NeuroSpinal Institute of Broward
REGENERATIVE MEDICINE

RHEUMATOID ARTHRITIS

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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 treatment and 6 months post-procedure, laboratory test results serve as evidence of repair process. Internationally recognized lab tests for monitoring Rheumatoid Arthritis:

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

PRELIMINARIES

A. Background: 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 (i.e. rheumatoid factors). Abnormal production of numerous cytokines, chemokines, and other inflammatory mediators have 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.
- **Immunomodulators:** Immunomodulators are biologic agents which include Anakinra (IL-1 receptor antagonist [IL-1ra]), Abatacept (inhibitor of T-cell activation), Tocilizumab (IL-6 receptor inibitor). These treatments help modulate the immune system which in turn controls the inflammatory response
- **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.

POTENTIAL BENEFITS OF STEM CELL TREATMENT

Adipose derived stem cells have the potential to repair cartilage and joint tissue[1].Mesenchymal stem cells release immunosuppressive factors which help alleviate and avoid further progression of the disease. Besides having immune modulatory abilities, mesenchymal stem cell therapy allows for tissue repair on damage caused by chronic inflammation[2]. Mesenchymal stem cells also induce the production of T regulatory cells, immune cells, which are responsible to abrogate autoimmune diseases[2]. Recent studies suggest that patients achieve stable remission after stem cell treatment, due to the 'resetting' of the immune system.

1. Maumus, Marie, David Guérit, KarineToupet, Christian Jorgensen, and Danièle Noël. "Mesenchymal Stem Cell-based Therapies in Regenerative Medicine: Applications in Rheumatology." Stem Cell Research & Therapy 2.2 (2011): 2-14. Print.

2. Jorgensen, Christian, Farida Djouad, Vanessa Fritz, Florence Apparailly, Pascale Plence, and Danielle Noël. "Mesenchymal Stem Cells and Rheumatoid Arthritis." Joint Bone Spine 70.6 (2003): 483-85. Print

3. Van Laar, J.M., Tyndall, A."Adult stem cells in the treatment of autoimmune disease. "Rheumatology. 45.10(2006):1187-1193. Print

TREATMENT & DELIVERY METHOD REQUIRED

A. Typical Recommended Treatment: Adipose Derived Stem

B. Typical Delivery Method Required: AutologousAd-SVFcontainingadultstem cellsare infused in 5-10 ml normalsaline intravenouslywith aslowbolus push, as well as with a direct injection of stem cells, resuspended in Platelet Rich Plasma, into the affected joints.

C. Recommended dosing: Recommended repeat dosing MSC's infused with normal saline IV push every 3 months based on symptoms. MSC's combined with PRP into affected joints based on specific symptoms as frequently as every 3 months.

POTENTIAL RISKS OF STEM CELL INJECTION

Thereare possibilities for unwanted effects related to the localanes thesia,harvesting procedure,and injection of stemcells.Even with the most establishe dprotocol,adequate technique,and carefula dministration; a medical team may encounter uncontrollable events.Although thereis no guarantee of any results, excellent results can be attained.The medical professional provides services in the most responsible,professiona land diligent manner,always considering that surgeries imply risks.The risksof complications of adipose tissue harvesting and stemcell infusion are very low. Possible risks include but are not limited to:

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

FREQUENTLY ASKED QUESTIONS

1. What are adult stem cells and how do they work?

Currently rheumatoid arthritis is treated with immune suppressive drugs such as methotrexate, steroids, and cyclosporine. These drugs have shown temporary improvement; however they have adverse effects on the patients and do not address the issue of damaged joints or extra-articular tissues caused by the chronic inflammation. Stem cell treatment has demonstrated an ability to induce healing activity as well as modulating activity on the immune system. Mesenchymal stem cells found in various tissues such as bone marrow and adipose, act as local mediators when a certain tissue is inflamed, and do not suppress the immune response of the whole body . Mesenchymal stem cells also induce the production of T regulatory cells, immune cells, which are responsible to abrogate autoimmune diseases. diligent manner,always considering that surgeries imply risks.The risksof complications of adipose tissue harvesting and stemcell infusion are very low. Possible risks include but are not

2. How are mesenchymal stem cells administered for rheumatoid arthritis treatment?

In general, the stem cells are given intravenous (IV) push. It can be joint specific as well

3. Does smoking or drinking affect the therapy?

Smoking and the consumption of alcohol has been shown to be harmful to stem cells. We advise that people do not smoke or drink during their treatment, and it must absolutely be avoided the week following the treatment.

4. How long will it take for me to see results after my treatment?

Each patient is unique, and there is no guarantee in results or how soon they can be observed. In general, patients who have seen results they have experienced improvement within 6 months after treatment.

5. Will I experience side effects after the treatment?

You may experience some discomfort in the injection site. If you experience any fever, headache, nausea or vomiting please contact us immediately. Negative, long term effects have not been seen, however like any other medical procedures there are risks for infections.

6. Can I exercise after my treatment?

Restrict yourself to light exercise and daily activities. For the first 3 weeks avoid excessive exercise, however you can continue normal daily activities right after treatment.

7.How long will the entire procedure take?

The procedure generally takes 2-3 hours.

8. Will anyone follow up with me after the procedure?

A team member will follow up with you 1 day, 1 week, 3 months, 6 months and 1 year after the procedure. Follow ups help us evaluate the effectiveness of our treatment, and improve treatment protocols. We will be monitoring your progress closely. We are happy to address any issues or questions at anytime.

SUPPORTING ARTICLES

1. Mesenchymal stem cells and rheumatoid arthritis

Authors: Christian Jorgensen a, Farida Djouad b, Vanessa Fritz b, Florence Apparailly b, Pascale Plence b, Danielle Noël b

Abstract:

Mesenchymal stem cells are progenitors for several connective tissue cell lineages including bone, cartilage, muscle, fat, and bone marrow cells [1]. Stem cells are found in adulthood in many tissues and may be involved in the pathogenesis of some autoimmune diseases. As mesenchymal stem cells can target diseased organs, they may hold potential as vehicles capable of expressing and secreting proteins with therapeutic effects. In addition, stem cells exhibit immunologic properties that may have beneficial effects in autoimmune diseases. Improved knowledge of the pathophysiology of immunologic diseases such as rheumatoid arthritis (RA) or Crohn's disease has opened up new avenues for immunotherapy, the most striking example to date being the demonstration of a role for TNF [2]. Administration of agents that antagonize this cytokine receptor has proven therapeutic efficacy in RA. The rule of mesenchymal cells will be discussed.

Joint Bone Spine 70 (2003) 483–485

2. The potential of stem cell therapy for osteoarthritis and rheumatoid arthritis

Authors: Keerthi, Naveen ; Chimutengwende-Gordon, Mukai ; Sanghani, Anita ; Khan, Wasim

Abstract:

Joint diseases are a major cause of disability and are a significant financial burden on health care systems. Regenerative medicine offers exciting possibilities for treating osteoarthritis and rheumatoid arthritis. As well as possessing the ability to differentiate into other tissue lineages, some stem cells such as mesenchymal stem cells possess immmunomodulatory properties that make them useful in the search for alternative treatments for rheumatoid arthritis specifically. Various studies have been carried out using animal models to evaluate the role of stem cells in the treatment of arthritis, with some research being translated into clinical studies. However, the number of patients used in some studies has left questions on the ability of stem cell therapy to treat arthritic conditions unanswered. This article reviews the innovative studies that have been carried out to treat arthritis using stem cells and also highlights the key challenges associated with these techniques.

3. Mesenchymal stem cell-based therapies in regenerative medicine: applications in rheumatology

Authors: Maumus, Marie ; Guérit, David ; Toupet, Karine ; Jorgensen, Christian ; Noël, Danièle

Abstract:

Growing knowledge on the biology of mesenchymal stem cells (MSCs) has provided new insights into their potential clinical applications, particularly for rheumatologic disorders. Historically, their potential to differentiate into cells of the bone and cartilage lineages has led to a variety of experimental strategies to investigate whether MSCs can be used for tissue engineering approaches. Beyond this potential, MSCs also display immunosuppressive properties, which have prompted research on their capacity to suppress local inflammation and tissue damage in a variety of inflammatory autoimmune diseases and, in particular, in rheumatoid arthritis. Currently, an emerging field of research comes from the possibility that these cells, through their trophic/regenerative potential, may also influence the course of chronic degenerative disorders and prevent cartilage degradation in osteoarthritis. This review focuses on these advances, specifically on the biological properties of MSCs, including their immunoregulatory characteristics, differentiation capacity and trophic potential, as well as the relevance of MSC-based therapies for rheumatic diseases.

Stem cell research & therapy, 2011, Vol.2(2), pp.14

Current stem cell research & therapy, 2013, Vol.8(6), pp.444-50

4. Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells in vitro in rheumatoid arthritis.

Authors: Gonzalez-Rey E1, Gonzalez MA, Varela N, O'Valle F, Hernandez-Cortes P, Rico L, Büscher D, Delgado M

Abstract:

OBJECTIVES

Adult mesenchymal stem cells were recently found to suppress effector T cell and inflammatory responses and have emerged as attractive therapeutic candidates for immune disorders. In rheumatoid arthritis (RA), a loss in the immunological self-tolerance causes the activation of autoreactive T cells against joint components and subsequent chronic inflammation. The aim of this study is to characterise the immunosuppressive activity of human adipose-derived mesenchymal stem cells (hASCs) on collagen-reactive T cells from patients with RA.

METHODS:

The effects of hASCs on collagen-reactive RA human T cell proliferation and cytokine production were investigated, as well as effects on the production of inflammatory mediators by monocytes and fibroblast-like synoviocytes from patients with RA.

RESULTS:

hASCs suppressed the antigen-specific response of T cells from patients with RA. hASCs inhibited the proliferative response and the production of inflammatory cytokines by collagen-activated CD4 and CD8 T cells. In contrast, the numbers of IL10-producing T cells and monocytes were significantly augmented upon hASC treatment. The suppressive activity of hASCs was cell-to-cell contact dependent and independent. hASCs also stimulated the generation of FoxP3 protein-expressing CD4(+)CD25(+) regulatory T cells, with the capacity to suppress collagen-specific T cell responses. Finally, hASCs downregulated the inflammatory response and the production of matrix-degrading enzymes by synovial cells isolated from patients with RA.

CONCLUSIONS:

The present work identifies hASCs as key regulators of immune tolerance, with the capacity to suppress T cell and inflammatory responses and to induce the generation/activation of antigen-specific regulatory T cells

Ann Rheum Dis. 2010 Jan;69(1):241-8. doi: 10.1136/ard.2008.101881

5. IntImmunopharmacol. 2017 Jun;47:59-69. doi: 10.1016/j.intimp.2017.03.016. Epub 2017 Mar 30.

Human adipose tissue-derived mesenchymal stem cells in rheumatoid arthritis: Regulatory effects on peripheral blood mononuclear cells activation.

Baharlou R1, Ahmadi-Vasmehjani A2, Faraji F1, Atashzar MR1, Khoubyari M3, Ahi S4, Erfanian S5, Navabi SS1.

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5: Research Center for Non-Communicable Diseases, School of Medicine, Jahrom University of Medical Sciences, Jahrom, Iran.

Abstract

BACKGROUND AND OBJECTIVES:

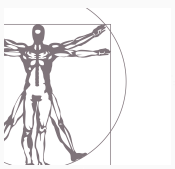
Mesenchymal stem cells (MSCs) are multipotent adult stem cells with immunomodulatory properties. The mechanisms by which MSCs inhibit the proliferation of pro-inflammatory T cells have not been fully elucidated yet. It is assumed that pro-inflammatory T-cells play an important role in the development of autoimmune diseases. We investigated the potential therapeutic effects of human adipose tissue derived (Ad)-MSCs on the peripheral blood mononuclear cells (PBMCs) of rheumatoid arthritis (RA) patients and healthy individuals, with a particular focus on Th17-associated cytokines.

MATERIALS AND METHODS:

PBMCs from RA patients and healthy donors were co-cultured with Ad-MSCs and HeLa with or without Phytohemagglutinin (PHA). Finally, IL-6, IL-17, IL-21, IL-23 and TGF-β levels were determined by ELISA and quantitative real-time RT-PCR on co-culture supernatants and PBMCs, respectively

RESULTS:

In co-culture interaction, Ad-MSCs inhibited IL-17 secretion by PBMCs compared to unstimulated PBMCs cultured alone. In addition, IL-21 expressions in PBMCs of the patient group, and IL-17 and IL-21 in healthy group were inhibited by Ad-MSCs compared to PBMCs cultured alone. TGF-β expression in healthy individuals remarkably increased in both MSC-treated groups with and without PHA in comparison to PHA-stimulated and -unstimulated PBMCs.



CONCLUSIONS:

This study demonstrates that human Ad-MSCs act as key regulators of immune tolerance by inhibiting the inflammation. Therefore, they can be attractive candidates for immunomodulatory cell-based therapy in RA.

KEYWORDS:

Adipose tissue-derived mesenchymal stem cells; Inflammation; Peripheral blood mononuclear cells; Rheumatoid arthritis; T helper 17 cells

PMID: 28364628 DOI: 10.1016/j.intimp.2017.03.016

5. Am J Transl Res. 2017 May 15;9(5):2595-2607. eCollection 2017.

Use of immune modulation by human adipose-derived mesenchymal stem cells to treat experimental arthritis in mice.

Zhang L1,2, Wang XY1, Zhou PJ1, He Z1, Yan HZ1, Xu DD1, Wang Y1, Fu WY3, Ruan BB3, Wang S1, Chen HX1, Liu QY1, Zhang YX2, Liu Z1, Wang YF1.

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3: Department of Pathogen Biology and Immunology, School of Basic Study, Guangdong Pharmaceutical UniversityGuangzhou 510632, China.

Abstract

Rheumatoid arthritis is a chronic and systemic autoimmune disease characterized by inflammatory cell infiltration and joint erosion. Human adipose-derived mesenchymal stem cells (hASCs) have shown the capacity of suppressing effector T cell activation and inflammatory cytokine expression. We investigated whether hASCs play a therapeutic role in collagen-induced arthritis (CIA) by administering a single dose of hASCs in mice with established CIA. In vivo, a beneficial effect was observed following hASC infusion as shown by a marked decrease in the severity of arthritis. Human ASCs were detectable in the joints, and reduced levels of pro-inflammatory cytokines and increased levels of anti-inflammatory cytokines were observed in the sera of the hASC-treated mice. Furthermore, hASC treatment induced the expansion of regulatory T cells (Tregs) both in the peripheral blood and in the spleen tissues. In vitro, hASCs downregulated the production of proinflammatory cytokines TNF-α, IL-1β, and IL-6 in mouse macrophages stimulated with lipopolysaccharide and inhibited the proliferation of human primary T cells in response to mitogens. Thus hASCs represent a novel and effective therapeutic strategy for RA.

KEYWORDS:

T cell; collagen-induced arthritis; hASC; immune; rheumatoid arthritis; therapy

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