MULTIPLE SCLEROSIS (MS)

1. MULTIPLE SCLEROSIS (MS) PROTOCOL

A. Clinical response: Clinical response demonstrates a decrease in progression of disease and evidence of an improved repair process. In addition to physical examinations prior to stem cell graft and 6 months post-procedure, laboratory test and imaging results serve as evidence of repair process. Internationally recognized lab tests for monitoring multiple sclerosis include:

- Complete blood count (CBC) with differential
- VDRL
- Auditory evoked potentials
- Vision evoked potentials
- Quantitative neurological exams
- EEG, MRI, CT scan or PET scan of the brain

B. Objective: To provide the patient with a treatment that stimulates his / her immune system, promote cellular regeneration and improve symptoms associated with Multiple Sclerosis. The endovascular/intravenous Ad-SVF Containing Adult Stem Cell Procedure should serve to compliment the patient's current treatment regimen or to promote healing when current treatment is not responding.

2. PRELIMINARIES

A. Background: Multiple Sclerosis is a chronic autoimmune condition and is one of the most common neurological causes of long-term disability. The myelin-producing oligodendrocytes of the central nervous system are the target of recurrent cell-mediated autoimmune attack.

B. Causes of Multiple Sclerosis: [1]

- ***Immunoloigic***
- ***Environmental***
- ***Infectious***
- ***Genetic***

C. Treatment options: The management of multiple sclerosis involves the treatment of the acute relapse, prevention of future relapse, treatment of complications, and management of the patient's disability. Treatment consists of immunomodulatory therapy for the underlying immune disorder and management of symptoms, as well as non-pharmacologic treatments, such as physical and occupational therapy. Decisions regarding early treatment can be guided by using the McDonald diagnostic criteria to help differentiate clinically isolated syndrome from a first episode of relapsing MS. (Currently, there are no approved treatments available for primary progressive MS (PPMS)).

- ***Immunomodulatory therapy for relapsing-remitting MS***: Disease-modifying therapies have shown beneficial effects in patients with relapsing MS, including reduced frequency and severity of clinical attacks. These agents appear to slow the progression of disability and the reduce accumulation of lesions within the brain and spinal cord. Disease-modifying medications for MS include: Interferon beta-1a (Avonex, Rebif), Interferon beta-1b (Betaseron, Extavia), Glatiramer (Copaxone), Natalizumab (Tysabri), Mitoxantrone (Novantrone) and Fingolimod (Gilenya)

- ***Surgical procedures*** that relate to MS are directed primarily at alleviating symptoms, such as dysphagia, significant limb spasticity or severe neuropathic pain.

3. AD-SVF CONTAINING ADULT STEM CELLS TREATMENT OPTION

A. Ad-SVF Containing Adult Stem Cells Procedure

- ***Initial patient evaluation***: A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

- ***Pre-op Evaluation / post-op medical consultation***: A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment. On the morning prior to procedure history and physical are performed by physician.

- ***Harvesting of adipose tissue***: Adipose tissue acquisition can be summarized as three step process:

    - ***Application of anesthetic / injection of tumescent solution***

    - ***Waiting time***

    - ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. A tissue sample is then obtained using 60 cc syringe(s) to aspirate 50 to 100 cc of adipose tissue. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

- **Autologous implant of Ad-SVF:** The stem cells obtained from the adipose tissue sample are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused via intravenous infusion, intrathecal injection, or through the carotid artery.

B. Post-op care for MS procedure:

- Patient remains under routine hospital care for 4 to 6 hours post-op
- Post-op evaluation before discharge and 24 hours post-op
- Patient maintains pressure dressing for 24 hours post-op
- 500 mg Ciprofloxacin PO bid for 7 days

C. Risks: There are possibilities for unwanted effects related to the local anesthesia, harvesting procedure, and injection of stem cells. Even with the most established protocol, adequate technique, and careful administration; a medical team may encounter uncontrollable events. Although there is no guarantee of perfect results, excellent results can be attained. The surgeon provides services in the most responsible, professional and diligent manner, always considering that surgeries imply risks. The risks of complications of adipose tissue harvesting and stem cell infusion are very low. Possible risks include but are not limited to:

- Pain at site of injections
- Bleeding at injection site
- Malaise
- Low-grade fever
- Hot flashes
- Itching at injection site
- Vascular spasm or obstruction
- Bruising
- Nerve or muscle injury
- Allergic reaction
- Dizziness
- Nausea
- Vomiting

D. Benefits: Adipose derived stem cells have the potential to repair nerve tissue. These stem cells also have immune modulating abilities. Adult stem cells possess the ability to repair damaged cells leading to tissue regeneration and ultimately promoting the healing process.

E. Follow-up Plan: Clinical response demonstrates a decrease of disease and improvement of symptoms associated with MS. Review of changes to internationally recognized lab results. Standards for follow-up:

- ***Pre- Ad-SVF implant***: Clinical evaluation of MS symptoms. Review & record current laboratory and or imaging results specific to MS.

- ***3 months after Ad-SVF implant***: Clinical evaluation of MS symptoms. Review & record current laboratory and imaging results specific to MS.

- ***6 months after Ad-SVF implant***: Clinical evaluation of MS symptoms, physical exam, and neurological assessment. Review & record current laboratory, imaging, visual evoked potential and nerve conduction study results.

MS – Adult Stem Cells Schedule of Events

1. **Initial Patient Evaluation:** A physician reviews the medical information, lab work, and diagnostic imaging provided by the patient in order to determine the stage of the medical condition and any other secondary conditions.

   A. Pre-Examination:
   - You will have a physical exam, which will include measuring your blood pressure, temperature and heart rate (vital signs).
   - Your doctor will discuss your medical history and any medications that you are taking.
   - Your doctor will assess how well you can perform your daily activities
   - If needed, you will have a urine or blood pregnancy test.
   - Blood will be taken.

   B. Additional Tests: should be done during or soon after this visit

   - Complete blood count (CBC) with differential
   - VDRL
   - Auditory evoked potentials
   - Vision evoked potentials
   - Quantitative neurological exams
   - EEG, MRI, CT scan or PET scan of the brain

   C. Review Results: After your doctor has reviewed the results of these tests, he or she will assess whether you are a good candidate for stem cell therapy. If you decide to obtain this therapy you will sign a consent form. A medical specialist to the specific condition to be treated provides a medical consultation at the location where the procedure will be performed. During pre-op evaluation informed consent is obtained from all patients and medical records are updated, including patient's most recent physical exam, most up-to-date lab results and imaging studies. Physician then performs surgical risk assessment.

2. **Pre-Operation / Stem Cell Procedure:**

   A. Two Weeks Before Procedure:

   - No Aspirin or medicines that contain aspirin or Ibuprofen since it interferes with normal blood clotting.
   - Discuss with your primary physician to discontinue anticoagulant drugs at least 1 week before the procedure.
   - Please discontinue all herbal medications as many have side effects that could complicate a surgical procedure by inhibiting blood clotting, affecting blood pressure, or interfering with anesthetics.
   - Please discontinue all diet pills whether prescription, over-the-counter or herbal.
   - NO SMOKING because nicotine reduces blood flow to the skin and can cause significant complications during healing.

- You may take Tylenol or generic forms of this drug.
- Purchase a compressive garment to wear after the lipoaspiration procedure.

B. Morning of the Procedure:

- Have a light breakfast.
- Take your regular prescribed medications
- Wear comfortable, loose-fitting clothes that do not have to be put on over your head.

3. Stem Cell Procedure:

A. Preparation & Harvesting of Adipose Tissue:

- ***Application of anesthetic / injection of tumescent solution***
- ***Waiting time (~15 – 20 minutes)***
- ***Acquisition of blood sample***
- ***Acquisition of adipose tissue:*** An area of the body with sufficient adipose tissue is selected; this is usually the periumbilical area. With the patient supine, the physician infiltrates a small amount of local anesthetic. Immediately following lipo-aspiration, adipose tissue sample is processed (minimally manipulated) to separate stem cells for use as graft.

B. Autologous implant of Ad-SVF: The stem cells obtained from the adipose tissue sample are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused via intravenous infusion, intrathecal injection, or through the carotid artery.

4. Recommended Post-Operation / Stem Cell Therapy Schedule:

A. Post-Op Medical Instruction - **(Please follow these instructions closely!)**

- Patient remains under routine hospital care for 4 to 6 hours post-op
- Post-op evaluation before discharge and 24 hours post-op
- Patient maintains pressure dressing for 24 hours post-op
- ***Post-op medication*** will be given to you the day of your surgery. They will consist of an antibiotic and a painkiller:
  - *Antibiotic*: Cephalexin/Cipro, please take as directed beginning the day after surgery
  - 500 mg Ciprofloxacin PO bid for 7 days
  - *Painkiller:* Please take as directed and only as needed for pain

    * If you are unable to take any of these medications, please contact your patient coordinator so we can arrange for other medications.
- ***Resume previous medication*** as directed by the physician

- ***Report any symptoms of feeling unwell***: fever, pain, etc. Patients should be seen promptly by an ophthalmologist for full evaluation should any of the above symptoms be encountered.
- It is recommended that the ***patient have a companion stay with him or her*** for at least 24 hours after discharge.
- You should ***expect some of blood-tinged anesthetic solution to drain from the incision sites*** during the first 24 to 48 hours. This will vary from patient to patient. Maxi-pads are recommended for bandages over your incision sites. You may take a shower 24 hours after the procedure.
- ***Compressive garments should be worn*** 24 hours a day for the first week and 12 hours a day for the second week.
- ***Do not shower for the first 24 hours***. ***Do not submerge yourself in any water*** (i.e. taking a bath or swimming) for the 1st week.
- ***If you experience nausea or vomiting it is probably due to the medication***. Please try to take it with food. If it persists, please contact our office.
- ***Diet-meals are not restricted.***
- ***Drink plenty of clear fluids***. We recommend 8 glasses of water or fruit juice every day.
- ***Do not drink any alcohol*** for 48 hours and limit alcohol intake for the first week.

B. <u>Post-Op Medical Consultation Schedule: 3 months & 6 months</u>

- Review of medical history
- Review of medication history
- Review of any adverse events since the previous visit
- Clinical evaluation of MS symptoms
- Review & record current laboratory and or imaging results specific to MS.

Your doctor will contact you by phone within the first week to follow up then future follow up visits will be arranged through your patient coordinator. If you need assistance before do not hesitate to contact us.

Multiple Sclerosis – Supporting Studies

Mult Scler. 2010 Apr;16(4):503-10. doi: 10.1177/1352458509359727. Epub 2010 Jan 19.

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

Freedman MS, Bar-Or A, Atkins HL, Karussis D, Frassoni F, Lazarus H, Scolding N, Slavin S, Le Blanc K, Uccelli A; MSCT Study Group.
Collaborators (29)

Source
University of Ottawa, Ottawa Hospital Research Institute, Ontario, Canada.
mfreedman@ottawahospital.on.ca

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.

Multiple Sclerosis – Supporting Studies

Int J Mol Sci. 2012 Nov 8;13(11):14470-91. doi: 10.3390/ijms131114470.

Experimental and therapeutic opportunities for stem cells in multiple sclerosis.

Patani R, Chandran S.

Source
Anne McLaren Laboratory for Regenerative Medicine, Stem Cell Institute, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 0SZ, UK.
siddharthan.chandran@ed.ac.uk.

Abstract
Multiple Sclerosis (MS) is an inflammatory demyelinating neurodegenerative disorder of the brain and spinal cord that causes significant disability in young adults. Although the precise aetiopathogenesis of MS remains unresolved, its pathological hallmarks include inflammation, demyelination, axonal injury (acute and chronic), astrogliosis and variable remyelination. Despite major recent advances in therapeutics for the early stage of the disease there are currently no disease modifying treatments for the progressive stage of disease, whose pathological substrate is axonal degeneration. This represents the great and unmet clinical need in MS. Against this background, human stem cells offer promise both to improve understanding of disease mechanism(s) through in-vitro modeling as well as potentially direct use to supplement and promote remyelination, an endogenous reparative process where entire myelin sheaths are restored to demyelinated axons. Conceptually, stem cells can act directly to myelinate axons or indirectly through different mechanisms to promote endogenous repair; importantly these two mechanisms of action are not mutually exclusive. We propose that discovery of novel methods to invoke or enhance remyelination in MS may be the most effective therapeutic strategy to limit axonal damage and instigate restoration of structure and function in this debilitating condition. Human stem cell derived neurons and glia, including patient specific cells derived through reprogramming, provide an unprecedented experimental system to model MS "in a dish" as well as enable high-throughput drug discovery. Finally, we speculate upon the potential role for stem cell based therapies in MS.

PMID: 23203076 [PubMed] PMCID: PMC3509592

Multiple Sclerosis – Supporting Studies

Stem Cells Transl Med. 2012 Jul;1(7):536-47. doi: 10.5966/sctm.2012-0015. Epub 2012 Jun 28.

Characterization of autologous mesenchymal stem cell-derived neural progenitors as a feasible source of stem cells for central nervous system applications in multiple sclerosis.

Harris VK, Faroqui R, Vyshkina T, Sadiq SA.

Source
Multiple Sclerosis Research Center of New York, New York, New York 10019, USA.

Abstract
Bone marrow mesenchymal stem cell-derived neural progenitors (MSC-NPs) are a potential therapeutic source of cells that have been shown to be efficacious in a preclinical model of multiple sclerosis (MS). To examine the feasibility of using MSC-NPs as an autologous source of cells to promote central nervous system (CNS) repair in MS, this study characterized human MSC-NPs from a panel of both MS and non-MS donors. Expanded MSCs showed similar characteristics in terms of growth and cell surface phenotype, regardless of the donor disease status. MSC-NPs derived from all MSCs showed a consistent pattern of gene expression changes that correlated with neural commitment and increased homogeneity. Furthermore, the reduced expression of mesodermal markers and reduced capacity for adipogenic or osteogenic differentiation in MSC-NPs compared with MSCs suggested that MSC-NPs have reduced potential of unwanted mesodermal differentiation upon CNS transplantation. The immunoregulatory function of MSC-NPs was similar to that of MSCs in their ability to suppress T-cell proliferation and to promote expansion of FoxP3-positive T regulatory cells in vitro. In addition, MSC-NPs promoted oligodendroglial differentiation from brain-derived neural stem cells that correlated with the secretion of bioactive factors. Our results provide a set of identity characteristics for autologous MSC-NPs and suggest that the in vitro immunoregulatory and trophic properties of these cells may have therapeutic value in the treatment of MS.

PMID: 23197858 [PubMed - indexed for MEDLINE] PMCID: PMC3659719

Multiple Sclerosis – Supporting Studies

Curr Stem Cell Res Ther. 2012 Nov;7(6):407-14.

Autologous mesenchymal stem cell therapy in progressive multiple sclerosis: an open label study.

Bonab MM, Sahraian MA, Aghsaie A, Karvigh SA, Hosseinian SM, Nikbin B, Lotfi J, Khorramnia S, Motamed MR, Togha M, Harirchian MH, Moghadam NB, Alikhani K, Yadegari S, Jafarian S, Gheini MR.

Source
Immunogenetics Research Centre, Department of Immunology, Tehran University of Medical Sciences, Tehran, Iran.

Abstract
Despite updating knowledge and a growing number of medications for multiple sclerosis (MS), no definite treatment is available yet for patients suffering from progressive forms of the disease. Autologous bone marrow derived mesenchymal stem cell (BM-MSC) transplantation is a promising method proposed as a therapy for MS. Although the safety of these cells has been confirmed in hematological, cardiac and inflammatory diseases, its efficacy in MS treatment is still under study. Patients with progressive MS (expanded disability status scale score: 4.0 -6.50) unresponsive to conventional treatments were recruited for this study. Twenty-five patients [f/m: 19/6, mean age: 34.7±7] received a single intrathecal injection of ex-vivo expanded MSCs (mean dose: 29.5×10(6) cells). We observed their therapeutic response for 12 months. Associated short-term adverse events of injection consisted of transient low-grade fever, nausea /vomiting, weakness in the lower limbs and headache. No major delayed adverse effect was reported. 3 patients left the study for personal reasons. The mean (SD) expanded disability status scale (EDSS) score of 22 patients changed from 6.1 (0.6) to 6.3 (0.4). Clinical course of the disease (measured by EDSS) improved in 4, deteriorated in 6 and had no change in 12 patients. In MRI evaluation, 15 patients showed no change, whereas 6 patients showed new T2 or gadolinium enhanced lesions (1 lost to follow-up). It seems that MSC therapy can improve/stabilize the course of the disease in progressive MS in the first year after injection with no serious adverse effects. Repeating the study with a larger sample size, booster injections and longer follow-up using a controlled study design is advised.

PMID: 23061813 [PubMed - indexed for MEDLINE]

Multiple Sclerosis – Supporting Studies

Lancet Neurol. 2012 Feb;11(2):150-6. doi: 10.1016/S1474-4422(11)70305-2. Epub 2012 Jan 10.

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.

Source
Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.

Abstract
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.

Zh Nevrol Psikhiatr Im S S Korsakova. 2011;111(2 Pt 2):72-6.

[Transplantation of mesenchymal stem cells in multiple sclerosis].

[Article in Russian]

Odinak MM, Bisaga GN, Novitskiĭ AV, Tyrenko VV, Fominykh MS, Bilibina AA, Krugliakov PV, Polyntsev DG.

Abstract
To assess safety and tolerability of treatment with autologic multipotent mesenchymal stem cells (MSC) in multiple sclerosis (MS), we have obtained autologic red bone marrow-derived MSC from 8 patients. Proliferation, immunophenotype and caryotype of MSC, their sterility, the absence of hemopoetic cells, chromosomal aberrations and signs of aging were controlled during the cell growth. The inverse injection of MSC in patient's blood was conducted in accordance to the elaborated protocol in a short intravenous infusion in dose 2.0 x 10(6)/kg of body mass once in 30 days. The duration of treatment was from 4 to 8 months. The efficacy of treatment was assessed after 4, 8 and 12 months. All patients tolerated repeated intravenous infusions of autologic MSC well with no significant side-effects as in the early as well in the remote periods of treatment. The distinct positive effect was seen in some cases 2 months after the beginning of treatment. The improvement of 0.5 point on EDSS was seen in 5/8 patients after 4 months. After 12 months, the improvement of 0.5-1 point on EDSS was seen in 6/8, stabilization in 1/8, progression in 1/8. These results revealed the safety of the elaborated protocol of treatment and the moderate clinical efficacy of treatment in non-curable patients or those with poor response to treatment that suggested continuing the study and enrollment of new patients.

PMID: 21919233 [PubMed - indexed for MEDLINE]

Multiple Sclerosis – Supporting Studies

Iran J Allergy Asthma Immunol. 2011 Sep;10(3):155-61. doi: 010.03/ijaai.155161.

FOXP3 gene expression in multiple sclerosis patients pre- and post mesenchymal stem cell therapy.

Mohajeri M, Farazmand A, Mohyeddin Bonab M, Nikbin B, Minagar A.

Source
Department of Cell and Mol. Biology, School of Biology, Faculty of Science, Tehran, Iran.

Abstract
Multiple Sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disorder of the central nervous system (CNS), which mainly affects young adults. Activated T lymphocytes promote the neuro-inflammatory cascade of MS by secreting pro-inflammatory cytokines and play a significant role in its pathogenesis. T lymphocytes may trigger the inflammation, which in turn leads to axonal loss and neurodegeneration observed in the course of MS. Currently, there is no cure for MS, however, one of the most promising neuroprotective research tools consists of the use of bone marrow derived mesenchymal stem cells (MSC). This method promotes immune system regulation and possibly induces neurological repair and re-myelination of the damaged axons. Recent studies have shown that MSC exert an immune regulatory function and induce T regulatory-cell proliferation, therefore, it may serve as a potentially useful treatment for immune-mediated diseases such as MS. In this pilot study a group of MS patients underwent MSC therapy and we assayed the expression of an X-linked transcription factor, FoxP3, as a specific marker of T Regulatory cells in peripheral blood, prior to and after the treatment. Using q RT-PCR for measurement of expression of FoxP3 by peripheral blood mononuclear cells, we found that in all subjects, except for one, the expression of FoxP3 at 6 months after intrathecal injection of MSC was significantly higher than the levels prior to treatment. Such significant enhanced expression of FoxP3 associated with clinical stability. Findings from this pilot study further support the potential of bone marrow derived MSC for treatment of MS patients.

PMID: 21891821 [PubMed - indexed for MEDLINE]

Multiple Sclerosis – Supporting Studies

Trials. 2011 Mar 2;12:62. doi: 10.1186/1745-6215-12-62.

The mesenchymal stem cells in multiple sclerosis (MSCIMS) trial protocol and baseline cohort characteristics: an open-label pre-test: post-test study with blinded outcome assessments.

Connick P, Kolappan M, Patani R, Scott MA, Crawley C, He XL, Richardson K, Barber K, Webber DJ, Wheeler-Kingshott CA, Tozer DJ, Samson RS, Thomas DL, Du MQ, Luan SL, Michell AW, Altmann DR, Thompson AJ, Miller DH, Compston A, Chandran S.

Source
Dept, of Clinical Neurosciences, University of Cambridge, UK. pc349@cam.ac.uk

Abstract
BACKGROUND:
No treatments are currently available that slow, stop, or reverse disease progression in established multiple sclerosis (MS). The Mesenchymal Stem Cells in Multiple Sclerosis (MSCIMS) trial tests the safety and feasibility of treatment with a candidate cell-based therapy, and will inform the wider challenge of designing early phase clinical trials to evaluate putative neuroprotective therapies in progressive MS. Illustrated by the MSCIMS trial protocol, we describe a novel methodology based on detailed assessment of the anterior visual pathway as a model of wider disease processes--the "sentinel lesion approach".

METHODS/DESIGN:
MSCIMS is a phase IIA study of autologous mesenchymal stem cells (MSCs) in secondary progressive MS. A pre-test : post-test design is used with healthy controls providing normative data for inter-session variability. Complementary eligibility criteria and outcomes are used to select participants with disease affecting the anterior visual pathway.

RESULTS:
Ten participants with MS and eight healthy controls were recruited between October 2008 and March 2009. Mesenchymal stem cells were successfully isolated, expanded and characterised in vitro for all participants in the treatment arm.

CONCLUSIONS:
In addition to determining the safety and feasibility of the intervention and informing design of future studies to address efficacy, MSCIMS adopts a novel strategy for testing neuroprotective agents in MS--the sentinel lesion approach--serving as proof of principle for its future wider applicability.

TRIAL REGISTRATION:
ClinicalTrials.gov (NCT00395200).

PMID: 21366911 [PubMed - indexed for MEDLINE] PMCID: PMC3059276

Multiple Sclerosis – Supporting Studies

Arch Neurol. 2010 Oct;67(10):1187-94. doi: 10.1001/archneurol.2010.248.

Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis.

Karussis D, Karageorgiou C, Vaknin-Dembinsky A, Gowda-Kurkalli B, Gomori JM, Kassis I, Bulte JW, Petrou P, Ben-Hur T, Abramsky O, Slavin S.

Source
Department of Neurology, Hadassah-Hebrew University Hospital, Ein Karem, Jerusalem IL-91120, Israel. karus@cc.huji.ac.il

Abstract
OBJECTIVE:
To evaluate the feasibility, safety, and immunological effects of intrathecal and intravenous administration of autologous mesenchymal stem cells (MSCs) (also called mesenchymal stromal cells) in patients with multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS).
DESIGN:

A phase 1/2 open-safety clinical trial. Patients Fifteen patients with MS (mean [SD] Expanded Disability Status Scale [EDSS] score, 6.7 [1.0]) and 19 with ALS (mean [SD] Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSFRS] score, 20.8 [8.0]) were enrolled. Intervention After culture, a mean (SD) of 63.2 × 10(6) (2.5 × 10(6)) MSCs was injected intrathecally (n = 34) and intravenously (n = 14). In 9 cases, MSCs were magnetically labeled with the superparamagnetic iron oxide ferumoxides (Feridex).

MAIN OUTCOME MEASURES:
The main outcome measure was the recording of side effects. Follow-up (≤25 months) included adverse events evaluation, neurological disability assessment by means of the EDSS, magnetic resonance imaging to exclude unexpected pathologies and track the labeled stem cells, and immunological tests to assess the short-term immunomodulatory effects of MSC transplantation.

RESULTS:
Twenty-one patients had injection-related adverse effects consisting of transient fever, and 15 reported headache. No major adverse effects were reported during follow-up. The mean ALSFRS score remained stable during the first 6 months of observation, whereas the mean (SD) EDSS score improved from 6.7 (1.0) to 5.9 (1.6). Magnetic resonance imaging visualized the MSCs in the occipital horns of the ventricles, indicating the possible migration of ferumoxides-labeled cells in the meninges, subarachnoid space, and spinal cord. Immunological analysis revealed an increase in the proportion of CD4(+)CD25(+) regulatory T cells, a decrease in the proliferative responses of lymphocytes, and the expression of CD40(+), CD83(+), CD86(+), and HLA-DR on myeloid dendritic cells at 24 hours after MSC transplantation.

CONCLUSION:
Transplantation of MSCs in patients with MS and ALS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects. Trial Registration clinicaltrials.gov Identifier: NCT00781872.

Multiple Sclerosis – Supporting Studies

Mult Scler. 2013 Apr;19(5):515-9. doi: 10.1177/1352458512464686. Epub 2012 Nov 1.

Mesenchymal stem cells as treatment for MS - progress to date.

Uccelli A, Laroni A, Freedman MS.

Source
Department of Neurosciences Ophthalmology and Genetics, University of Genoa, Italy.
auccelli@neurologia.unige.it

Abstract
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).

PMID: 23124791 [PubMed - indexed for MEDLINE]

Multiple Sclerosis – Supporting Studies

Immunotherapy. 2012 May;4(5):529-47. doi: 10.2217/imt.12.41.

The potential of mesenchymal stromal cells as a novel cellular therapy for multiple sclerosis.

Auletta JJ, Bartholomew AM, Maziarz RT, Deans RJ, Miller RH, Lazarus HM, Cohen JA.

Source
National Center for Regenerative Medicine, Case Western Reserve University, Cleveland, OH 44106, USA. jeffery.auletta@case.edu

Abstract
Multiple sclerosis (MS) is an inflammatory neurodegenerative disease of the CNS for which only partially effective therapies exist. Intense research defining the underlying immune pathophysiology is advancing both the understanding of MS as well as revealing potential targets for disease intervention. Mesenchymal stromal cell (MSC) therapy has the potential to modulate aberrant immune responses causing demyelination and axonal injury associated with MS, as well as to repair and restore damaged CNS tissue and cells. This article reviews the pathophysiology underlying MS, as well as providing a cutting-edge perspective into the field of MSC therapy based upon the experience of authors intrinsically involved in MS and MSC basic and translational science research.

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Multiple Sclerosis – Supporting Studies

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Mesenchymal stem cells for the treatment of multiple sclerosis and other neurological diseases.

Uccelli A, Laroni A, Freedman MS.

Source
Department of Neurosciences, Ophthalmology, and Genetics, University of Genoa, Italy. auccelli@neurologia.unige.it

Abstract
The rationale for use of adult stem cells as a treatment for neurological diseases such as multiple sclerosis arose from the hope that they had the capacity to foster repair of the CNS through tissue integration and differentiation into neural cells. Evidence from preclinical studies suggested that mesenchymal stem cells (MSCs), a subset of adult progenitor cells, are an effective therapy in preclinical animal models of neurological diseases such as experimental autoimmune encephalomyelitis, a model for multiple sclerosis, and stroke. In experimental autoimmune encephalomyelitis, intravenous injection of MSCs ameliorates clinical course and decreases demyelination, immune infiltrates, and axonal loss. Surprisingly, these effects do not require full CNS engraftment by MSCs, but rely on the capacity of MSCs to inhibit pathogenic immune responses and release neuroprotective and pro-oligodendrogenic molecules favouring tissue repair. These results led to the conclusion that therapeutic use of MSCs should initially focus on individuals with multiple sclerosis and persistent inflammation. Small clinical studies in different neurological diseases have suggested that MSCs are safe, paving the road for larger phase 2 studies addressing the effect of MSCs on clinical outcomes and markers of disease activity.

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Multiple Sclerosis – References

[1] What Causes MS? *National Multiple Sclerosis Society.* 2013. Web. 12/12/13.

Uccelli A, Laroni A, Freedman MS. Mesenchymal stem cells for the treatment of multiple sclerosis and other neurological diseases. (2011). Lancet Neurol. doi: 10.1016/S1474-4422(11)70121-1.

Harris VK, Faroqui R, Vyshkina T, Sadiq SA. Characterization of autologous mesenchymal stem cell-derived neural progenitors as a feasible source of stem cells for central nervous system applications in multiple sclerosis. (2012). doi: 10.5966/sctm.2012-0015.