RHEUMATOID ARTHRITIS (RA)

1. RHEUMATOID ARTHRITIS (RA) 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 results serve as evidence of repair process. Internationally recognized lab tests for monitoring Rheumatoid Arthritis (RA) includes:

- X-rays of affected joints
- Serum rheumatoid factor
- Anti-cyclic citrullinated peptide antibody (Anti-CCP)
- Erythrosedimentation rate (ESR)
- C-reactive Protein (CRP)
- Anti-RA33 assay
- Antinuclear antibody assay (ANA)

B. Objective: To provide the patient with a treatment that stimulates his / her immune system, promote cellular regeneration and improve symptoms associated with Rheumatoid Arthritis. 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. Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause. The hallmark feature of this condition is persistent symmetric polyarthritis (synovitis) that affects the hands and feet, although any joint lined by a synovial membrane may be involved. CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major cellular roles in the pathophysiology of RA, while B lymphocytes produce autoantibodies (ie, rheumatoid factors). Abnormal production of numerous cytokines, chemokines, and other inflammatory mediators has been demonstrated in patients with RA. Ultimately, inflammation and exuberant proliferation of synovium leads to destruction of various tissues, including cartilage, bone, tendons, ligaments, and blood vessels. Extra-articular involvement of organs such as the skin, heart, lungs, and eyes can be significant.

B. Treatment options: The American College of Rheumatology developed recommendations and algorithms for the use of non-biologic and biologic DMARDs for patients with rheumatoid arthritis.

- ***DMARDs*** can be classified into xenobiotic and biologic agents. These treatments represent the most important measure in the successful treatment of rheumatoid arthritis. These agents can delay or prevent disease progression and ultimately decrease destruction of joints and subsequent loss of function. The Xenobiotic DMARDs: Gold salts (aurothiomalate, auranofin), D-penicillamine, chloroquine

and hydroxychloroquine (HCQ), sulfasalazine (SSZ), MTX, azathioprine (AZP), and cyclosporin A.

- ***Immunodulators***: Immunomodulators are biologic agents which include Anakinra (IL-1 receptor antagonist [IL-1ra]), Abatacept (inhibitor of T-cell activation), Tocilizumab (IL-6 receptor inibitor)

- ***Glucocorticoids*** are potent anti-inflammatory drugs and are commonly used in patients with RA to bridge the time until DMARDs are effective.

- ***NSAIDs*** interfere with prostaglandin synthesis through inhibition of the enzyme cyclooxygenase (COX), thus reducing swelling and pain. NSAIDS do not delay joint destruction and, therefore, when used alone, are not sufficient to treat RA.

- ***Surgery*** in patients with RA can relieve pain, correct deformities and improve joint function.

3. AD-SVF CONTAINING ADULT STEM CELLS TREATMENT OPTION

A. Ad-SVF Containing Adult Stem Cells Procedure

- ***Initial patient evaluation***: A physician revises 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.

- ***Preparation of Platelet Rich Plasma (PRP)***: Using a standard phlebotomy technique the patient's own blood sample is obtained. After collection of whole blood, sample is of growth factors / cytokines upon platelet rupture. PRP also enhances stem cell proliferation.

- ***Autologous implant of Ad-SVF***: The stem cells obtained from the adipose tissue sample and the PRP are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused via intravenous infusion.

- ***Procedure for Intra-articular / intranodular stem cell application***: In specific cases, the infusion of stem cells may need to be provided via intra-articular injection to affected joints. Prepare a viscous mixture containing: 2 cc of washed adipose tissue and 10 cc AdSVF / stem cells. Alternatively, mix 10 cc AdSVF / stem cells and 2 cc HA 20mg/ml. Mark the injection site and using aseptic technique prepare and drape the area. Apply 1% lidocaine into the area. Inject AdSVF / stem cells mixture using a 10 cc syringe and a 1 1/2" x 22 G needle or a 1"x 18G needle for mixture containing adipose tissue. After infiltration of sample observe area for bleeding. Swab area with Povidone-Iodine (Betadine ®) and apply bandage.

B. 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:

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

C. Benefits: Adipose derived stem cells have the potential to repair cartilage and joint 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.

D. Follow-Up Plan: Clinical response demonstrates a decrease of disease activity and improvement of symptoms and decrease in frequency of flare-ups associated with rheumatoid arthritis. Review of criteria from American College of Rheumatology during pre-op evaluation and 6 months after treatment. International standards for follow-up:

- ***Pre-Ad-SVF implant***: Clinical evaluation of RA symptoms, taking note of any changes in flare-up frequency. Review & record current laboratory results specific to RA.

- ***3 months after Ad-SVF implant***: Clinical evaluation of RA symptoms, taking note of any changes in flare-up frequency. Review & record current laboratory results specific to RA.

- ***6 months after Ad-SVF implant***: Clinical evaluation of RA symptoms, taking note of any changes in flare-up frequency. Review & record current laboratory results specific to RA and X-ray report. Review of criteria from American College of Rheumatology.

RA – 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
   - X-rays of affected joints
   - Serum rheumatoid factor
   - Anti-cyclic citrullinated peptide antibody (Anti-CCP)
   - Erythrosedimentation rate (ESR)
   - C-reactive Protein (CRP)
   - Anti-RA33 assay
   - Antinuclear antibody assay (ANA)

   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.
   - You may take Tylenol or generic forms of this drug.
   - 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.
- 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 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. Preparation of Platelet Rich Plasma (PRP): Using a standard phlebotomy technique the patient's own blood sample is obtained. After collection of whole blood, sample is of growth factors / cytokines upon platelet rupture. PRP also enhances stem cell proliferation.

C. Autologous implant of Ad-SVF: The stem cells obtained from the adipose tissue sample and the PRP are applied to the patient using appropriate protocol for their condition. Autologous Ad-SVF containing adult stem cells are infused via intravenous infusion.

D. Procedure for Intra-articular / intranodular stem cell application: In specific cases, the infusion of stem cells may need to be provided via intra-articular injection to affected joints. Prepare a viscous mixture containing: 2 cc of washed adipose tissue and 10 cc AdSVF / stem cells. Alternatively, mix 10 cc AdSVF / stem cells and 2 cc HA 20mg/ml. Mark the injection site and using aseptic technique prepare and drape the area. Apply 1% lidocaine into the area. Inject AdSVF / stem cells mixture using a 10 cc syringe and a 1 1/2" x 22 G needle or a 1"x 18G needle for mixture containing adipose tissue. After infiltration of sample observe area for bleeding. Swab area with Povidone-Iodine (Betadine ®) and apply bandage.

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

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

- ***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
  - *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***: dizziness, changes in heart rate, pain, or fever. Patients should be seen promptly by an physician 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.

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.

RA – Supporting Studies

Nat Rev Rheumatol. 2012 Aug;8(8):493-8. doi: 10.1038/nrrheum.2012.98. Epub 2012 Jul 10.

Regenerative medicine in rheumatic disease-progress in tissue engineering.

Ringe J, Burmester GR, Sittinger M.

Source

Tissue Engineering Laboratory and Berlin-Brandenburg Center for Regenerative Therapies, Department of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.

Abstract
Joint destruction occurs in both osteoarthritis and rheumatoid arthritis. Even in the era of biologic agents, this destruction can be delayed but not averted. As cartilage has limited ability to self-regenerate, joint arthroplasty is required. Here, we outline current tissue engineering procedures (including autologous chondrocyte implantation and in situ mesenchymal stem cell recruitment) that are routinely applied for the regenerative treatment of injured or early osteoarthritic cartilage. Potential future regenerative therapies, including administration of multipotent or pluripotent stem cells, are also discussed. In the future, cell-free, material-based (for cartilage lesions) or cell-free, factor-based (for osteoarthritic cartilage) therapies to facilitate the recruitment of repair cells and improve cartilage metabolism are likely to become more important. Moreover, delivery of anti-inflammatory factors or immunomodulatory cells could be a regenerative treatment option for rheumatoid arthritis. Tissue engineering faces a crucial phase to translate products into clinical routine and the regulatory framework for cell-based products in particular is an important issue.

PMID: 22782007 [PubMed - indexed for MEDLINE]

RA – Supporting Studies

Nat Rev Rheumatol. 2009 Jul;5(7):392-9. doi: 10.1038/nrrheum.2009.104.

Mesenchymal stem cells: innovative therapeutic tools for rheumatic diseases.

Djouad F, Bouffi C, Ghannam S, Noël D, Jorgensen C.

Source
Inserm, U844, Montpellier, France.

Abstract
Mesenchymal stem cells (MSCs), or multipotent mesenchymal stromal cells as they are also known, have been identified in bone marrow as well as in other tissues of the joint, including adipose, synovium, periosteum, perichondrium, and cartilage. These cells are characterized by their phenotype and their ability to differentiate into three lineages: chondrocytes, osteoblasts and adipocytes. Importantly, MSCs also potently modulate immune responses, exhibit healing capacities, improve angiogenesis and prevent fibrosis. These properties might be explained at least in part by the trophic effects of MSCs through the secretion of a number of cytokines and growth factors. However, the mechanisms involved in the differentiation potential of MSCs, and their immunomodulatory and paracrine properties, are currently being extensively studied. These unique properties of MSCs confer on them the potential to be used for therapeutic applications in rheumatic diseases, including rheumatoid arthritis, osteoarthritis, genetic bone and cartilage disorders as well as bone metastasis.

PMID: 19568253 [PubMed - indexed for MEDLINE]

RA – Supporting Studies

Best Pract Res Clin Rheumatol. 2010 Aug;24(4):565-74. doi: 10.1016/j.berh.2010.01.008.

Stem cells in the treatment of inflammatory arthritis.

Tyndall A, van Laar JM. Author information

Abstract

Autologous haematopoietic stem cell transplantation in patients with rheumatoid arthritis (RA) resulted in a positive short-term outcome clinically with low treatment-related toxicity. However, early conditioning regimens were of low immunoablative intensity and most patients relapsed. Mechanistic studies suggest that residual lesional effector cells may have been responsible for the relapses. The introduction of biopharmaceuticals has, for the moment, reduced the need for further experimental studies. Juvenile idiopathic arthritis patients, mostly of the systemic subgroup, have shown nearly 33% durable drug-free remission, but with significant toxicity, including fatal macrophage-activation syndrome early in the programme. Later modifications to the protocol have reduced this toxicity. Mesenchymal stem cells (MSCs), derived from several sources including bone marrow and adipose tissue, are being tested as tissue-regenerative and immunomodulating agents in many autoimmune diseases and animal models of inflammatory arthritis have been positive. MSCs and other stromal cells derived from actively inflamed synovium and peripheral blood of RA patients do not always demonstrate a full range of differentiation potential compared with healthy MSCs, although their immunomodulalatory capacity is unimpaired.

PMID: 20732653 [PubMed - indexed for MEDLINE]

RA – Supporting Studies

Cell Immunol. 2010;264(1):7-17. doi: 10.1016/j.cellimm.2010.04.002. Epub 2010 Apr 8.

Autologous stromal vascular fraction cells: a tool for facilitating tolerance in rheumatic disease.

Ichim TE, Harman RJ, Min WP, Minev B, Solano F, Rodriguez JP, Alexandrescu DT, De Necochea-Campion R, Hu X, Marleau AM, Riordan NH.

Author information

Abstract
Since the days of Medawar, the goal of therapeutic tolerogenesis has been a "Holy Grail" for immunologists. While knowledge of cellular and molecular mechanisms of this process has been increasing at an exponential rate, clinical progress has been minimal. To provide a mechanistic background of tolerogenesis, we overview common processes in the naturally occurring examples of: pregnancy, cancer, oral tolerance and anterior chamber associated immune deviation. The case is made that an easily accessible byproduct of plastic surgery, the adipose stromal vascular fraction, contains elements directly capable of promoting tolerogenesis such as T regulatory cells and inhibitory macrophages. The high content of mesenchymal and hematopoietic stem cells from this source provides the possibility of trophic/regenerative potential, which would augment tolerogenic processes by decreasing ongoing inflammation. We discuss the application of this autologous cell source in the context of rheumatoid arthritis, concluding with some practical examples of its applications.

PMID: 20537320 [PubMed - indexed for MEDLINE]

RA – Supporting Studies

Scand J Rheumatol. 2010;39(1):1-11. doi: 10.3109/03009740903030324.

Autologous stem cell transplantation in autoimmune and rheumatic diseases: from the molecular background to clinical applications.

Szodoray P, Varoczy L, Szegedi G, Zeher M.
Author information

Abstract
Autoimmune diseases have a multifactorial origin. Because of disturbances of the immune system, autoreactive T and B cells target self-antigens, leading to permanent organ damage. Despite novel therapeutic protocols, the disease course is chronic and in many instances the outcome is lethal. The efficacy of stem cell therapy has been observed in autoimmune animal models and in autoimmune diseases related to haematological abnormalities. Although the therapy is more than 30 years old, its broad spread has been delayed by the serious side-effects due to the conditioning treatments based on oncological protocols. Evaluation of the data of patients who have undergone autologous stem cell therapy reinforced the view that protocols used for conditioning treatments, mostly causing lymphoablation, and procedures carried out in specialist centres significantly reduced mortality, with an almost optimal therapeutical efficacy. New, multicentre investigations have been launched to compare the efficacy of various protocols. In this review, we summarize certain aspects of the molecular background of autologous stem cell transplantation and also depict the response to therapy in various autoimmune and rheumatic diseases.

PMID: 20132064 [PubMed - indexed for MEDLINE]

RA – Supporting Studies

Curr Stem Cell Res Ther. 2009 Jan;4(1):61-9.

Mesenchymal stromal cells in rheumatoid arthritis: biological properties and clinical applications.

Kastrinaki MC, Papadaki HA.
Author information

Abstract

Mesenchymal stromal cells (MSC) isolated from a variety of adult tissues including the bone marrow (BM), have the capacity to differentiate into different cell types such as bone and cartilage and have therefore attracted scientific interest as potential therapeutic tools for tissue repair. MSC display also immunosuppressive and anti-inflammatory properties and their putative therapeutic role in a variety of inflammatory autoimmune diseases is currently under investigation. Joint destruction, caused by persistent inflammation, renders rheumatoid arthritis (RA) a possible clinical target for cartilage and bone repair using BM MSCs for their tissue repair and immunoregulatory effects. A number of studies, based mainly on experimental animal models, have recently provided interesting data on the potential of BM-MSCs to suppress local inflammation and tissue damage in RA whereas tissue engineering and cell-scaffold technology represents an emerging field of research. This review deals with the biological repair/regeneration of joint tissues in RA via MSC-based therapies. In view of the current interest in the autologous usage of BM MSC in RA, all available data on the biological properties of patient MSCs including the immunoregulatory characteristics, differentiation capacity towards osteocytes/chondrocytes, clonogenic/proliferative potential and molecular/protein profile and the possible influence of the RA milieu will be also summarized.

PMID 19149631 [PubMed - indexed for MEDLINE]

RA – Supporting Studies

Autoimmunity. 2008 Dec;41(8):625-31. doi: 10.1080/08916930802198550.

Stem cell transplantation in rheumatoid arthritis.

Snowden JA, Kapoor S, Wilson AG.

Abstract
The therapeutic potential of high dose cytotoxic therapy and stem cell transplantation (SCT) in severe rheumatoid arthritis (RA) was originally supported by animal studies and serendipitous clinical cases where allogeneic and autologous procedures were shown to ameliorate and potentially cure the disease. Phase I and Phase II clinical studies established the feasibility, safety and efficacy of autologous stem cell mobilisation and transplantation. Although it was clear that the effects of high dose chemotherapy and autologous SCT could safely achieve profound responses, sustained control of disease usually required the reintroduction of disease modifying agents. Responses were improved with dose escalation of the conditioning regimen, and also with post-SCT therapy, such as rituximab, but were not observed with graft manipulation. Phase III studies were attempted, but recruitment was compromised by the increasingly widespread use of biological anti-rheumatic agents. Autologous SCT is now only reasonably considered in relatively rare patients whose disease has resisted conventional and biological treatments, and small numbers of cases continue to be registered with the EBMT. Occasional patients treated with allogeneic and syngeneic SCT continue to stimulate academic interest, particularly as some appear to be cured, but significant logistical and toxicity issues mean that routine and widespread application is unrealistic. In summary, SCT continues to have a limited therapeutic potential in rare patients with RA refractory to modern therapy and sufficient fitness for the procedure. From a scientific perspective, ablation of the dysfunctional rheumatoid immune system and its reconstruction with SCT has provided useful insights into the pathophysiology of RA.

PMID: 18958746 [PubMed - indexed for MEDLINE]

RA – References

Snowden JA, Kapoor S, Wilson AG. (2008) Stem cell transplantation in rheumatoid arthritis. Autoimmunity. doi: 10.1080/08916930802198550.

Djouad F, Bouffi C, Ghannam S, Noël D, Jorgensen C. Mesenchymal stem cells: innovative therapeutic tools for rheumatic diseases. Nat Rev Rheumatol. 2009 Jul;5(7):392-9. doi: 10.1038/nrrheum.2009.104.