PHASE I CLINICAL TRIAL OF AUTOLOGOUS MESENCHYMAL STEM CELL-DERIVED NEURAL PROGENITORS INJECTED INTRATHECALLY IN MULTIPLE SCLEROSIS

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INTRODUCTION

- There is a critical unmet need to develop therapies that target CNS repair and neuroprotection in order to better help patients with progressive MS.
- MSC-NPs (mesenchymal stem cell-derived neural progenitors) represent a neural subpopulation of bone marrow-derived MSCs with reduced mesodermal pluripotency and minimized risk of ectopic differentiation.
- In preclinical studies in mouse experimental autoimmune encephalomyelitis (EAE), we established that intrathecal delivery of MSC-NPs was associated with cell migration to lesion areas, suppression of local inflammatory immune response, and trophic support for damaged cells at the lesion site. These pathological features were associated with improvement in clinical scores of EAE.
- Preliminary clinical experience with autologous MSC-NPs in a small number of patients further supports the safety and tolerability of this treatment.
- In August 2013, the FDA approved the IND application to conduct a phase I safety and tolerability study of autologous intrathecal (IT) MSC-NPs in MS.

OBJECTIVE

To establish safety and tolerability of intrathecal autologous mesenchymal stem cell-derived neural progenitor (MSC-NP)-based regenerative therapy in multiple sclerosis.

DESIGN AND METHODS

The study is a 20 patient, open-label, phase I clinical study of autologous MSC-NPs administered intrathecally in three injections of up to 10 million cells per injection, spaced three months apart. Pre-administration quality testing of autologous MSC-NPs expanded from bone marrow aspirates includes analysis of sterility, purity, identity, and chromosomal stability. Primary safety outcomes include adverse event assessments. Secondary outcomes to observe trends in efficacy include neurological exam, MRI, evoked potentials, and urodynamic testing.

Primary outcome:

- Evaluation of safety and tolerability of 3 IT administrations of autologous MSC-NPs (treatment phase = 9 months)
- Evaluation of long term safety (30 months)

Secondary outcome:

- Preliminary evaluation of efficacy (3 months after 3rd dose)
- Long term evaluation of sustained efficacy (30 months)

RESULTS

Figure 1. Schematic representation of autologous MSC expansion and MSC-NP isolation for IT injection.

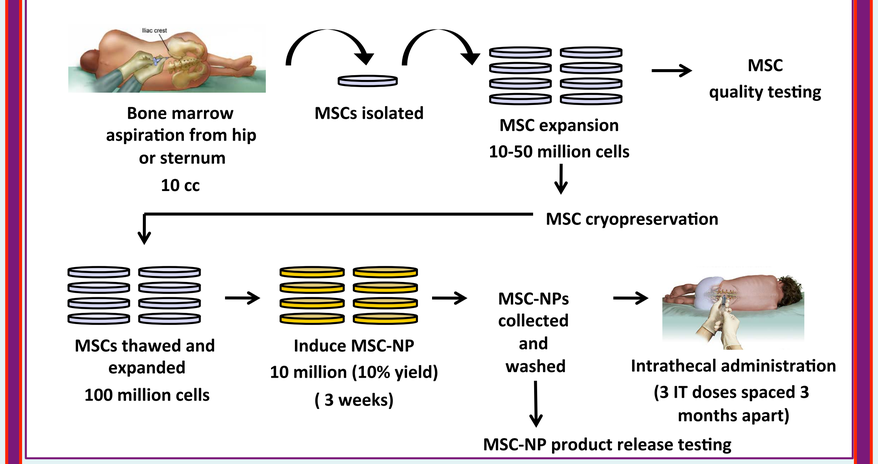

Table 1. Enrollment Criteria

INCLUSION CRITERIA
Diagnosis of MS as defined by McDonald criteria
Diagnosis of secondary progressive or primary progressive MS
Between ages 18-70
Significant disability shown by an EDSS >3.0 that was not acquired within last 12 months
Stable disease state as evidenced by lack of Gd-enhancing lesions on MRI, stable MRI disease burden (number of T2 lesions and size of lesions) in last 6 months, and no significant changes in EDSS (1 pt or more) in the last 12 months
EXCLUSION CRITERIA
Because the trial will include safety and tolerability outcomes, subjects who may be at a greater risk for complications will be excluded. Exclusion conditions include pregnancy, abnormal liver function, history of malignancy, cirrhosis, hypertension, thyroid or other endocrine disorder, history of CNS infection, preexisting blood disease, coagulation disorder, history of substance abuse, infectious diseases, and cognitive dysfunction.
Allergy to antibiotics
Use of steroids or systemic chemotherapeutic/anti-mitotic medications within 3 months of study start date

RESULTS

Table 2. Patient Demographics

Study Subject	Gender	Age	MS subtype	EDSS	Disease duration	Previous DMTs
1	M	34	PPMS	8.5	13	ITMTX, RTX, NAT
2	F	32	SPMS	7	12	ITMTX, RTX
3	M	64	SPMS	4	14	ITMTX, GA
4	M	35	SPMS	5	13	NAT
5	F	33	SPMS	6.5	20	ITMTX
6	F	62	SPMS	6.5	32	ITMTX, RTX
7	F	26	SPMS	5	10	RTX, NAT
8	F	54	SPMS	6	18	ITMTX, NAT
9	F	37	SPMS	6	16	NAT
10	F	36	PPMS	6.5	14	ITMTX, NAT
11	F	48	SPMS	6	19	ITMTX, RTX, NAT
12	F	60	SPMS	7	32	NAT, CP
13	F	44	SPMS	5.5	11	ITMTX, RTX
14	M	48	PPMS	7	10	ITMTX, CC
15	M	55	PPMS	6.5	22	βIFN-Av, MITO, IVIG
16	M	44	SPMS	7	20	ITMTX
17	F	52	SPMS	4.5	13	NAT
18	M	56	SPMS	4.5	17	βIFN-Av
19	M	57	SPMS	3.5	18	ITMTX, CP
20	F	50	SPMS	7.5	32	ITMTX, NAT, FINGO

SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis
ITMTX, intrathecal methotrexate; RTX, rituximab; CC, Cellcept; NAT, Natalizumab; CP, cyclophosphamide; β-IFN-Av, beta interferon (Avonex); MITO, mitxantrone; FINGO, fingolimod; GA, glatiramir acetate; IVIG, intravenous immunoglogulins

Table 3. Preliminary outcomes of 1st study subject

Summary: Subject #1 received initial IT dose of autologous MSC-NPs in April 2014	
Baseline screening	MRI, neurological exam, evoked potentials, urodynamics testing, blood work, informed consent.
Bone marrow-derived MSCs	MSCs expanded and tested for growth, adipogenic and osteogenic differentiation, cell surface marker expression, and gene expression. Multiple aliquots banked.
MSC-NP dose	MSC-NPs were expanded and passed product release and sterility testing. **10 million MSC-NPs were injected IT.**
Follow up visits	1 day, 1 week, and 1 month follow up visits post dose. 2 month follow up MRI showed no change.
Adverse events	None

CONCLUSIONS

The MSC-NP trial is the first of its kind to test intrathecal administration of neural progenitors as a regenerative therapy for MS and its results will determine the design of future trials.

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