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Research Paper

Phase I Trial of Intrathecal Mesenchymal Stem Cell-derived Neural Progenitors in Progressive Multiple Sclerosis

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ABSTRACT

Background: Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system and is one of the leading causes of disability in young adults. Cell therapy is emerging as a therapeutic strategy to promote repair and regeneration in patients with disability associated with progressive MS.
Methods: We conducted a phase I open-label clinical trial investigating the safety and tolerability of autologous bone marrow mesenchymal stem cell-derived neural progenitor (MSC-NP) treatment in 20 patients with progressive MS. MSC-NPs were administered intrathecally (IT) in three separate doses of up to 1×10^7 cells per dose, spaced three months apart. The primary endpoint was to assess safety and tolerability of the treatment. Expanded disability status scale (EDSS), timed 25-ft walk (T25FW), muscle strength, and urodynamic testing were used to evaluate treatment response. This trial is registered with ClinicalTrials.gov, number NCT01933802.
Findings: IT MSC-NP treatment was safe and well tolerated. The 20 enrolled subjects completed all 60 planned treatments without serious adverse effects. Minor adverse events included transient fever and mild headaches usually resolving in <24 h. Post-treatment disability score analysis demonstrated improved median EDSS suggesting possible efficacy. Positive trends were more frequently observed in the subset of SPMS patients and in ambulatory subjects (EDSS ≤ 6.5). In addition, 70% and 50% of the subjects demonstrated improved muscle strength and bladder function, respectively, following IT MSC-NP treatment.
Interpretation: The possible reversal of disability that was observed in a subset of patients warrants a larger phase II placebo-controlled study to establish efficacy of IT MSC-NP treatment in patients with MS.
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1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS). Although the cause of the MS is unknown, the disease is characterized pathologically by early acute lesions made up of discrete areas of inflammatory demyelination that either resolve by remyelination or evolve into chronic lesions with associated axonal loss, oligodendroglial cell loss and glial scarring. Lesions of inflammatory demyelination may be visualized by MRI imaging of the CNS. Clinically, most patients have disease onset in young adulthood with characteristic symptom relapses and remissions (RRMS). Over time, RRMS may evolve to a secondary progressive (SPMS) phase with accrual of permanent disability. In about 10–15% of patients the disease course is primarily progressive from onset (PPMS). Available disease modifying therapies may prevent or delay disease progression through immunosuppression and immunomodulation (Comi et al., 2017). Once progressive disability is established, however, there are no therapies currently available to protect, repair, or regenerate neural tissue in order to restore neurological function (Ontaneda et al., 2017). Common clinical manifestations of patients with SPMS or PPMS include motor weakness with progressive paralysis, sensory dysfunction, bladder/bowel dysfunction, coordination difficulties and cognitive decline. Cell-based therapies are currently under investigation to alleviate some of these clinical symptoms as a strategy to target progressive decline, which remains a major unmet need in MS.

Mesenchymal stem cells (MSCs) extracted from various tissues including bone marrow have multipotent mesodermal differentiation potential, but more importantly have demonstrated ability to promote tissue repair through the release of paracrine factors (Meirelles Lda et al., 2009). Intravenous administration of MSCs or conditioned media derived from MSCs is protective against experimental autoimmune encephalomyelitis (EAE) in mice through immunomodulatory mechanisms (Bai et al., 2012; Payne et al., 2013; Rafei et al., 2009; Rajan et al., 2016; Zappia et al., 2005), thus forming the preclinical basis for

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clinical safety testing of intravenous (Cohen et al., 2017; Connick et al., 2012; Llufriu et al., 2014) or intrathecal (Karussis et al., 2010; Mohyeddin Bonab et al., 2007; Yamout et al., 2010) transplantation of autologous MSCs in patients with MS. MSCs are also capable of neuroprotection, promotion of oligodendrogenesis, and inhibition of gliosis, and thus may impact multiple aspects of MS pathology in the CNS (Chen et al., 2001; Li et al., 2005; Rivera et al., 2006; Shen et al., 2011; Steffenhagen et al., 2012; Zhang et al., 2006).

MSC-derived neural progenitors (MSC-NPs) are a subpopulation of MSCs that exhibit neuroectodermal lineage characteristics with reduced capacity to undergo mesodermal differentiation (Fu et al., 2008; Harris et al., 2012a; Harris et al., 2012b; Hermann et al., 2004; Mareschi et al., 2006). These properties are theorized to minimize the risk of ectopic differentiation after CNS transplantation (Grigoriadis et al., 2011). Similar to MSCs MSC-NPs exhibit immunoregulatory and trophic properties both in vitro and in vivo along with upregulation of candidate trophic factors including hepatocyte growth factor (HGF) (Harris et al., 2012b; Harris et al., 2012a; Cristofanilli et al., 2011). Intrathecal (IT) delivery of MSC-NPs during the chronic phase of EAE resulted in neurological recovery associated with increased spinal cord myelination decreased immune infiltration in the CNS and increased recruitment of endogenous progenitor cells (Harris et al., 2012b). Importantly multiple doses rather than a single dose were necessary to demonstrate improvement in neurological function (Harris et al., 2012b)

The clinical feasibility of IT MSC-NP treatment in MS was initially investigated in six patients with advanced MS treated with two to five injections of escalating doses of autologous MSC-NPs (Harris et al., 2016). Patients were followed an average of 7.4 years after initial injection. There were no serious adverse events or safety concerns noted, and the treatments were well-tolerated (Harris et al., 2016). Four of the six patients showed a measurable clinical improvement following MSC-NP treatment. Based on these pre-clinical and early clinical studies, we initiated an open-label phase I trial using IT autologous MSC-NPs to establish safety and tolerability and to determine efficacy trends in 20 patients with progressive MS. The outcomes of this study support the overall safety and tolerability of this therapeutic approach, in addition to revealing possible evidence of efficacy.

2. Methods

2.1. Study Design and Oversight

The study was an open-label, single-arm, phase I clinical trial to evaluate safety and tolerability of repeated IT administration of autologous MSC-NPs in 20 patients with progressive MS (Fig. 1). All study activities were conducted at the Tisch MS Research Center of New York. The study was conducted as an FDA investigational new drug, and is registered with ClinicalTrials.gov, number NCT01933802. The study was approved by Western Institutional Review Board and was conducted in accordance with the Helsinki Declaration. All patients gave written informed consent. An independent external data and safety monitoring board evaluated all safety data.

The treatment phase of the study consisted of three separate IT injections of up to 1×10^7 autologous MSC-NPs spaced three months apart. The dose and dosing schedule were based on a preclinical study in mouse EAE, as well as observed safety and tolerability in an early clinical dose escalation study (Harris et al., 2016; Harris et al., 2012b). All patients were assessed on the day of treatment, and one day, one week,

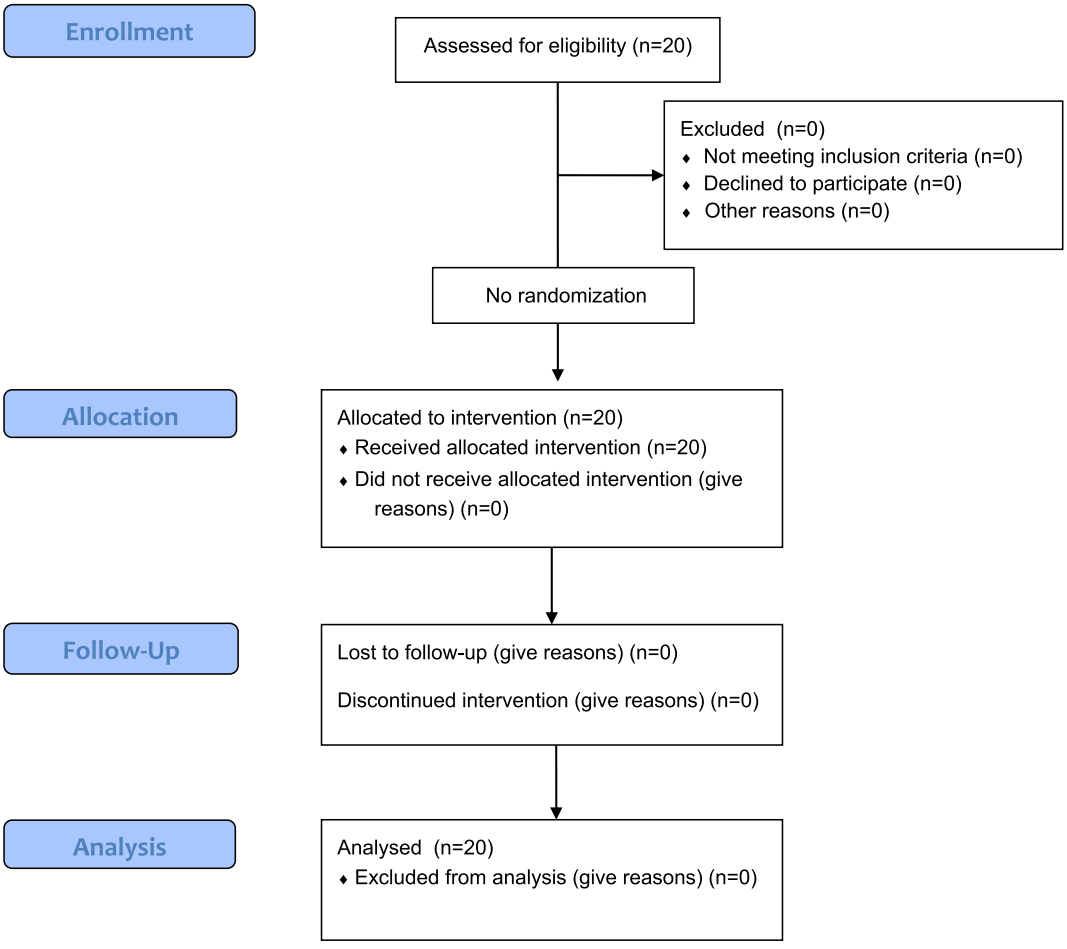

Fig. 1. CONSORT flowchart for single-arm, open-label, phase 1 clinical trial of intrathecal autologous MSC-NP in patients with progressive MS.

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