SAFETY AND DOSING OF AUTOLOGOUS MESENCHYMAL STEM CELL NEURAL PROGENITORS INJECTED INTRATHECALLY IN MULTIPLE SCLEROSIS PATIENTS: RESULTS OF A PILOT STUDY

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INTRODUCTION

• There is an urgent need for therapies in MS that can stop or reverse progression through strategies of regeneration, remyelination, and neuronal repair.

• Mesenchymal stem cell-derived neural progenitors (MSC-NPs) represent a neural subpopulation of bone marrow MSCs with demonstrated therapeutic benefit when injected intrathecally into mice with EAE.

• This study represents a chart review of the initial clinical experience of intrathecal autologous MSC-NPs in MS patients and was conducted as an exploratory procedure to inform safety and dosing of this novel cellular therapy.

OBJECTIVE

To optimize dosing and to establish short-term and long-term safety of intrathecal injections of autologous MSC-NPs in patients with MS.

DESIGN AND METHODS

Autologous MSC-NPs were generated by isolation and expansion of MSCs from bone marrow aspirates, followed by 3 week cultivation in neural progenitor medium containing EGF and bFGF. MSC-NPs were collected, counted, and washed prior to intrathecal injection. Quality control included sterility testing and chromosomal analysis.

Six patients with progressive forms of MS and one with spinal cord atrophy were given intrathecal autologous MSC-NPs with informed consent as part of an exploratory pilot study. Data on the short-term and long-term safety was analyzed as an IRB-approved chart review. Subjects were evaluated for degree of disability (EDSS) and adverse events before and after each treatment.

Table 1. Patient demographics

Patient ID	Gender	Age	MS subtype	EDSS	Disease duration	Concurrent DMT
004-GG	M	64	SPMS	8.0	27	ITMTX
010-DS	F	36	SPMS	7.0	11	ITMTX, CC
023-AL	F	39	SPMS	6.5	22	NAT
030-VG	F	48	SPMS	6.5	19	RTX
007-PG	M	28	PPMS	7.0	7	ITMTX, RTX
025-TY	F	43	PPMS	9.0	16	ITMTX
012-LC	M	30	Spinal cord atrophy	6.5	11	none

SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis
ITMTX, intrathecal methotrexate; RTX, rituximab; CC, Cellcept; NAT, Natalizumab

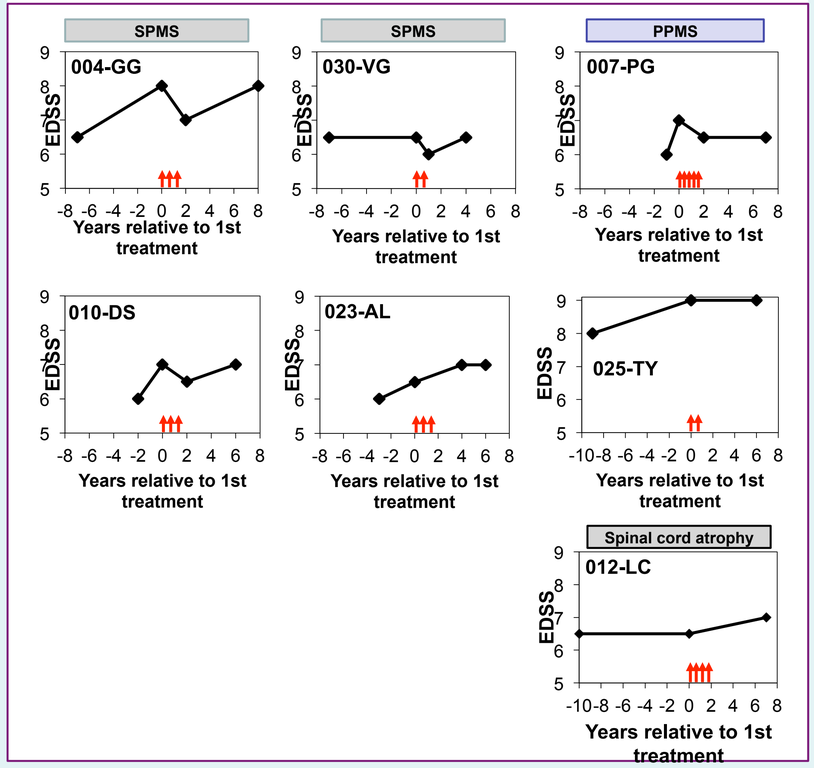
RESULTS

Table 2. Dosing, dosing frequency, and clinical outcomes after IT administration of autologous MSC-NPs. Each patient received 2-5 separate doses (average 3 doses) of autologous MSC-NPs spaced 2 to 8 months apart (average 4.5 months apart). Doses escalation ranged from $5x10^3$ to $1.6x10^7$ cells. Long-term follow up of patients ranges 6.7 to 8.4 (average 7.4 years) since the first injection. There were no significant short-term or long-term adverse events.

Patient ID	Treat-ment #	Cell dose (million)	Time interval (months)	Outcome	Adverse Event (AE)	AE treatment
004-GG	1	0.005		No change	None	N/A
	2	0.014	2	No change	None	N/A
	3	0.06	8	Improved: EDSS - 8 to 7	None	N/A
010-DS	1	0.1		No change	None	N/A
	2	2.7	5	No change	None	N/A
	3	5.5	7	Improved EDSS: 7 to 6.5; Bladder function; Walking endurance	None	N/A
023-AL	1	0.2		No change	None	N/A
	2	1.4	3	No change	None	N/A
	3	16.0	6	No change	None	N/A
030-VG	1	2.3		No change	None	N/A
	2	14.0	4	Improved EDSS: 6.5 to 6.0 Improved endurance and bladder function. Relapsed after treatment ceased.	Mild Headache	Resolved with Tylenol
007-PG	1	0.03		No change	None	N/A
	2	0.047	3	No change	None	N/A
	3	2.0	3	Improved: Bowel function	Mild Headache	Resolved in 24 hours with Tylenol
	4	3.8	6	Improved EDSS - 7 to 6.5	None	N/A
	5	9.0	3	Improvements maintained	Mild Headache	Resolved in 24 hours with Tylenol
025-TY	1	5.0		No change	Mild Headache	Resolved with Tylenol
	2	6.9	5	Improved: Moved R index finger and thumb and began speaking (patient quadriplegic and could not speak)	Headache (1 week) and mild fever	Headache resolved in 1 week and fever 24 hours with Tylenol
012-LC	1	0.1		No change	None	N/A
	2	0.03	3	No change	None	N/A
	3	4.0	4	No change	None	N/A
	4	2.4	5	No change	None	N/A

RESULTS

Figure 1. Changes in EDSS score after MSC-NP administration. EDSS scores for each study subject before and after receiving autologous MSC-NPs. Red arrows represent IT injections. 4 out of 6 MS patients demonstrated improved EDSS after MSC-NP treatment, which was sustained in one PPMS patient. _



CONCLUSIONS

- **Based on these initial findings, we determined that a dose of 2 to 10 million MSC-NPs administered by IT injection every 3 months would be safe and feasible.**
- **Phase I safety and tolerability study of autologous IT MSC-NP treatment for 20 MS patients has commenced (FDA approval of IND in Aug 2013).**

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