Stem Cell Therapy in Some Rheumatic Diseases: Is Mesenchymal Stem Cell Transplantation A Hope for Refractory Autoimmune Diseases?

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Abstract: Stem cells are cells with the potential to develop into many different types of cells in the body. They serve as a repair system for the body. There are two main types of stem cells: embryonic stem cells and adult stem cells.

Doctors and scientists are excited about stem cells because they have potential in many different areas of health and medical research. Immunoablative therapy and hematopoietic stem cell transplantation (HSCT) is an intensive treatment modality aimed at'resetting' the dysregulated immune system of a patient with immunoablative therapy and allow outgrowth of a nonautogressive immune system from reinfused hematopoietic stem cells, either from the patient (autologous HSCT) or a healthy donor (allogeneic HSCT).

Animal studies have demonstrated that HSCs play an important role in the pathogenesis of autoimmune diseases AD. Adoptive transfer of HSCs after immunoablative therapy caused, prevented, or cured AD.

Multipotent mesenchymal stromal cells (MSCs) are of a rapidly moving field in rheumatology, initially based on their cartilage/bone differentiation potential now partly eclipsed by their capacity to counteract adverse host immune responses, improve angiogenesis and prevent fibrosis. Indeed, MSCs are the progenitors of multiple tissues including bone, cartilage, muscle, fat and tendon. At present, MSCs seem to be the best candidates for cell therapy to regenerate injured tissue as they are easily isolated from bone marrow (BM) or adipose tissue and can be rapidly amplified. This has open novel therapeutic applications for various diseases including RA, bone and cartilage genetic disorders as well as bone metastasis.

In this review I discuss role of stem cell therapy in various rheumatic diseases.

Keywords: Stem cells rheumatic diseases.

INTRODUCTION

In the last years many progress in the knowledge of stem cell lineages have been reported, opening new perspectives in cellular immune-modulatory therapies and regenerative medicine. From the beginning, autoimmune diseases were considered as potential targets for these new therapies and several teams actively are studying the role that these cells might play in the pathogenesis of these diseases and its possible therapeutic [1]. Broadly speaking, stem cells can be characterized as either embryonic or adult stem cells. In theory, embryonic stem cells (ESs) appear to be the most versatile stem cell type for application in regenerative medicine. In the hierarchy of ESs, cells taken from the fertilized oocyte are called totipotent [2]. These totipotent cells are then able to specialize, forming the blastocyst from which the embryo will develop. ESs from within this blastocyst are called pluripotent as these cells go on to specialize to form all three of the germ layers. Fully developed adult tissues and organs contain niches of multipotent adult stem cells. Originally these multipotent adult stem cells were described as being able to differentiate into varying cell lineages from within their respective germ layer [2]. The development of induced pluripotent stem cells (iPS) [3] and the characterization of adult stem cells differentiating into cell types of differing germ layers have complicated the nomenclature of adult stem cells and therefore, flexibility and caution is required when defining specific stem cell type.

HISTORY OF STEM CELL TRANSPLANTATION IN AUTO IMMUNE DISEASES

15 years, more than 1,500 patients worldwide have received a hematopoietic stem cell transplant, mostly autologous, as treatment for a severe autoimmune disease (AD). A recent retrospective analysis of 900 patients showed that the majority had multiple sclerosis, systemic sclerosis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and juvenile idiopathic arthritis (JIA; n = 65) and idiopathic cytopenic purpura. An overall 85% 5-year survival and 43% progression-free survival was seen, with 100-day transplant-related mortality (TRM) ranging between 1% (RA) and 11% (SLE and JIA). Around 30% of patients in all disease subgroups had a complete response, despite full immune reconstitution. In many patients, morphological improvement was documented beyond

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any predicted known effects of intense immunosuppression alone. Multipotent mesenchymal stromal cells (MSCs), including autologous MSCs, have recently been tested in various ADs, exploiting their immune-modulating properties and apparent low acute toxicity. Despite encouraging small phase I/II studies, no positive data from randomized, prospective studies are as yet available [4].

AUTOLOGUS STEM CELL TRANSPLANTATION IN SLE

Systemic lupus erythematosus (SLE) is responsive to treatment with immunosuppressives and steroids, but often pursues a relapsing or refractory course resulting in increasing incapacity and reduced survival. Autologous stem cell transplantation (ASCT) following immunoablative chemotherapy is a newer therapy for autoimmune disease of potential use in severe SLE. A retrospective registry survey was carried out by the European Blood and Marrow Transplant and European League Against Rheumatism (EBMT/EULAR) registry. Data was collected from 53 patients with SLE treated by ASCT in 23 centres. Disease duration before ASCT was 59 (2-155) months (median, range), 44 (83%) were female, and median age was 29 (9-52) years. At the time of ASCT a median of seven American College of Rheumatology (ACR) diagnostic criteria for SLE were present (range 2-10) and 33 (62%) had nephritis. Peripheral blood stem cells were mobilized with cyclophosphamide and granulocyte colony stimulating factor in 93% of cases. Ex vivo CD34 stem cell selection was performed in 42% of patients. Conditioning regimens employed cyclophosphamide in 84%, anti-thymocyte globulin in 76% and lymphoid irradiation in 22%. The mean duration of follow-up after ASCT was 26 (0-78) months. Remission of disease activity (SLEDAI < 3) was seen in 33/50 (66%; 95%CI 52-80) evaluable patients by six months, of which 10/31 (32%; 95%CI 15-50) subsequently relapsed after six (3-40) months. Relapse was associated with negative anti-double stranded DNA (anti-dsDNA) antibodies before ASCT (P = 0.007). There were 12 deaths after 1.5 (0-48) months, of which seven (12%; 95%CI 3-21) were related to the procedure. Mortality was associated with a longer disease course before ASCT (P = 0.036). In conclusion, this registry study demonstrates the efficacy of ASCT for remission induction of refractory SLE, although mortality appeared high. The safety of this procedure is likely to be improved by patient selection and choice of conditioning regimen. The return of disease activity in one-third of patients might be reduced by long-term immunosuppressive therapy post-ASCT [5].

Alchi and co workers [6] reviews the efficacy and safety of ASCT in 28 SLE patients from eight centres reported to the European Group for Blood and Marrow Transplantation (EBMT) registry between 2001 and 2008. Results Median disease duration before ASCT was 52 (nine to 396) months, 25/28 SLE patients (89%) were female, age 29 (16-48) years. At the time of ASCT, eight (one to 11) American College of Rheumatology (ACR) diagnostic criteria for SLE were present and 17 (60%) patients had nephritis. Peripheral blood stem cells were mobilized with cyclophosphamide and granulocyte-colony stimulating factor in 93% of patients, and ex vivo CD34 stem cell selection was performed in 36%. Conditioning regimens were employed with either low (n = 10) or intermediate (18) intensities. With a median follow-up of 38 (one to 110) months after ASCT, the five-year overall survival was 81 ± 8%, disease-free survival was 29 ± 9%, relapse incidence (RI) was 56 ± 11% and non-relapse mortality was 15 ± 7%. Graft manipulation by CD34+ selection was associated with a lower RI (p = 0.001) on univariate analysis. There were five deaths within two years after ASCT: three caused by infection, one by secondary autoimmune disease and one by progressive SLE. This study also suggests a beneficial effect of ex vivo graft manipulation on prevention of relapses post-transplantation in SLE.

ALLOGENIC STEM TRANSPLANTATION IN SLE

Allogeneic haematopoietic stem cell transplantation (HSCT), or 'allografting', is an established treatment for haematological malignancies and genetic defects, but not autoimmune diseases (ADs). The risk of graft-versus host disease (GvHD) and the difficulties in finding a suitable donor have hampered clinical studies on allografting in AD. Yet there is a good scientific rationale for allografting in AD as it theoretically is the only treatment of AD with curative potential. Its main aim is to replace a patient's dysfunctional immune system with an allograft from a healthy donor so as to restore normal immune regulation. This is in contrast with autologous HSCT, in which a patient's own stem cells are re-infused after intensive immunosuppressive therapy. In patients with a haematological condition and concomitant AD such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), allografting resulted in long-term improvements of disease activity [7,8]

Allogeneic HSCT may be considered for poor-prognosis patients who have failed conventional treatment including biologicals (RA or juvenile

idiopathic arthritis) or autologous HSCT (SSc or SLE), which is now being examined in prospective clinical trials. Nevertheless, the clinical evidence in favour of allografting is sparse and the risks are considerable. In our opinion, patients with end-stage disease or serious co-morbidities should not be transplanted. The risks of HSCT in general (both autologous and allogeneic) may be particularly high in patients who have been heavily pre-treated with different immunosuppressive drugs, including biologicals, or who suffer from severe organ damage (or both). Patient selection is therefore critical and patients should be offered HSCT only if they have treatment-resistant life threatening disease yet a reasonable lifespan to allow logistical preparations for HSCT to be made. Patients should also have acceptable organ function to with stand unintended consequences of intensive immunosuppressive treatment and be willing to accept the risks of allografting. In terms of donor selection, sibling or matched unrelated donor transplants are preferred to minimise the risk of GvHD.

STEM CELL TRANSPLANTATION IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic disease that results in significant morbidity, impaired quality of life, and a reduced life expectancy [9,10].

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 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 mobilization and transplantation. Although it was clear that the effects of high dose chemotherapy and autologous HSCT 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. SCT continues to have a limited therapeutic potential in rare patients with RA refractory to modern therapy and sufficient [11, 12].

MESENCHYMAL STEM CELLS (MSCS) IN ARTHRITIS

Mesenchymal stem cells (MSCs), the non hematopoietic progenitor cells found in various adult tissues, are characterized by their ease of isolation and their rapid growth *in vitro* while maintaining their differentiation potential, allowing for extensive culture expansion to obtain large quantities suitable for therapeutic use. These properties make MSCs an ideal candidate cell type as building blocks for tissue engineering efforts to regenerate replacement tissues and repair damaged structures as encountered in various arthritic conditions [13].

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 [14].

MESENCHYMAL STEM CELL AND OSTEOAR-THRITIS

OA is the most common type of arthritis [15]. Its clinical manifestations include joint pain and impairment to movement, and surrounding tissues are often affected with local inflammation. The etiology of OA is not completely understood; however, injury, age, and genetics have been considered among the risk factors. OA is a progressively debilitating disease that affects mostly cartilage, with associated changes in bone. Cartilage has limited intrinsic healing and regenerative capacities. Current pharmacologic treatment for early OA has seen limited success, and various surgical procedures, including debridement, drilling, osteochondral transplantation, autologous perichondral and periosteal grafts, and autologous chondrocyte implantation, are able to relieve pain temporarily but eventually fail [16]. Due to the increasing incidence of OA and the aging population coupled with inefficient therapeutic choices, novel cartilage repair strategies are in need.

The availability of large quantities of MSCs and their potential for ready chondrogenic differentiation after prolonged *in vitro* expansion have made MSCs the most hopeful candidate progenitor cell source for cartilage tissue engineering. MSCs loaded on a 3-D scaffold under appropriate differentiation cues can undergo chondrogenic differentiation, and the resulting construct can be used as a replacement tissue for cartilage repair. *In vitro* cartilage tissue engineering has attracted a lot of research effort and attention from biologists, engineers, and clinicians in the past 10 years. In addition to being used for structural replacement as the aim of cartilage tissue engineering in cartilage repair, MSCs have been used directly in cell therapy for OA cartilage repair *in situ*. OA is associated with progressive and often severe inflammation. For tissue engineering or cell therapy to be successful, measures must be taken to control such an inflammatory environment. Because MSCs have been shown to possess anti-inflammatory function, they are also a suitable cell type for this purpose. Several characteristics of MSCs make them attractive in this respect. First, MSCs have been shown to be able to migrate and engraft onto multiple musculoskeletal tissues, especially sites of injury, and undergo site-specific differentiation. More importantly, while there, MSCs can exert significant effects on local environment and resident endogenous tissue progenitor cells through direct or indirect interactions and soluble factors. In addition, MSCs have shown potent anti-inflammatory and immunosuppressive activities. Taken together, these properties make MSCs a promising candidate for cell therapy for diseases that often involve the immune system, such as OA and RA.

A study by Murphy and colleagues [17] employing MSCs in a goat OA model highlighted the regenerative effect of MSC cell therapy in OA. Trauma-induced OA was simulated in this model by unilateral excision of the medial meniscus and resection of the anterior cruciate ligament, followed by exercise. Autologous MSCs in hyaluronan solution were injected intra-articularly to test their effect. In the control animals without MSCs, OA development was observed as expected, with substantial fibrillation and erosion of large areas of articular cartilage, accompanied by osteophyte formation and changes to the subchondral bone. In the MSC-treated joints, there was marked regeneration of the medial meniscus and decreased cartilage destruction and bone changes. Injected labeled MSCs were not observed to be engrafted on articular cartilage. Labeled MSCs were seen engrafted in the neomeniscus, though not in a large enough quantity to account for the majority of the newly formed tissue. These findings suggested that the beneficial effect of MSCs on cartilage protection and on OA progression was not due to the direct structural contribution of MSCs. Based on knowledge gained from other systems, it is possible that the injected MSCs in this case acted to induce endogenous progenitor cells through various direct or indirect interactions to regenerate meniscus, which in turn retarded cartilage degeneration associated with OA. Based on the goat study, a procedure using direct injection of adult stem cells into the patient's knee to repair

OA model [17] and a mouse model of collagen-induced arthritis (CIA) [18], transplanted cells were not detected in joint cartilage. Investigation into the mechanisms of MSC trafficking and homing, possibly through the regulation of various chemokines and receptors, as well as adhesion molecules and their receptors (reviewed in [19], is currently an actively pursued area of research and will likely provide insights into means of increasing engraftment of MSCs onto articular cartilage for more efficient treatment of arthritis. Despite the low engraftment efficiency, MSC-based procedures have been found to exert a therapeutic effect in various disease models, including arthritis, possibly through their trophic effect and their anti-inflammatory and immunosuppressive activities, which can significantly affect the local environment and resident endogenous tissue progenitor cells in carrying out the regenerative function.

MESENCHYMAL STEM CELL AND RHEUMATOID ARTHRITIS

RA is a complex multisystem autoimmune disease characterized by cartilage and bone destruction associated with local production of inflammatory mediators, such as TNF-α and IL-1β. The etiology of RA is not completely understood, and multiple cells are thought to contribute to the pathogenic progression, with T cells [20] and fibroblast-like synoviocytes (FLSs) [21] playing central roles in orchestrating the disease progression of inflammation and tissue damage. Although it is still debatable, RA is believed to be a T cell-driven inflammatory synovitis disease in which T cells and synoviocytes participate in a complex network of cell- and mediator-driven events leading to joint destruction. Both antigen-activated $CD4^+$ T helper 1 (Th1) and $CD8^+$ T cells are reported to be involved in the pathogenesis of RA. After being triggered and activated, T cells stimulate monocytes, macrophages, and FLSs to produce inflammatory mediators, including IL-1, TNF-α, IFN-γ, and IL-6, and secrete MMPs, leading to the systemic inflammation that eventually results in joint destruction [20,22]. Pharmacological

interventions aiming at reducing inflammation, including methotrexate and anti-TNF-α drugs (infliximab, adalimumab, and etanercept), have been used to treat RA symptoms [23]. Recently, for patients who do not respond to conventional treatment, autologous hematopoietic stem cell transplantation after immune ablation treatment has become an option. However, this comes with a high risk of side effects, including mortality. Joint destruction in RA and the anti-inflammatory and immune-suppressive properties of MSCs suggest that RA may be a candidate disease for cartilage and bone repair using MSC therapy.

MSCs have been identified in synovium and SF that share characteristics of bone marrow derived-MSCs, with clonogenic and multipotential differentiation potentials. The origin of SF-MSCs is not clear. From gene array profiling, it has been observed that SF-MSCs are more similar to synovial MSCs than bone marrow MSCs [24]. This finding can suggest that SF-MSCs are derived from synovium instead of bone marrow or are the result of phenotypic changes due to their local environment. Furthermore, the relationship between FLS and MSC is not fully elucidated. It has been reported that a fraction of the RA FLS population shows properties that are associated with MSCs in that they can differentiate into chondrocytes, osteoblasts, adipocytes, and muscle cells despite the pathological condition [25-26]. Currently, the biological roles MSCs play in RA pathophysiology are unknown. However, MSCs isolated from RA patients and patients with other autoimmune diseases seem to be similar to normal MSCs in that they are clonogenic and possess multipotential differentiation capacity. More importantly, they can also inhibit the proliferation of autologous and allogeneic peripheral blood mononuclear cells (PBMCs) in a dose-dependent manner. The inhibition was observed with MSCs and PBMCs either from healthy donors or from patients suffering from autoimmune diseases [27]. This indicates that MSCs from RA patients can potentially be used for immunomodulatory cell therapy. Recently, in a more specific study, allogeneic MSCs were tested against T cells from RA patients which react to collagen type II [28]. MSCs or MSC-differentiated chondrocytes were able to inhibit collagen type II-stimulated T-cell proliferation and activation in a dose-dependent manner. In addition, MSCs and their chondrocyte progeny alike inhibited the secretion of proinflammatory cytokines IFN-γ and TNF-α by $CD4^+$ and $CD8^+$ cells while increasing the secretion of IL-10 and restoring the secretion of IL-4. It was also shown that TGF-β played a significant role in the inhibitory effects of MSCs in this case.

MESENCHYMAL STEM CELL AND SLE

There are 2 important studies in which allogeneic MSC were transplanted in patients with severe-refractory SLE. In both, no pretransplant conditioning was utilized because of the well known low MSC immunogenicity. Fifteen lupus patients received 1 intravenous infusion of 1×10^6 MSC/Kg, and both the clinical (by SLEDAI score) and the laboratory (DNA, ANA) results were clearly favorable [29]. Another study by the same investigators was performed with umbilical MSC, utilizing low-dose cyclophosphamide (CY) conditioning in about half of them, in 16 lupus patients, again with significant amelioration in SLEDAI and laboratory results [30], which were accompanied by an increase in peripheral Treg cells, a feature that was also found in other SLE patients treated with conventional autologous HSCT [31].

Further clinical trials with more patients, longer periods of follow up, and comparisons with standard treatment will be needed to determine the efficacy and safety of this novel approach to the treatment of lupus.

CONCLUSIONS

Haematogenous stem cell transplantation can play role in severe refractory rheumatic diseases. Mesenchymal stem cell transplantation is a future hope for treatment of RA and OA.

REFERENCES

[1] Cipriani P, Carubbi F, Liakouli V, Marrelli A, Perricone C, Perricone R, *et al.* Stem cells in autoimmune diseases: Implications for pathogenesis and future trends in therapy. Autoimmun Rev 2012; doi:pii: S1568-9972(12)00262-5. 10.1016/j.autrev.2012.10.004. [Epub ahead of print].

[2] Rossant J. Stem cells from the mammalian blastocyst. Stem Cells 2001; 19: 477-82. http://dx.doi.org/10.1634/stemcells.19-6-477

[3] Takahashi K, Tanabe K, Ohnuki M, *et al*. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007; 131: 861-72. http://dx.doi.org/10.1016/j.cell.2007.11.019

[4] Tyndall A. Application of autologous stem cell transplantation in various adult and pediatric rheumatic disease. Pediatr Res 2012; 71(4 Pt 2).

[5] Alexander T, Gualandi F, Gruhn B, Ouyang J, Rzepecki P, Held G, *et al.* EBMT Autoimmune Disease Working Party members. Autologous stem cell transplantation for systemic lupus erythematosus. Lupus 2004; 13(3): 168-76.

[6] Alchi B, Jayne D, Labopin M, Kotova O, Sergeevicheva V, Alexander T, *et al.* EBMT Autoimmune Disease Working Party members. Autologous haematopoietic stem cell transplantation for systemic lupus erythematosus: data from the European Group for Blood and Marrow Transplantation registry. Lupus 2013; 22(3): 245-53. http://dx.doi.org/10.1177/0961203312470729

[7] Snowden JA, Kearney P, Kearney A, Cooley HM, Grigg A, Jacobs P, *et al.* Long-term outcome of autoimmune disease

following allogeneic bone marrow transplantation. Arthritis Rheum 1998; 41: 453-9. http://dx.doi.org/10.1002/1529-0131(199803)41:3<453::AID-ART11>3.0.CO;2-#

[8] Hinterberger W, Hinterberger-Fischer M, Marmont A. Clinically demonstrable anti-autoimmunity mediated by allogeneic immune cells favorably affects outcome after stem cell transplantation in human autoimmune diseases. Bone Marrow Transpl 2002; 30: 753-9. http://dx.doi.org/10.1038/sj.bmt.1703686

[9] Wong JB, Ramey DR, Singh G. Long-term morbidity, mortality, and economics of rheumatoid arthritis. Arthritis Rheum 2001; 44: 2746-9. http://dx.doi.org/10.1002/1529-0131(200112)44:12<2746::AID-ART461>3.0.CO;2-Z

[10] Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. Am J Med 2002; 113: 400-8. http://dx.doi.org/10.1016/S0002-9343(02)01243-3

[11] Bingham SJ, Moore JJ. Stem cell transplantation for autoimmune disorders Rheumatoid arthritis. Best Pract Res Clin Haematol 2004; 17(2): 263-76. http://dx.doi.org/10.1016/j.beha.2004.05.002

[12] Snowden JA, Passweg J, Moore JJ, Milliken S, Cannell P, Van Laar J, *et al*. Autologous hemopoietic stem cell transplantation in severe rheumatoid arthritis: a report from the EBMT and ABMTR. J Rheumatol 2004; 31(3): 482-8.

[13] Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. Arthritis Res Therapy 2008; 10: 223. http://dx.doi.org/10.1186/ar2514

[14] Kastrinaki MC, Pontikoglou C, Klaus M, Stavroulaki E, Pavlaki K, Papadaki HA. Biologic characteristics of bone marrow mesenchymal stem cells in myelodysplastic syndromes. Curr Stem Cell Res Ther 2011; 6(2): 122-30. http://dx.doi.org/10.2174/157488811795495422

[15] Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, *et al.* National Arthritis Data Workgroup: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008; 58: 26-35. http://dx.doi.org/10.1002/art.23176

[16] Hunziker EB. Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. Osteoarthritis Cartilage 2002; 10: 432-63. http://dx.doi.org/10.1053/joca.2002.0801

[17] Murphy JM, Fink DJ, Hunziker EB, Barry FP. Stem cell therapy in a caprine model of osteoarthritis. Arthritis Rheum 2003; 48: 3464-74. http://dx.doi.org/10.1002/art.11365

[18] Augello A, Tasso R, Negrini SM, Cancedda R, Pennesi G. Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis. Arthritis Rheum 2007; 56: 1175-86. http://dx.doi.org/10.1002/art.22511

[19] Fox JM, Chamberlain G, Ashton BA, Middleton J. Recent advances into the understanding of mesenchymal stem cell trafficking. Br J Haematol 2007; 137: 491-502. http://dx.doi.org/10.1111/j.1365-2141.2007.06610.x

[20] Fournier C. Where do T cells stand in rheumatoid arthritis? Joint Bone Spine 2005; 72: 527-32. http://dx.doi.org/10.1016/j.jbspin.2004.12.012

[21] Mor A, Abramson SB, Pillinger MH. The fibroblast-like synovial cell in rheumatoid arthritis: a key player in inflammation and joint destruction. Clin Immunol 2005; 115: 118-28. http://dx.doi.org/10.1016/j.clim.2004.12.009

[22] Fox DA. The role of T cells in the immunopathogenesis of rheumatoid arthritis: new perspectives. Arthritis Rheum 1997; 40: 598-609. http://dx.doi.org/10.1002/art.1780400403

[23] Toussirot E, Wendling D. The use of TNF-alpha blocking agents in rheumatoid arthritis: an update. Expert Opin Pharmacother 2007; 8: 2089-107. http://dx.doi.org/10.1517/14656566.8.13.2089

[24] Morito T, Muneta T, Hara K, Ju YJ, Mochizuki T, Makino H, *et al.* Synovial fluid-derived mesenchymal stem cells increase after intra-articular ligament injury in humans. Rheumatology (Oxford) 2008; 47: 1137-43. http://dx.doi.org/10.1093/rheumatology/ken114

[25] Marinova-Mutafchieva L, Williams RO, Funa K, Maini RN, Zvaifler NJ. Inflammation is preceded by tumor necrosis factor-dependeninfiltration of mesenchymal cells in experimental arthritis. Arthritis Rheum 2002; 46: 507-13. http://dx.doi.org/10.1002/art.10126

[26] Jones EA, English A, Henshaw K, Kinsey SE, Markham AF, Emery P, *et al.* Enumeration and phenotypic characterization of synovial fluid multipotential mesenchymal progenitor cells in inflammatory and degenerative arthritis. Arthritis Rheum 2004; 50: 817-27. http://dx.doi.org/10.1002/art.20203

[27] Bocelli-Tyndall C, Bracci L, Spagnoli G, Braccini A, Bouchenaki M, Ceredig R, *et al.* Bone marrow mesenchymal stromal cells (BM-MSCs) from healthy donors and auto-immune disease patients reduce the proliferation of autologous- and allogeneic-stimulated lymphocytes *in vitro*. Rheumatology (Oxford) 2007; 46: 403-408. http://dx.doi.org/10.1093/rheumatology/kel267

[28] Zheng ZH, Li XY, Ding J, Jia JF, Zhu P. Allogeneic mesenchymal stem cell and mesenchymal stem cell-differentiated chondrocyte suppress the responses of type II collagen-reactive T cells in rheumatoid arthritis. Rheumatology (Oxford) 2008; 47: 22-30. http://dx.doi.org/10.1093/rheumatology/kem284

[29] Liang J, Zhang H, Hua B, *et al*. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. Ann Rheumatic Dis 2010; 69(8): 1423-29. http://dx.doi.org/10.1136/ard.2009.123463

[30] Sun L, Wang D, Liang J, *et al*. Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. Arthritis Rheum 2010; 62(8): 2467-75. http://dx.doi.org/10.1002/art.27548

[31] Zhang L, Bertucci AM, Ramsey-Goldman R, Burt RK, Datta SK. Regulatory T cell (Treg) subsets return in patients with refractory lupus following stem cell transplantation, and TGF-β-producing CD8+ Treg cells are associated with immunological remission of lupus. J Immunol 2009; 183(10): 6346-58. http://dx.doi.org/10.4049/jimmunol.0901773

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