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Multiple Sclerosis

1. Stem cell transplantation and mesenchymal cells to treat autoimmune diseases
Alan Tyndall, Jacob M. van Laar
La Presse Medicale 2016

Since the start of the international stem cell transplantation project in 1997, over 2000 patients have received a haematopoietic stem cell transplant (HSCT), mostly autologous, as treatment for a severe autoimmune disease, the majority being multiple sclerosis (MS), systemic sclerosis (SSc) and Crohn's disease. There was an overall 85% 5-year survival and 43% progression-free survival. Around 30% of patients in all disease subgroups had a complete response, often durable despite full immune reconstitution. In many cases, e.g. systemic sclerosis, morphological improvement such as reduction of skin collagen and normalization of microvasculature was documented, beyond any predicted known effects of intense immunosuppression alone. It is hoped that the results of the three running large prospective randomized controlled trials will allow modification of the protocols to reduce the high transplant-related mortality which relates to regimen intensity, age of patient, and comorbidity. Mesenchymal stromal cells (MSC), often incorrectly called stem cells, have been the intense focus of *in vitro* studies and animal models of rheumatic and other diseases over more than a decade. Despite multiple plausible mechanisms of action and a plethora of positive *in vivo* animal studies, few randomised controlled clinical trials have demonstrated meaningful clinical benefit in any condition so far. This could be due to confusion in cell product terminology, complexity of clinical study design and execution or agreement on meaningful outcome measures. Within the rheumatic diseases, SLE and rheumatoid arthritis (RA) have received most attention. Uncontrolled multiple trial data from over 300 SLE patients have been published from one centre suggesting a positive outcome; one single centre comparative study in 172 RA was positive. In addition, small numbers of patients with Crohn's disease, multiple sclerosis, primary Sjögren's disease, polymyositis/dermatomyositis and type II diabetes mellitus have received MSC therapeutically. The possible reasons for this apparent mismatch between expectation and clinical reality will be discussed.

2. The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group
Mark S Freedman, Amit Bar-Or, Harold L Atkins, Dimitrios Karussis, Francesco Frassoni, Hillard Lazarus, Neil Scolding, Shimon Slavin, Katarina Le Blanc, Antonio Uccelli
Multiple Sclerosis Journal 2012

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.

3. Mesenchymal Stem Cells as Treatment for MS – Progress to Date
Antonio Uccelli, Alice Laroni, and Mark S Freedman
Multiple Sclerosis Journal 2012

The unmet need for therapies capable of repairing the central nervous system (CNS) damage occurring in many diseases including multiple sclerosis (MS) has sparked the interest of the neurological community for stem cell-based therapies. An exhaustive amount of preclinical data has shown that the intravenous administration of mesenchymal stem cells (MSC), a subset of progenitor cells isolated from many mesodermal tissues, effectively ameliorates experimental autoimmune encephalomyelitis (EAE), a model of MS, through the release of anti-inflammatory and neuroprotective molecules. Based on these results, several small pilot clinical trials in subjects with advanced MS have demonstrated that MSC administration is safe and provided an early signal of clinical effectiveness. The current aim of clinicians and scientists interested in the development of MSC-based strategies for the treatment of MS is to have the ultimate demonstration in large clinical trials that MSC can inhibit CNS inflammation and foster tissue repair as realized clinically, with functional recovery, or visualized by magnetic resonance imaging (MRI).

4. Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke
Osamu Honmou, Kiyohiro Houkin, Takuya Matsunaga, Yoshiro Niitsu, Sumio Ishiai, Rie Onodera, Stephen G. Waxman and Jeffery D. Kocsis
Brain 2011

Transplantation of human mesenchymal stem cells has been shown to reduce infarct size and improve functional outcome in animal models of stroke. Here, we report a study designed to assess feasibility and safety of transplantation of autologous human mesenchymal stem cells expanded in autologous human serum in stroke patients. We report an unblinded study on 12 patients with ischaemic grey matter, white matter and mixed lesions, in contrast to a prior study on autologous mesenchymal stem cells expanded in foetal calf serum that focused on grey matter lesions. Cells cultured in human serum expanded more rapidly than in foetal calf serum, reducing cell preparation time and risk of transmissible disorders such as bovine spongiform encephalomyelitis. Autologous mesenchymal stem cells were delivered intravenously 36-133 days post-stroke. All patients had magnetic resonance angiography to identify vascular lesions,

and magnetic resonance imaging prior to cell infusion and at intervals up to 1 year after. Magnetic resonance perfusion-imaging and 3D-tractography were carried out in some patients. Neurological status was scored using the National Institutes of Health Stroke Scale and modified Rankin scores. We did not observe any central nervous system tumours, abnormal cell growths or neurological deterioration, and there was no evidence for venous thromboembolism, systemic malignancy or systemic infection in any of the patients following stem cell infusion. The median daily rate of National Institutes of Health Stroke Scale change was 0.36 during the first week post-infusion, compared with a median daily rate of change of 0.04 from the first day of testing to immediately before infusion. Daily rates of change in National Institutes of Health Stroke Scale scores during longer post-infusion intervals that more closely matched the interval between initial scoring and cell infusion also showed an increase following cell infusion. Mean lesion volume as assessed by magnetic resonance imaging was reduced by >20% at 1 week post-cell infusion. While we would emphasize that the current study was unblinded, did not assess overall function or relative functional importance of different types of deficits, and does not exclude placebo effects or a contribution of recovery as a result of the natural history of stroke, our observations provide evidence supporting the feasibility and safety of delivery of a relatively large dose of autologous mesenchymal human stem cells, cultured in autologous human serum, into human subjects with stroke and support the need for additional blinded, placebo-controlled studies on autologous mesenchymal human stem cell infusion in stroke.

5. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study

Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, Du MQ, Luan SL, Altmann DR, Thompson AJ, Compston A, Scott MA, Miller DH, Chandran S.
Lancet Neurology 2012

BACKGROUND:
More than half of patients with multiple sclerosis have progressive disease characterised by accumulating disability. The absence of treatments for progressive multiple sclerosis represents a major unmet clinical need. On the basis of evidence that mesenchymal stem cells have a beneficial effect in acute and chronic animal models of multiple sclerosis, we aimed to assess the safety and efficacy of these cells as a potential neuroprotective treatment for secondary progressive multiple sclerosis.
METHODS:
Patients with secondary progressive multiple sclerosis involving the visual pathways (expanded disability status score 5·5-6·5) were recruited from the East Anglia and north London regions of the UK. Participants received intravenous infusion of autologous bone-marrow-derived mesenchymal stem cells in this open-label study. Our primary objective was to assess feasibility and safety; we compared adverse events from up to 20 months before treatment until up to 10 months after the infusion. As a secondary objective, we chose efficacy outcomes to assess the anterior visual pathway as a model of wider disease. Masked endpoint analyses was used for electrophysiological and selected imaging outcomes. We used piecewise linear mixed models to assess the change in gradients over time at the point of intervention. This trial is registered with ClinicalTrials.gov, number NCT00395200.
FINDINGS:
We isolated, expanded, characterised, and administered mesenchymal stem cells in ten patients.

The mean dose was 1·6×10(6) cells per kg bodyweight (range 1·1-2·0). One patient developed a transient rash shortly after treatment; two patients had self-limiting bacterial infections 3-4 weeks after treatment. We did not identify any serious adverse events. We noted improvement after treatment in visual acuity (difference in monthly rates of change -0·02 logMAR units, 95% CI -0·03 to -0·01; p=0·003) and visual evoked response latency (-1·33 ms, -2·44 to -0·21; p=0·020), with an increase in optic nerve area (difference in monthly rates of change 0·13 mm(2), 0·04 to 0·22; p=0·006). We did not identify any significant effects on colour vision, visual fields, macular volume, retinal nerve fibre layer thickness, or optic nerve magnetisation transfer ratio.

INTERPRETATION:

Autologous mesenchymal stem cells were safely given to patients with secondary progressive multiple sclerosis in our study. The evidence of structural, functional, and physiological improvement after treatment in some visual endpoints is suggestive of neuroprotection.

FUNDING:

Medical Research Council, Multiple Sclerosis Society of Great Britain and Northern Ireland, Evelyn Trust, NHS National Institute for Health Research, Cambridge and UCLH Biomedical Research Centres, Wellcome Trust, Raymond and Beverly Sackler Foundation, and Sir David and Isobel Walker Trust.

6. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience.

Burman J, Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P, Vrethem M, Fredrikson S, Martin C, Sandstedt A, Uggla B, Lenhoff S, Johansson JE, Isaksson C, Hägglund H, Carlson K, Fagius J

J Neurol Neurosurg Psychiatry 2014

BACKGROUND:

Autologous haematopoietic stem cell transplantation (HSCT) is a viable option for treatment of aggressive multiple sclerosis (MS). No randomised controlled trial has been performed, and thus, experiences from systematic and sustained follow-up of treated patients constitute important information about safety and efficacy. In this observational study, we describe the characteristics and outcome of the Swedish patients treated with HSCT for MS.

METHODS:

Neurologists from the major hospitals in Sweden filled out a follow-up form with prospectively collected data. Fifty-two patients were identified in total; 48 were included in the study and evaluated for safety and side effects; 41 patients had at least 1 year of follow-up and were further analysed for clinical and radiological outcome. In this cohort, 34 patients (83%) had relapsing-remitting MS, and mean follow-up time was 47 months.

RESULTS:

At 5 years, relapse-free survival was 87%; MRI event-free survival 85%; expanded disability status scale (EDSS) score progression-free survival 77%; and disease-free survival (no relapses, no new MRI lesions and no EDSS progression) 68%. Presence of gadolinium-enhancing lesions prior to HSCT was associated with a favourable outcome (disease-free survival 79% vs 46%, p=0.028). There was no mortality. The most common long-term side effects were herpes zoster reactivation (15%) and thyroid disease (8.4%).

CONCLUSIONS:

HSCT is a very effective treatment of inflammatory active MS and can be performed with a high degree of safety at experienced centres.