Commentary

Mesenchymal Stem Cell-derived Neural Progenitor Cells in Progressive Multiple Sclerosis: Great Expectations

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Despite advances in treatment of relapsing multiple sclerosis (MS) with approval of over a dozen disease modifying therapies (DMTs), there is an unmet need for effective treatment of progressive disease. Cell based therapeutic strategies have generated great interest in this regard (Scolding et al., 2017). While hematopoietic stem cell transplantion has demonstrated the most benefit in patients with highly active inflammatory disease (Nash et al., 2017), mesenchymal stem cells (MSCs) are hypothesized to have a wide range of neuroprotective and repair-promoting functions, which may be more relevant to treatment of progressive MS (Cohen, 2013).

MSCs are pluripotent, non-hematopoietic precursor cells that can be isolated from various tissues, including bone marrow and adipose, and culture-expanded to purity. MSC transplantation is being explored in a wide range of tissue injury conditions (Scolding et al., 2017; Cohen, 2013; Korbling and Estrov, 2003). Several studies involving experimental autoimmune encephalomyelitis (EAE) models demonstrated that beneficial effects of MSCs may be exerted by their secretome (Rajan et al., 2016; Zhang et al., 2005). Over a dozen small clinical trials of MSCs in MS indicate overall safety and tolerability, with some support of benefit on clinical and MRI measures of disease activity and/or tissue integrity (Scolding et al., 2017).

In a recent article published in EBioMedicine, Harris and colleagues report results of an open-label, single-arm phase I clinical trial of autologous mesenchymal stem cell-derived neural progenitor cells (MSC-NPs) administered by intrathecal (IT) injection in 20 patients with progressive multiple sclerosis (Harris et al., 2018). Patients with Expanded Disability Status Scale (EDSS) score ≥ 3.0 and either primary or secondary progressive MS underwent three IT injections of MSC-NPs three months apart. MSCs were isolated, culture-expanded, cryopreserved, and thawed, then again culture-expanded in NP maintenance medium to generate MSC-NPs (Harris et al., 2012a). The results indicated that IT administration of MSC-NPs was generally safe and well-tolerated, although most patients experienced transient fever (9 of 60 injections [15%]) or headache (43 of 60 injections [72%]) following injections.

Clinical assessments, brain MRI, and urodynamic testing were performed to assess safety and as exploratory efficacy outcomes. The authors reported improvement in 15 subjects in several clinical parameters, including EDSS, Medical Research Council (MRC) muscle strength testing, timed 25-foot walk, and bladder symptoms. Two patients exhibited ongoing worsening, and three had no change in neurological status. Even though the pre- to post-treatment difference in median EDSS was not statistically significant, some patients exhibited substantial improvement. Eight patients had at least a 0.5-point improvement in EDSS at study completion, with 4 of these 8 having improvement of 2 points or more. The authors suggest that benefit was greater in patients ambulatory at baseline. Additionally, urodynamic assessments indicated at least 20% improvement in bladder capacity in 4 of 18 subjects at 3 month follow-up.

This study is of interest in terms of the cell product. Thawed cells were partially differentiated into an NP-like phenotype via treatment with epidermal and basic fibroblast growth factors (GF) to increase secretion of hepatocyte GF, gliad derived neurotrophic factor, insulin-like GF, and leukemia inhibitory factor (Harris et al., 2018).
Whether this increased neurotrophic factor production contributes to efficacy in humans, as demonstrated in prior EAE studies, will require confirmation (Harris et al., 2012a). Additionally, thawing several weeks prior to administration, with further culture expansion and differentiation, may circumvent known issues with MSC disruption following cryopreservation and thawing by allowing cells to recover (Scolding et al., 2017; Francois et al., 2012; Harris et al., 2012b). Other key aspects include IT administration and use of multiple doses of MSC-NPs.

As this was an open-label, uncontrolled study, caution is needed when interpreting the reported efficacy. The general public’s enthusiasm regarding stem cells is substantial, which further increases the need for appropriate, controlled clinical trial design to avoid confounding and expectation effects. Efficacy measures evaluated, including EDSS, MRC muscle strength, and bladder symptoms, depend on somewhat subjective assessments and can be effort-dependent. Urodynamic testing provided objective evidence of therapeutic effect. Standard MRI lacks pathologic specificity for demyelination and remyelination. Therefore, it is not surprising that the MRI measures employed in this study did not demonstrate benefit.

These results plus those of other studies are encouraging and justify larger, controlled studies of MSC transplantation in MS. An important caveat, however, is that several unanswered questions remain, including the optimal route of administration, dose, dosing interval, and cell culture protocol to maximize cell yield and potency, as well as cryopreservation/thawing procedures to preserve the desired biological characteristics of the cell product (Scolding et al., 2017). Such practical considerations should be addressed in future studies. The mechanism of action of MSCs, particularly that of MSC-NPs, also is uncertain. Further work is needed to delineate and optimize the effects of the MSC secretome that result in the beneficial effects demonstrated in in vitro and in animal models. Given the methodological complexities of cell administration, administration of the secretome or purified constituents may be more practical.

Disclosure of Interest

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