *Autoimmun Rev* 2015; 14:293–303.
- Bai L, Lennon DP, Caplan AJ, et al. Hepatocyte growth factor mediates mesenchymal stem cell-induced recovery in multiple sclerosis models. *Nat Neurosci* 2012;15: 862–870.
- Bielekova B, Komori M, Xu Q, Reich DS, Wu T. Cerebrospinal fluid IL-12p40, CXCL13 and IL-8 as a combinatorial biomarker of active intrathecal inflammation. *PLoS One* 2012;7:e48370.
- Matejckova Z, Mares J, Sladkova V, et al. Cerebrospinal fluid and serum levels of interleukin-8 in patients with multiple sclerosis and its correlation with Q-albumin. *Mult Scler Relat Disord* 2017;14:12–15.
- Kelland EE, Gilmore W, Weiner LP, Lund BT. The dual role of CXCL8 in human CNS stem cell function: multipotent neural stem cell death and oligodendrocyte progenitor cell chemotaxis. *Glia* 2011;59:1864–1878.
- Filipovic R, Jakovcevski I, Zecevic N. GRO-alpha and CXCR2 in the human fetal brain and multiple sclerosis lesions. *Dev Neurosci* 2003;25:279–290.
- Omari KM, John G, Lango R, Raine CS. Role for CXCR2 and CXCL1 on glia in multiple sclerosis. *Glia* 2006;53:24–31.
- Carlson T, Kroenke M, Rao P, Lane TE, Segal B. The Th17-ELR+ CXC chemokine pathway is essential for the development of central nervous system autoimmune disease. *J Exp Med* 2008;205:811–823.
- Croituru-Lamoury J, Lamoury FM, Zaunders JJ, Veas LA, Brew BJ. Human mesenchymal stem cells constitutively express chemokines and chemokine receptors that can be upregulated by cytokines, IFN-beta, and Copaxone. *J Interferon Cytokine Res* 2007;27:53–64.
- Dziembowska M, Tham TN, Lau P, Vitry S, Lazarini F, Dubois-Dalcq M. A role for CXCR4 signaling in survival and migration of neural and oligodendrocyte precursors. *Glia* 2005;50:258–269.
- Patel JR, McCandless EE, Dorsey D, Klein RS. CXCR4 promotes differentiation of oligodendrocyte progenitors and remyelination. *Proc Natl Acad Sci USA* 2010;107:11062–11067.
- Trettel F, Di Castro MA, Limatola C. Chemokines: key molecules that orchestrate communication among neurons, microglia and astrocytes to preserve brain function. *Neuroscience* 2020;439:230–240.

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