CSCI Reference Library

Rheumatoid Arthritis

1. Potential of bone regenerative therapy with mesenchymal stem cells in rheumatoid arthritis
Yamaoka K
Clinical Calcium Journal 2016

Mesenchymal stem cell(MSC)exists throughout the body. The discovery of the immunosuppressive effect with low immunogenicity has led MSC as a new tool for cell therapy in various diseases. Within the arthritis animal model, periarticular implantation of bone marrow derived MSC with a scaffold has demonstrated treatment effect with low cell number whereas systemic administration had limited effect. Bone marrow derived MSC suppressed in vitro osteoclastogenesis and osteoblastogenesis of MSC was enhanced in the presence of IL-1β.On the other hand, experiments with adipose-derived MSC suggested the involvement in abnormal tissue calcification in the presence of IL-6. Therefore, MSC generated from the appropriate tissue and clarification of the major cytokines involved in pathogenesis is necessary when considering regenerative therapy for destructed joint in RA patients.

2. Intravenous administration of expanded allogeneic adipose-derived mesenchymal stem cells in refractory rheumatoid arthritis (Cx611): results of a multicentre, dose escalation, randomised, single-blind, placebo-controlled phase Ib/IIa clinical trial

Jose M Álvaro-Gracia, Juan A Jover, Rosario García-Vicuña, Luis Carreño, Alberto Alonso, Sara Marsal, Francisco Blanco, Victor M Martínez-Taboada, Peter Taylor, Cristina Martín-Martín, Olga DelaRosa, Ignacio Tagarro, Federico Díaz-González
Annals of Rheumatic Diseases 2016

Objectives To evaluate the safety and tolerability of the intravenous administration of Cx611, a preparation of allogeneic expanded adipose-derived stem cells (eASCs), in patients with refractory rheumatoid arthritis (RA), as well as to obtain preliminary clinical efficacy data in this population.
Methods It is a multicentre, dose escalation, randomised, single-blind (double-blind for efficacy), placebo-controlled, phase Ib/IIa clinical trial. Patients with active refractory RA (failure to at least two biologicals) were randomised to receive three intravenous infusions of Cx611: 1 million/kg (cohort A), 2 million/kg (cohort B), 4 million/kg (cohort C) or placebo, on days 1, 8 and 15, and they were followed for therapy assessment for 24 weeks.
Results Fifty-three patients were treated (20 in cohort A, 20 in cohort B, 6 in cohort C and 7 in placebo group). A total of 141 adverse events (AEs) were reported. Seventeen patients from the group A (85%), 15 from the group B (75%), 6 from the group C (100%) and 4 from the placebo group (57%) experienced at least one AE.
Eight AEs from 6 patients were grade 3 in intensity (severe), 5 in cohort A (lacunar infarction, diarrhoea, tendon rupture, rheumatoid nodule and arthritis), 2 in cohort B (sciatica and RA) and 1 in the placebo group (asthenia). Only one of the grade 3 AEs was serious (the lacunar infarction).

American College of Rheumatology 20 responses for cohorts A, B, C and placebo were 45%, 20%, 33% and 29%, respectively, at month 1, and 25%, 15%, 17% and 0%, respectively, at month 3.
Conclusions The intravenous infusion of Cx611 was in general well tolerated, without evidence of dose-related toxicity at the dose range and time period studied. In addition, a trend for clinical efficacy was observed. These data, in our opinion, justify further investigation of this innovative therapy in patients with RA.

3. Intra-articular Injection for the Management of Rheumatoid Arthritis Patients with Knee Osteoarthritis-Current Evidence and Future Prospects
Chen-Liang Chou and Yi-Tien Su
Journal of Arthritis 2015

4. Effects of Transplantation of CTLA4Ig-Overexpressing Adipose Tissue-Derived Mesenchymal Stem Cells in Mice With Sustained Severe Rheumatoid Arthritis.
Choi EW, Shin IS, Song JW, Lee M, Yun TW, Yang J, Choi KS, Kim SJ.
Cell Transplant 2016

CTLA4Ig has therapeutic potential for rheumatoid arthritis patients unresponsive to methotrexate (MTX) or TNF-α blockers. However, recombinant CTLA4Ig proteins are short acting and expensive. Adipose tissue-derived mesenchymal stem cells (ASCs) present an ideal stem cell source for practical regenerative medicine due to their abundant availability and their beneficial properties including immunomodulation, homing activity, paracrine effects, and differentiation ability. Therefore, we aimed to determine whether CTLA4Ig and human ASCs show synergistic effects on immunomodulation and clinical improvement of sustained severe rheumatoid arthritis in a mouse model. hASCs overexpressing CTLA4Ig (CTLA4Ig-hASC) were serially transplanted into mice with collagen-induced arthritis. Arthritic mice were subjected to four treatments based on their arthritis score on day 62 postimmunization: control (C group), hASC (H group), CTLA4Ig-hASC (CT group), and MTX (MTX group). A group of healthy mice was used as a normal control (N). Mice in the N and C groups were infused with 150 μl saline, and 2 × 10(6) hASCs or CTLA4Ig-hASCs in 150 μl of saline were intravenously administered to those in the H and CT groups, respectively, on days 63, 70, 77, and 84 after CII immunization. About 1 mg/kg of methotrexate was intraperitoneally administered to the MTX group three times a week for 4 weeks. Serial hASC and CTLA4Ig-hASC transplantation modulated various cytokines and chemokines related to the development of rheumatoid arthritis. Both treatments protected against destruction of cartilage, with CTLA4Ig-hASCs being most effective. Serum levels of CII autoantibodies and C-telopeptide of type II collagen were significantly low in the group transplanted with CTLA4Ig-hASCs. In vitro, ASC and CTLA4Ig-hASC treatment significantly decreased T-bet and GATA-3 expression in splenocytes from arthritic mice, and CTLA4Ig-hASC treatment significantly increased the ratio of Treg/Th17 (CD4(+)CD25(+)FoxP3(+)/CD4(+)CD25(+)RORγt) cells. Serial hASC and CTLA4Ig-hASC transplantation offers promising treatment for rheumatoid arthritis, and CTLA4Ig-hASCs showed stronger therapeutic effects than nontransduced hASCs.

5. Mesenchymal stem cells are conditionally therapeutic in preclinical models of rheumatoid arthritis

Anastasia Papadopoulou, Minas Yiangou, Evangelia Athanasiou, Nikolaos Zogas, Panayotis Kaloyannidis, Ioannis Batsis, Athanasios Fassas, Achilles Anagnostopoulos, Evangelia Yannaki
Annals of the Rheumatic Diseases 2012

Objective The role of mesenchymal stem cells (MSC) in experimental arthritis is undoubtedly conflicting. This study explored the effect of bone marrow-derived MSC in previously untested and pathogenetically different models of rheumatoid arthritis (RA).
Methods MSC were tested both in an induced (adjuvant-induced) and a spontaneous (K/BxN) arthritis model. Arthritis was assessed clinically and histologically. The proliferation of splenocytes and fibroblast-like synoviocytes (FLS) in the presence of MSC was measured by radioactivity incorporation. Toll-like receptor (TLR) expression was measured by real-time PCR. T-regulatory cell (Treg) frequency, T-cell apoptosis and cytokine secretion were monitored by flow cytometry.
Results MSC, in vitro, strongly inhibited critical cell populations; splenocytes and FLS. In contrast, MSC proved ineffective in vivo, unless they were administered before disease onset, an effect implying that the inflammatory arthritic milieu potentially abrogates MSC immunomodulatory properties. In order to alleviate inflammation before MSC infusion, the authors administered, at arthritis onset, a short course with a proteasome inhibitor, bortezomib, whereas MSC were infused when established disease was expected. The bortezomib plus MSC group demonstrated a significantly decreased arthritis score over arthritic, MSC-only, bortezomib-only groups, also confirmed by histology and immunohistochemistry. The bortezomib plus MSC combination restored TLR expression and Treg frequency in blood and normalised FLS and splenocyte proliferation, apoptosis and cytokine secretion.
Conclusion MSC lose their immunomodulatory properties when infused in the inflammatory micromilieu of autoimmune arthritis. Conditioning of the recipient with bortezomib alters the disease microenvironment enabling MSC to modulate arthritis. Should milieu limitations also operate in human disease, this approach could serve as a strategy to treat RA by MSC.

6. Mesenchymal stem cells, autoimmunity and rheumatoid arthritis.
El-Jawhari JJ, El-Sherbiny YM, Jones EA, McGonagle D.
QJM, Oxford University Press 2014

The vast majority of literature pertaining to mesenchymal stem cells (MSC) immunomodulation has focussed on bone marrow-derived MSC that are systemically infused to alleviate inflammatory conditions. Rheumatoid arthritis (RA) is the commonest autoimmune joint disease that has witnessed significant therapeutic advances in the past decade, but remains stubbornly difficult to treat in a subset of cases. Pre-clinical research has demonstrated that bone marrow, adipose, synovial and umbilical cord-derived MSC all suppress the functions of different immune cells thus raising the possibility of new therapies for autoimmune diseases including RA. Indeed, preliminary evidence for MSC efficacy has been reported in some cases of RA and systemic lupus erythromatosis. The potential use of bone marrow-MSC (BM-MSC) for RA therapy is emerging but the use of synovial MSC (S-MSC) to suppress the exaggerated immune response within the inflamed joints remains rudimentary. Synovial fibroblasts that are likely derived from S-MSCs, also give rise to a cell-cultured progeny termed fibroblast-like synoviocytes (FLS), which are key players in the perpetuation of joint inflammation and destruction. A better understanding of the link between these cells and their biology could be a

key to developing novel MSC-based strategies for therapy. The review briefly focuses on BM-MSC and gives particular attention to joint niche synovial MSC and FLS with respect to immunoregulatory potential therapy roles.