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The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group

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Abstract

Current therapies for multiple sclerosis effectively reduce inflammation, but do little in terms of repair to the damaged central nervous system. Cell-based therapies may provide a new strategy for bolstering regeneration and repair through neuro-axonal protection or remyelination. Mesenchymal stem cells modulate pathological responses in experimental autoimmune encephalitis, alleviating disease, but also stimulate repair of the central nervous system through the release of soluble factors. Autologous and allogeneic mesenchymal stem cells have been safely administered to individuals with hemato-oncological diseases and in a limited number of patients with multiple sclerosis. It is therefore reasonable to move mesenchymal stem cells transplantation into properly controlled human studies to explore their potential as a treatment for multiple sclerosis. Since it is likely that the first such studies will probably involve only small numbers of patients in a few centers, we formed an international panel comprising multiple sclerosis neurology and stem cell experts, as well as immunologists. The aims were to derive a consensus on the utilization of mesenchymal stem cells for the treatment of multiple sclerosis, along with protocols for the culture of the cells and the treatment of patients. This article reviews the consensus derived from our group on the rationale for mesenchymal stem cell transplantation, the methodology for generating mesenchymal stem cells and the first treatment protocol for multiple sclerosis patients.

Keywords

multiple sclerosis, disease modifying therapies, mesenchymal stem cell, consensus

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Introduction

There is considerable interest in the use of cell-based therapies as a potentially useful treatment modality for a variety of chronic diseases, including multiple sclerosis (MS). The attraction seems to be an almost hopeful sense that cells will go beyond where regular immunomodulatory or immunosuppressive therapies stop, in directing the repair of central nervous system (CNS) damage. Though embryonic stem cells can be differentiated into neural cells via in vitro stimulation and manipulation, their safety in human treatment has not been established. However, adult stem cells such as mesenchymal stem cells (MSC) and neural precursor cells have been proposed as possible treatments for MS due to their therapeutic plasticity.[1–4] MSC are a heterogeneous population of stromal cells isolated from

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multiple species, residing in most connective tissues including bone marrow, adipose tissue, umbilical cord blood and perivascular tissues. MSC can differentiate into cells of the mesenchymal lineage, such as bone, cartilage and fat but, under certain circumstances, have been reported to acquire the phenotype of cells of the endodermal and neuroectodermal lineage, suggesting some potential for 'transdifferentiation'. Within the bone marrow they are tightly intermingled with and support hematopoiesis and the survival of hematopoietic stem cells in a quiescent state.[5] In addition, MSC derived from the bone marrow have unique properties after expansion in culture such that they can modulate innate and adaptive immunity.[6] Further, MSC migrate to sites of inflammation and protect damaged tissues, including the CNS, properties that supported their use as a new immunosuppressive strategy for immune-mediated diseases including autoimmunity and possibly could spare patients from the ravages of chemotherapy or other immunosuppressants.[1] These features in particular of MSC merited their use to control life-threatening graft-versus-host-disease (GvHD) in allogeneic bone marrow transplant recipients, helping to lower transplant-related mortality associated with donor cell immune-mediated recipient organ injury.[7] It therefore follows logically that a panel of clinician and stem cells experts, interested to test this immunomodulatory property of MSC to control autoimmune diseases, such as MS, decided to meet in Paris on 11–12 March 2009, forming the 'International MSCT Study Group' with the aim of sharing the scientific evidence regarding MSC and derive a consensus on their possible use for MS.

Mesenchymal stem cells for clinical use

Ex vivo-expanded MSC have been brought to the clinical therapeutic level for several purposes: to repair damaged tissues,[8] to produce enzymes missing in patients with metabolic disorders,[9] to promote hematopoietic engraftment after autologous[10] and allogeneic stem cell transplantation and for immunosuppression in GvHD[7,11] or autoimmune disorders. The first recipients of culture-expanded MSC were given autologous cells as a safety trial.[12] To date, several hundreds of patients have received MSC infusions and no untoward effects have been reported.

As MSC are rare cells in the post-natal body, ex vivo expansion is required to generate a sufficient number of cells for clinical treatment. Despite several protocols utilized for ex vivo expansion, it is rare to attain more than $1–2 \times 10^6$ MSC/kg weight in adults. This potentially limits achieving the higher and possibly more effective therapeutic doses suggested by animal experiments. In an attempt to facilitate international multicenter trials, a group of centers organized in the Developmental Committee of the European Group for Blood and Marrow Transplantation (EBMT) adopted a common bone marrow MSC expansion protocol. The EBMT–MSC expansion consortium provides a standardized protocol for expansion of clinical grade MSC, including Standard Operating Procedures and guidelines for the phenotypic characterization of the cells and release criteria for the cell batch. Harmonized production and phenotypic characterization of the cells allows collaborative trials using cells generated under similar conditions in several academic centers. Several such studies are underway, evaluating the efficacy of MSC in prevention and treatment of GvHD and for promotion of engraftment and prevention of graft rejection in haploidentical and cord blood transplants.

The majority of clinical infusions given have used cells isolated by adherence to plastic and expanded in vitro in the presence of 10% fetal calf serum (FCS). Intravenous (IV) infusion of such cells has so far been safe, without major toxic side effects.[10,11,13,14] Batch-to-batch differences and the banning of animal protein in the culture medium in some European countries, however, has led researchers to seek an alternative culture protocol; replacing FCS with platelet lysates, serum-free media or autologous serum have all been suggested. However, the clinical experience using MSC generated by alternative methods is still limited, and it remains unclear whether such cells retain the in vivo properties ascribed to FCS-MSC. Malignant transformation upon culture has been described for mouse but not human MSC, but the risk still remains a concern.[15] As a safety measure, minimal expansion may still be recommended.

The rationale for MSC transplantation in MS

The rationale for the use of MSC in the treatment of MS comes from preclinical studies in the commonly used animal model of MS, experimental autoimmune encephalomyelitis (EAE), demonstrating that IV-infused MSC could improve the clinical course and pathology scores of EAE induced with myelin oligodendrocyte glycoprotein; the proposed mechanism was through the induction of peripheral immune tolerance.[16] IV administration of human-derived MSC also improved disease in a proteolipid protein-induced EAE model in SJL mice, an effect that was attributed to the endogenous production of neurotrophins.[17] Further studies confirmed that MSC can also inhibit pathogenic B-cell responses such as the production of myelin-specific antibodies.[18] Many other groups have now confirmed that MSC are endowed with a striking therapeutic effect in different EAE models when

injected IV,[19,20] intraventricularly,[21] and even intra-peritoneally.[22] Interestingly, in the latter study MSC exerted their therapeutic effect via the paracrine conversion by metalloproteinases of CCL2 from agonist to antagonist of pathogenic T cell functions.[22] A common finding in most of these studies was the very limited number of injected MSC that seemed to make their way to the inflamed CNS, with little evidence that trans-differentiation into neural cells was taking place.[18–20,22] However, in another study, a limited number of intraventricularly injected MSC acquired the phenotype of neural cells at immunostaining[21].

Regardless of the possible occurrence of some level of trans-differentiation, it is clear that the early beneficial effect observed in EAE following MSC transplantation (MSCT) is mainly due to their immunomodulatory and other therapeutic properties. Indeed, MSC can protect axons and improve neuronal survival,[18,21,23] possibly via anti-apoptotic effects,[24] anti-oxidant effects,[25] or the release of trophic factors.[26] Other intriguing experiments show that MSC can induce endogenous neurogenesis[27] and oligodendrogenesis.[19,28,29] These preclinical animal studies together indicate that MSC are bestowed with several characteristics that offer therapeutic benefits in vivo in EAE, and therefore possibly in MS, through immunomodulatory mechanisms, and also through promoting cell growth and differentiation chiefly mediated by the release of soluble molecules in a 'bystander' fashion.[6] On the other hand, controversy surrounds whether MSC, which have shown the capability for in vitro differentiation into various specialized organ-specific cells, will do so in vivo.[30] It is more likely that any 'repair' function is still mediated by incumbent cells, as was suggested by experiments in which remyelination and reduction of astrogliosis was observed after MSC injection.[19]

MSC transplantation preliminary clinical experience in MS

Reports have started to emerge of small numbers of patients with MS who received IV or intrathecal (IT) infusions of MSC cells with some purported benefit.[2] The preliminary results of an early phase I/II study of MSCT in neurological diseases reported on administration of autologous MSC to 19 amyotrophic lateral sclerosis and 15 MS patients. MSC were given as a combination of IT and IV injections, at doses up to $60–70 \times 10^6$ cells per injection per patient, Patients were followed for 6–28 months for the main purpose of determining feasibility and safety. No patient experienced significant side effects except for those of mild meningeal irritation, such as headache and fever, in those receiving IT injections of cells. Magnetic resonance imaging (MRI) in 20 of the patients did not reveal any unexpected pathology 1 year following MSCT. No injection-related (early or late) infections were reported. The only additional data available on the use of MSC in MS include a small study in 10 patients with MS from Iran, which reported no significant adverse events.[31] To date, it is not known whether MSC injected IT have any advantage over IV administration. While IT administration may introduce a greater number of cells into the areas of tissue inflammation and damage, experimental results to date suggest that IV injection suffices to obtain significant inhibition of the pathogenic immune-mediated injury process as well as neuroprotection and tissue repair through the different paracrine mechanisms reported in pre-clinical studies.[16–20,22] Despite this controversy regarding route of administration, these preliminary safety data are in line with those obtained in hemato-oncological disorders and confirm that MSC can be considered a relatively safe treatment for life-threatening and severe diseases. However, there have been no carefully controlled studies to date examining clinical and scientific outcomes in MS with any sort of rigor.[4]

The weight of reviewed evidence from pre-clinical and clinical studies of MSCT supports the expectation that MSC could modulate the immune responses that correlate with inflammatory disease activity in MS. It would therefore make the most sense to transition into clinical MS trials with a focus on confirming whether or not this treatment is capable of reducing inflammatory MS disease activity. Equally important would be to understand the mechanisms by which this occurs and to explore the possibility that MSCT may also contribute to repair. It was acknowledged that although the greatest hope for MSCT was to repair damaged tissue, as with other stem cell-based therapeutic strategies, we also have no clear way of measuring changes that are compatible with repair outside of functional improvement. With the primary goal of demonstrating that MSCT will control MS inflammatory disease activity, we set out to devise a clinical trial strategy.

New perspective for the exploitation of MSC in MS: an international consensus

Given their unique 'homing' properties, established safety of IV infusion and their potential ability to regulate immune responses and promote localized 'repair', it is not surprising that many researchers are looking to MSCT as a less toxic (compared with bone marrow transplantation(BMT) and more 'natural' (in harnessing the body's own innate mechanisms) therapeutic approach to the treatment of autoimmune diseases including MS.[32] This is reminiscent, however, of the ongoing attempts to prove that autologous hematopoietic stem cell transplantation (AHSCT) is an effective way

of treating aggressive MS, where many groups around the world have established their own interpretation of efficacy based on patient choice and regimens that all differ.[33] As a consequence, a compilation of many small, mostly uncontrolled studies has been carried out, making it difficult to determine whether or not BMT is truly effective. Only recently were there attempts at randomized, controlled studies of BMT in MS, but these have faltered in being unable to recruit patients both in the USA and Western Europe. To avoid the same fate for MSCT in MS, we have formed the 'International MSCT Study Group' to share the evidence to date regarding MSCT in MS, derive a consensus on what cells should be used for transplantation and develop a treatment protocol and experimental program that will eventually attest to the efficacy of MSCT and understand the mechanisms that underlie that benefit.

To form the nidus for an international study group, two of us (MSF and AU) contacted colleagues around the world that we knew were either involved in MSC research or who have expressed intent on doing so, and invited them to a 1-day meeting in order to arrive at a consensus on the type of cells to be used and the types of MS patients to study. We included neurologists with expertise in MS, neuroimmunologists who have experience in disease and therapeutic mechanistic studies, and hematologists with experience in the study and use of MSC. Not all colleagues invited were able to attend. This paper reflects the views only of those that were in attendance at the meeting in Paris, France, on 12 March 2009. Funds were acquired from the MS Society of Canada, the Consortium of Multiple Sclerosis Centers and the ECTRIMS foundation to support the travel and logistics of this meeting.

The arrived-at consensus was to move forward with small clinical trials that involved the agreed-upon preparation and dosage of autologous MSC, and commence with phase I-II safety and 'proof of principle' studies examining the response to a single infusion. Given the complexity of these patients, we felt that individual sites could be capable of treating up to 30 patients. The focus would be on patients continuing to show inflammatory activity despite attempts to treat with immunomodulatory medications. Given that such patients may be treatable with a growing number of existing and newly approved agents and there would be ethical concerns regarding a 'non-treatment' paradigm, we felt that the longest a patient should go without treatment is 6 months. The initial 6 months should suffice in order to demonstrate, using sensitive MRI metrics, that MSCT is capable of reducing focal inflammatory activity similar to what has been demonstrated for AHSCT.[34] The delayed paradigm will ensure that all patients do get MSCT either at baseline or after 6 months while the media (non-cellular therapy) group will serve as control. All selected patients would undergo a MSC harvest and cells prepared as per protocol. They would then be randomized to receive an infusion of cryopreserved autologous MSC or control (suspension media) and followed for 6 months, whereupon all media-treated patients would receive their previously cryopreserved MSC and both groups followed for up to 1 year. The primary endpoint would be the difference in MRI activity between initially treated group with MSC versus 'sham' or media-treated patients at 6 months, and secondarily to examine the effect on these 'early' versus 'delayed' treated patients at 1 year. With this design, we could assess not only the efficacy of treatment versus placebo, but also examine the duration of a single infusion (the originally treated group). Thus all patients would receive MSCT. Further study details are as follows.

Study design

The design would be a randomized double-blind semi-'crossover' study comparing treatment with autologous MSC versus suspension media on patients with new MRI activity at 6 months. The main secondary outcome will compare the 'early' versus 'delayed' treatment at 12 months on both MRI and clinical outcomes.

Inclusion criteria

1. Inflammatory forms of MS
   a. Relapsing-remitting MS patients
   b. Secondary progressive MS (SPMS) patients with continued relapses
   c. Primary progressive MS (PPMS) patients with Gadolinium (Gd)-enhancing MRI lesions and positive cerebrospinal fluid (CSF) (oligoclonal banding)
      (i) About 20% of PPMS patients will have enhancing lesions, especially if triple-dose Gadolinium is used
2. Age 18–50 years
3. Disease duration $\geq$2 and $\leq$10 years
4. Expanded disability status scale (EDSS) 3.0–6.5
5. Progression, continued relapses or worsening MRI after at least a year of attempted therapy as evidenced by one or more of the following:
   a. Increase of $\geq$1 EDSS point (if baseline EDSS $\leq$ 5.0) or 0.5 EDSS points (if baseline EDSS $\geq$5.5), or quantifiable, objective evidence of equivalent progression
   b. $\geq$1 moderate-severe relapses in past 18 months
   c. $\geq$1 Gadolinium enhancing lesions (double or triple dose Gd)
   d. $\geq$1 new T2 lesion
   e. For PPMS only, $\geq$1 Gd-enhancing lesions

6. Evidence of recent inflammatory disease, as evidenced by any one of the following:
   a. ≥1 moderate-severe relapses in past 18 months
   b. ≥1 Gd-enhancing lesions (single, double or triple dose Gd)
   c. ≥1 new T2 lesion
   d. For PPMS only, ≥1 Gd-enhancing lesions

Exclusion criteria

1. SPMS without ongoing relapses
2. PPMS without positive CSF or Gd-enhancing lesions
3. ≤3 months since treatment with any immunosuppressive therapy
4. ≤1 month since last treatment with interferon-β or glatiramer acetate
5. Corticosteroid treatment ≤30 days
6. Relapse ≤60 days

Mesenchymal stem cell product

1. Cryopreserved autologous MSC, ex vivo-expanded preferably no later than the third passage in culture, at the dose of $1–2 \times 10^6$ MSC/kg weight for a single IV infusion or the equivalent suspension media (control)
2. Autologous MSC will undergo quality control before release/administration including phenotype, karyotype, mutagenesis test and microbiological analysis
   a. Excess cells should be preserved for a safety 'back-up', immunology and exploratory studies

Treatment outcomes

1. The primary outcome will be safety
2. The second co-primary outcome measure would be the reduction in the number and volume of new enhancing lesions over 6 months in the MSC versus media-treated patients
3. Secondary outcomes between the 'early' versus the 'delayed' treated groups at 12 months include:
   a. Combined unique MRI activity (new or enlarging T2, or enhancing or re-enhancing lesions)
   b. EDSS or functional subscore changes
   c. Relapses
      (i) Number
      (ii) Proportion relapse-free
   d. Disease-free patients (no relapse, progression or MRI activity)
4. Exploratory Outcomes
   a. Optical Coherence Tomography
   b. Evoked potentials
   c. Other MRI outcomes
   d. Other clinical outcomes
   e. Biological 'proof of principel studies' addressing the effect of MSCT on immune responses

Study protocol

All acceptable patients will be randomized to receive immediate versus delayed treatment with either autologous MSC or equivalent volume of suspension media at baseline. At 6 months, patients and investigators will continue to be blinded to therapy, but treatments will be reversed (i.e. those who received initial MSC will receive suspension media and vice versa). One pre-baseline MRI scan will be performed at baseline minus 2 months, then again, as a minimum, at baseline, 1, 3, 6 and 12 months. A separate neurologist blinded from the treating physician should conduct neurological assessments. Any sustained EDSS progression or moderate-severe relapse occurring within the first 6 months would trigger a potential 'escape' from the protocol.

Of equal importance to the clinical outcome of this study are the results of mechanistic studies that would be performed to understand how this treatment might be working in humans and to gain insight on whether indeed there are signs of 'repair'. Consensus was clearly obtained on these and all aspects of this protocol.

We hope that other researchers who are interested in pursuing MSCT as a potential treatment for MS will join in, following this consensus protocol and sharing data in future meetings of the study group. By combining the results of many small study groups using the same cell product, monitoring protocol, mechanistic studies and outcome measures, we should be able to jointly establish the safety and efficacy of MSCT in MS. Future questions we need to address include the need for more cell infusions, the duration effect of a single infusion, whether MSC derived after a treatment are any different than those before treatment, and whether exploratory studies looking for signals of repair warrant further trials of 'repair' versus 'anti-inflammatory' paradigms.

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