Autoimmune diseases represent the failure of normal immune regulatory processes, characterized by activation and expansion of immune cell subsets in response to nonpathogenic stimuli, that are derived from self-antigens. In the last few decades, hematopoietic stem cell transplantation emerged as a rescue therapy for different, severe, refractory autoimmune diseases. The rationale for this therapeutic strategy in autoimmune diseases is the ablation of an aberrant, self-reactive immune system by chemotherapy, and the regeneration of a new and self-tolerant immune system from by transplanted stem cells. In the last few decades, thousands of patients worldwide have received hematopoietic stem cell transplantation, mostly autologous, as treatment for a severe autoimmune disease with promising results. In this review, the authors report the recent available progresses about potential therapeutic role of stem cells in autoimmune diseases.

Keywords: autoimmune diseases • hematopoietic stem cells • mesenchymal stem cells • regenerative medicine • stem cells transplantation

In the last few years, many progresses in the knowledge of stem cell lineages have been reported, pointing out new perspectives in regenerative medicine. Autoimmune diseases represent the failure of normal immune regulatory processes characterized by the activation and expansion of self-reactive immune cell subsets in response to nonpathogenic stimuli. A stem cell defect may be postulated in the pathogenesis of autoimmune diseases because these disorders can be treated by stem cell transplantation [1]. In fact, thousands of patients, worldwide, received hematopoietic stem cell (HSCT) transplantation, mostly autologous, as treatment for a severe autoimmune disease with promising results [1].

On these bases, the authors reviewed the available literature concerning the therapeutic role of both mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) in rheumatoid diseases.

Mesenchymal stem cells
MSCs were firstly isolated from the bone marrow (BM) in 1968 [3] and, subsequently, in 1999, their ability to self-renew and differentiate toward many different cells of mesodermal lineage was reported [3]. MSCs are responsible for the normal turnover and maintenance of adult mesenchymal tissues and their pleiotropic nature allows them to sense and respond to an inflammatory event and/or damage in the local environment. MSCs are defined according to the ability to adhere to plastic; the expression of a panel surface marker (CD73+, CD90+, CD105+, CD45−, CD14−, CD11b− and CD34−), which identifies their phenotype; and the ability to differentiate toward chondrocytes, osteoblasts or adipocytes [4]. Besides these three lineages, according to environmental factors, such as growth factors, hypoxia and the extracellular 3D environment, MSCs may differentiate toward several other lineages, such as myocytes, tendinocytes, ligamentocytes, cardiomyocytes, neuronal cells and others [1]. Therefore, their ability to differentiate towards cells outside the mesenchymal lineage may open new perspective in regenerative medicine.
MSCs have been identified in BM and also in other tissues including adipose, periosteum, perichondrium, synovium and cartilage. Adipose tissue is a major source of adipose-derived stromal cells that are multipotent cells with characteristics similar to BM-derived MSCs, but easier to isolate in higher numbers. However, several genomic, proteomic and functional differences among MSCs derived from BM and adipose tissue were described [1, 5].

MSCs may exert immune-modulatory properties through the action on different immune cells both in vitro and in vivo models [6, 7]. Several pieces of evidence pointed out their ability to suppress T- and B-cell proliferation mediating irreversible G0/G1 phase arrest, to inhibit the differentiation of monocytes into immature dendritic cells and to affect natural killer cell function. Their capability to modulate immune responses is due on both cell contact-dependent mechanisms and soluble factors, such as prostaglandin-E2, TGF-β, nitric oxide and IL-10. In addition, MSCs may modulate T-cell phenotype, resulting in the generation of cells with regulatory activity [8–12]. MSCs are considered to be immune-privileged: these cells express low levels of cell-surface HLA class I molecules, whereas HLA class II, CD40, CD80 and CD86 are not detectable on the cell surface. This remarkable feature of MSCs allow them to escape to the immune surveillance [13]. The large extent of their immunologically privileged phenotype and their immunosuppressive capacity are, thus, considered the most intriguing aspect of their biology, introducing the possibility that these cells may be used as effective therapy in autoimmune diseases [7, 8].

The clinical benefit from MSCs treatment of autoimmune diseases was first reported in experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis. Zappa et al. showed the efficacy of MSC treatment in EAE, halting the autoimmune attack to myelin antigens and promoting nervous tissue repair through their integration in the CNS [14]. In addition, the administration of intravenous xenogenic human MSCs to EAE mice models demonstrated both clinical and histological improvements. Subsequently, several works reported the efficacy of MSC treatment for EAE regardless of the donors and the route of injections [15–17].

Recently, autologous BM-derived MSCs were used for the treatment of refractory Crohn’s disease. In this study, nine adult patients with refractory Crohn’s disease received two intravenous doses of BM-derived MSCs after ex vivo expansion. No side effect was observed and the results showed a significant clinical improvement assessed by Crohn’s disease activity index [18].

In systemic lupus erythematosus (SLE), two recent studies employed both BM-derived MSCs [19] and MSCs obtained from umbilical cord [20]. In the first paper, 15 patients with persistently active SLE, unresponsive to conventional immunosuppressive regimens, underwent MSC transplantation. All patients clinically improved with a marked decrease in the SLE disease activity index and the levels of 24 h proteinuria. No serious adverse events were reported [19]. The second study described a single-arm trial, involving 16 SLE patients refractory to standard treatment that underwent to umbilical cord MSC transplantation. The results reported a significant reduction in disease activity for all patients, no recurrence and no treatment-related deaths [20]. Of note, in both studies, MSC transplantation produced an improvement in clinical and laboratory parameters of the disease. Actually, there are hundreds of trials registered on ClinicalTrials.gov [21], and in Table 1 the authors summarized some recent clinical trials concerning the use of stem cells in autoimmune disease. Many clinical trials, in different phases have been already published, or are ongoing worldwide to understand the safety and efficacy of MSC transplantation in autoimmune disease, as it has been recently reported [22].

Despite these encouraging results using MSCs, their mechanisms of action are not still fully understood (Figure 1). Many of the unsolved questions about the therapeutic effects are focused on their homing to injured tissues. Although earlier studies showed the efficacy of MSCs in the model of CNS autoimmune disease, they did not clarify whether the integration of MSC in the nervous system is an essential step to obtain therapeutic benefits. It is well known that, after intravenous injection, MSCs are largely trapped in lungs, where they are rapidly degraded, and only few cells enter in systemic circulation [23]; it is difficult to explain the systemic effects observed during therapy by the small numbers of possibly engrafted cells. In this light, it is possible to speculate that the main immune-modulatory activity of MSCs could be exerted in the secondary lymphoid organs where MSCs may inhibit the homing of specific T cells to the CNS [24]. As far as the small number of MSCs engrafted in the CNS are concerned, these cells may modulate the local autoimmune attack and stimulate endogenous neurogenesis [25]. In fact, the real role of MSCs in the homeostasis of normal or damaged tissues is still unclear. In injured tissue, these cells may block autoimmune reactions turning off the T-cell surveillance, and providing a tissue-intrinsic reservoir of progenitors for reparative processes. Therefore, the use of exogenous MSCs in vivo may provide a milieu of immune-modulating and ‘trophic’ factors, which may be involved to re-establish and support
the homeostasis. Although these papers support the hypothesis of MSCs immunotherapy in humans, at present, some limitations in our knowledge, such as the identity of these cells, the physiological relevance of their immune-regulatory properties, the duration of engraftment, and their phenotypic changes when exposed to damaged tissues, suggest to analyze these results with caution and many further clinical trials may be required.

<table>
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<tr>
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<td>Phase I clinical trial</td>
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<td>Juvenile systemic sclerosis</td>
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<td>Phase I clinical trial</td>
<td>Autologous HSCT</td>
<td>Improvement of clinical conditions</td>
<td>[69]</td>
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EBMT: European Group for Blood and Marrow Transplantation; EULAR: European League Against Rheumatism; HSCT: Hematopoietic stem cell; MSC: Mesenchymal stem cell.
are needed to clarify whether MSCs transplantation will be an effective therapy for incurable autoimmune diseases [26].

**Hematopoietic stem cells**

HSCs are the best characterized population of adult stem cells, they reside in the BM and generate progenitors that become progressively restricted to different lineages [27]. HSCs have two defining properties: capacity of self-renewal by producing additional stem cells; and differentiation into mature blood cell lineages reconstituting the entire blood system of a recipient [28]. HSCs preferentially reside in two specific microenvironments: in the osteoblast niche, near the trabecular bone, and in the vascular niche adjacent to blood vessels [28,29]. In these niches, which are able to drive hematopoiesis, HSPCs remain in a relatively quiescent state, and receive signals for their proliferation [30,31]. During aging, HSPCs undergo quantitative, phenotypic and functional changes. Although the exact mechanism is poorly understood, BM microenvironment, cell-intrinsic processes and systemic factors may contribute to the aging process of these cells [32]. In fact, aged HSPCs display a reduced sensitivity to growth factors, reduced ability to support both erythropoiesis and T-cell generation, and, finally, impaired capacity to generate myeloid cells [33,34].
In the last decades, HSCT emerged as a rescue therapy for refractory autoimmune diseases, following the successful treatments for hematologic, oncologic and immunodeficiencies [35]. HSCs may be obtained from the patient (autologous) or from a different person, usually an HLA-identical sibling or, alternatively, an unrelated donor (allogeneic). Prior to undergo HSCT, patients receive a conditioning regimen, with or without radiation therapy, which may result in ablation of the BM. Patients undergoing allogeneic transplants also receive immunosuppressive drugs to prevent graft-versus-host disease (GvHD) [35,36].

The rationale for HSCT in autoimmune diseases consist in the ablation of an aberrant, self-reactive immune system by chemotherapy, and regeneration of a new and self-tolerant immune system by HSCs. On these basis, Muraro et al. demonstrated the generation of a new, naive T-cell repertoire, emerging from the thymus of patients with multiple sclerosis who had been treated with ablative conditioning and autologous HSCT. In this study, a different and more diverse T-cell receptor repertoire after post-transplant regeneration was reported [37]. Furthermore, many pieces of evidence pointed out the role of other immune activities, such as thymic reactivation, expansion of naive T cells and improved repertoire in patients with autoimmune disease after HSCT [38].

However, the analysis of immune reconstitution following autologous transplant showed a marked lymphopenia in the first year after transplantation. Interestingly, this cytopenia was observed to affect the lymphocyte subsets differently. B cells, natural killer cells and CD8^+ T cells display a rapid and complete reconstitution to pretransplantation levels, on the contrary, the recovery of CD4^+ T cells has consistently been observed to be delayed, and often incomplete until up 2 years of follow-up [35]. The observation that quantitative recovery of lymphocytes was not correlated to inflammatory activity or disease relapse revealed that numeric immune deficit is an insufficient explanation for a prolonged absence of autoimmune disease activity after autologous HSCT [35]. Furthermore, serological evidence of attenuation of immunological memory suggests that the B-cell compartment may undergo a renewal through autologous HSCT. Brinkman et al. reported an immunoablative effect of autologous HSCT. They showed a decrease of the immunological memory for a recall antigen boosted before harvest following nonrigorous T-cell depletion of the autograft [38].

In addition, autoimmune disease can, therefore, be regarded as the final outcome of a series of events that may include not only a genetic susceptibility, but also the failure of the checkpoints available to prevent autoimmunity, following exposure to environmental challenges, mainly infections. Therefore, it is possible to postulate that the normalization of different immune regulatory mechanisms might play a role in the suppression of autoimmunity following autologous HSCT [35]. The CD4^+CD25^high T cells, expressing FoxP3, were reported to be more resistant to irradiation than effector cells and probably mediated the amelioration of experimental GvHD [39]. Furthermore, the study of children with juvenile idiopathic arthritis (JIA) following autologous HSCT reported an increase of CD4^+CD25^high T cells after transplantation, and their frequency directly correlated with clinical remission [40]. Therefore, a restoration of immune regulation may also be involved in the post-transplant clinical benefits.

**HSCT & autoimmune diseases**

In the last decades, many patients worldwide have received HSCT, mostly autologous, as treatment for multiple sclerosis, systemic sclerosis (SSc), SLE, rheumatoid arthritis, JIA and idiopathic cytopenic purpura. A recent retrospective analysis showed that, at present, the 5-year survival rate is 85% and the progression-free survival rate is 43%, although these rates widely varies according to the specificity of the autoimmune disease. By multivariate analysis, the 100-day transplant-related mortality rate has been strongly associated with the transplant centers’ experience and type of autoimmune disease. Interestingly, an age less than 35 years, date of transplantation after 2000 and diagnosis were associated with progression-free survival rate. This largest cohort worldwide showed that autologous HSCT may induce sustained remissions for more than 5 years in patients with severe autoimmune diseases, that are refractory to the conventional therapy and suggest that the disease, rather than transplant technique, appears to be the most relevant prognostic factor, reflecting the high biological heterogeneity of autoimmunity [41].

A composite retrospective analysis, in the UK, provides useful information regarding frequency, indications, type of HSCT and broad outcomes in the context of translational and developmental steps of treatment in patients with poor prognosis and/or affected by a refractory severe autoimmune diseases. Within the UK, sustained responses were achieved in 30–40% of patients with autologous HSCT, and 60–70% with allogeneic HSCT, although toxicity was significant in both treatments. However, the irreversible and advanced vital organ damage, which more frequently characterizes connective tissue diseases from the beginning, associated to a greater risk of disease progression and nonrelapse mortality rate might explain why, in these diseases the outcome is generally
worse when compared with nonconnective tissue diseases transplanted patients [42].

Systemic lupus erythematosus
SLE is a severe, potentially life-threatening, disease. Since the first consensus statement in 1997, many autologous BM transplantations or HSCTs have been reported worldwide for SLE [43].

The largest number of cases was published by the European League Against Rheumatism (EULAR)/European Group for Blood and Marrow Transplantation (EBMT) database and the Immunotherapy Center of the Northwestern University in Chicago (IL, USA). Jayne et al. reported on 53 patients with severe relapsing or refractory SLE treated by autologous HSCT of whom the clinical data were collected in the EBMT/EULAR registry. During the mean follow-up, a decrease of the disease activity (SLE disease activity index of <3) was observed in 66% of patients after 6 months. However, 32% out of improved patients, subsequently relapsed. The survival rate was 62% at 48 months, with an higher transplant-related mortality rate of 12% at 1 year [44].

A comparable North American single-center study of autologous HSCTs in SLE showed a significant lower treatment-related mortality rate (approximately 2%). Autologous non-myeloablative HSCT results in amelioration of disease activity, improvement in serologic markers, and either stabilization or reversal of organ dysfunction. The overall 5-year survival rate was 84% [45].

Recently, the current state of autologous HSCT in SLE was reviewed at a meeting of the autoimmune working party of EBMT [46]. There was general agreement among experts in this field, suggesting that, in patients with severe SLE refractory to conventional immunosuppressive treatments, autologous HSCT may achieve sustained clinical remissions (ranging from 50 to 70% disease-free survival rate at 5 years), associated to qualitative immunological changes, not seen after different conventional treatments. However, this clinical benefit seems to be associated with an increase in short-term mortality rate in most of the available studies. Improving patient selection, long-term follow-up of patients after autologous HSCT, optimization of induction and maintenance treatments, associated to detailed analysis of the activities of the immune system may be considered as key areas for future research. The development of better transplant registries, defining a core set of clinical data and standardizing biological sample collections may improve on one hand the collaborations among involved groups of scientists and possibly on the other hand, the comparison of different studies will be more feasible [46]. To conclude, learning from what has been obtained from other different therapeutic regimens, the role of autologous HSCT in the treatment of severe SLE should be optimally established in randomized controlled trials.

Antiphospholipid antibody syndrome is a prothrombotic autoimmune disorder causing arterial or venous thromboses and pregnancy-associated morbidity. A post hoc analysis of published data from SLE patients showed that after HSCT, antiphospholipid autoantibodies significantly decreased in patients with previous elevated levels of these autoantibodies. In an open-label trial of patients with SLE and antiphospholipid antibody syndrome, patients assuming chronic anticoagulation therapy prior to undergo autologous HSCT were able to discontinue this long-term therapy, and 78% out of the transplanted patients remaining thrombosis-free at a median follow-up of 15 months [47].

Rheumatoid arthritis
The therapeutic potential of high-dose cytotoxic therapy and stem cell transplantation in 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 II clinical studies established the feasibility, safety and efficacy of autologous stem cell mobilization and transplantation [48,49]. The analysis of 73 patients from EBMT and the Autologous Blood and Marrow Transplant Registry were performed to evaluate RA patients treated with autologous HSCT. Transplanted patients presented a significant functional improvement, despite of the treatment with disease-modifying antirheumatic drugs. Responses were measured using the ACR criteria. The 67% out of patients achieved, at least, the ACR 50% response, and a significant reduction in the level of disability, measured by the Health Assessment Questionnaire, was observed. Most patients restarted disease-modifying antirheumatic drugs within 6 months for persistent or recurrent disease activity, which provided a better disease control in approximately half the cases. No direct transplant related mortality rate was observed [50].

Although it was clear that the effects of high-dose chemotherapy and autologous HSCT may safely achieve profound responses, sustained control of disease usually required the reintroduction of disease-modifying agents. Clinical responses were further improved with dose escalation of the conditioning regimen, and with post-HSCT therapy [50]. Several Phase III studies were attempted, but the recruitment was compromised by the increasingly widespread use of biological antirheumatic agents. Autologous HSCT is now reasonably considered for those patients whose disease resisted to conventional and biological treatments, and only few...
new cases continue to be registered with the EBMT. In this setting, HSCT continues to have a limited therapeutic potential in rare patients with RA, refractory to modern therapy and sufficient fitness for the invasive procedures.

Systemic sclerosis
Several nonrandomized trials of HSCT in SSc reported improvements in skin scores \cite{51,52}, which is well known to correlate with both the severity and the mortality rate of the disease. Two small nonrandomized studies suggested that HSCT may improve lung function \cite{53,54}. Furthermore, several groups have published findings of normalization of microvasculature in SSc patients following autologous HSCT \cite{55,56}. None of these observations is readily explained by either sustained immunosuppression or direct effects on fibroblasts and endothelial cells, and they suggest a more profound modulation of the inflammatory niche by mechanisms not still fully elucidated.

Since 2001, the efficacy, safety and long-term effects of autologous HSCT in SSc have been studied in a Phase II and 2 Phase III randomized controlled trials in Europe and North America (Table 2). ASSIST was a North American Phase II trial designed to assess the efficacy and safety of autologous nonmyeloablative HSCT versus monthly pulse intravenous cyclophosphamide in patients with SSc. The study was early stopped for the strong benefit observed in the transplanted arm. A total of 19 patients were enrolled, ten patients were randomized to receive HSCT, while nine patients received 6 monthly pulses of cyclophosphamide. Patients in the control group were allowed to switch to HSCT 12 months after enrollment. All ten patients who were randomly allocated to receive HSCT improved all the clinical conditions evaluated by modified Rodnan skin score and functional pulmonary test. On the other hand, treatment failure and/or disease progression occurred in eight out of nine controls. Of note, after 1 year of treatment, the mean modified Rodnan skin score decreased in the transplant group and conversely increased in the control group. No deaths were recorded in the ASSIST trial \cite{57}.

ASTIS was a Phase III trial. From 2001 to 2009, 156 patients were recruited in 28 centers in Europe and one in Canada. A total of 79 and 77 patients were randomized into high-dose immunosuppression followed by HSCT or 12 monthly pulses of intravenous cyclophosphamide, respectively. The primary end point of the ASTIS trial was event-free survival rate, defined as the time in days, starting from the day of randomization until the occurrence of death owing to any cause, or the development of persistent major organ failure. The first published results of the ASTIS trial demonstrated a
better event-free survival and overall survival rate in the HSCT group [58,59].

The SCOT trial is a North American randomized controlled Phase III trial, designed to compare high-dose immunosuppressive therapy and HSCT to monthly pulse cyclophosphamide. The SCOT trial’s primary end point is the Global Rank Composite Score at 54 months after randomization. The Global Rank Composite Score is based on the following hierarchy of different outcomes: death, event-free survival rate, forced vital capacity, modified Scleroderma Health Assessment Questionnaire and modified Rodnan skin score. Until now, no data are available about the results of this trial, except of the mortality rate [60]. In this trial, the mortality rate was subjected to independent reviews and this rate was approximately 10%. Total related mortality rate is difficult to predict in individual SSC patients since these patients seem to develop cardiopulmonary complications, especially during the conditioning steps of HSCT. These data might be related to the high-dose cyclophosphamide direct cardiotoxicity in patients with an higher cardiovascular risk linked to their altered cardiopulmonary function [61,62].

Although autologous HSCT in severe SSCs has resulted in rapid and sustained improvement of skin thickening and functional ability [63], the clear demonstration of improvement and/or stabilization of the functions of the affected organs, need further prospective, controlled, randomized studies to evaluate the real place of HSCT in the treatment of this disease.

Other immune disease

Autologous HSCT may induce a good clinical response in several different autoimmune diseases, refractory to conventional therapies [64].

Polymyositis and dermatomyositis are inflammatory myopathies characterized by elevated serum levels of muscle enzymes, proximal muscle weakness and other complications, including interstitial lung disease. Recently, a single-arm trial evaluated the clinical effect of HSCT in ten patients, refractory to standard therapy or that presented severe systemic manifestations. A decrease in the serum levels of creatinine kinase, an increase of the muscle strength and an improvement of the myositis-related interstitial lung disease were reported after transplant [65].

There are few published reports of HSCT in patients with refractory vasculitides, such as granulomatosis with polyangiitis (Wegener’s granulomatosis), a necrotizing vasculitis affecting small and medium blood vessels. Although improvements in joint pain, fevers, pulmonary infiltrates, orbital granulomas and a decrease of the autoantibodies titers have been reported, the limited number of cases cannot allow any definitive conclusions regarding this cell therapy in affected patients [66,67].

JIA represents a heterogeneous collection of inflammatory arthritides with the age of onset less than 16 years. In a retrospective analysis of 34 patients with refractory systemic or polyarticular JIA who failed to respond to high dose of methotrexate and/or anti-TNF-α therapy, they were treated with autologous HSCT after different conditioning regimens. Although, HSCT induced a drug-free remission of JIA and a profound increase in general wellbeing in the large proportion of patients, the procedure was associated to an increase in the mortality risk. Severe infections were a common adverse event in these patients and transplant related mortality rate was 9% out of the treated patients [68]. In a Phase II single-arm prospective trial of autologous HSCT in JIA, 15 out of 22 children reported a clinical improvement and eight reached complete clinical remission [69].

Juvenile SSC is a rare multisystem disorder characterized by skin and visceral fibrosis. Five children affected by juvenile SSC, which presented a severe lung disease, after the cyclophosphamide-based conditioning regimen underwent HSCT. After a median follow-up of 37.5 months, all children were still alive and three of them in clinical remission [70].

Complications of stem cell transplant

Transplant-related mortality rate, defined by the Milan consensus as death within the first 3 months of transplant, remains a major concern when considering HSCT. Stem cell therapy in rheumatic diseases demonstrated a transplant-related mortality rate, approximately of 5%, which is similar to the reported results in the hematology/oncology literature, and several side effects [71]. During the cell mobilization and conditioning phases, a variety of adverse events have been reported: allergic reactions to cyclophosphamide and anti-thymocyte globulin, fever, bone pain, infections, nausea, vomiting and elevations in liver enzymes [71]. Infections and bleeding risks are highest during the aplastic phase and, later during the T-cell reconstitution phase, infection remains the major concern [71,72].

Additional risks in the SSC patient population undergoing HSCT is the potential development of lung toxicity from total body irradiation and renal crisis from high-dose glucocorticoids used as prophylaxis for the anti-thymocyte globulin-induced cytokine storm. In addition, the use of cyclophosphamide for mobilization or for conditioning may increase the cardiovascular risk in SSC patients [73,74]. In this regard, EULAR/EBMT consensus statements recommend to exclude from HSCT, patients with cardiac dysfunction including pulmonary hypertension and heart failure. ECG,
transthoracic echocardiography and long-term ambulatory cardiac monitoring are recommended to evaluate cardiac status prior to considering HSCT, and right and left heart catheterization may be considered in the assessment of SSc patients [61,62]. Macrophage activation syndrome has also been reported following HSCT in the pediatric literature [79].

A late complication of allogeneic HSCT is the development of a new autoimmune disease, probably due to repopulation of the immune system by uncontrolled autoimmune clones [76]. In the EBMT registry, 10% of the patients who underwent autologous HSCT for primary autoimmune disease, developed a secondary autoimmune disease, such as autoimmune hemolytic anemia, autoimmune thrombocytopenia, antiphospholipid antibody syndrome, myasthenia gravis, RA, sarcoidosis, vasculitis, psoriasis and psoriatic arthritis. By multivariate analysis, it has been assessed that patients who underwent autologous HSCT, the list of risk factors for developing secondary autoimmune diseases included: a diagnosis of SLE prior to transplant, an interval between diagnosis of autoimmune disease and HSCT minor of 61 months, and use of anti-thymocyte globulin in the conditioning regimen, combined with CD34+ selection [77,78].

Furthermore, relapse of the previous rheumatic disease has been reported in long-term follow-up. Data from the EBMT/EULAR database, and the International Bone Marrow Transplantation Registry indicate a relapse rate of 32% for adult and pediatric patients with SLE, who underwent autologous HSCT [42,50,77–80]. Relapse rate was significantly higher (73%) in patients with RA, treated with autologous HSCT [50]. Although, the relapse rate may depend in part on the type of cells and the conditioning regimen administered, the extent and severity of the specific autoimmune disease may represent a bias in the evaluation of survival rate outcome data.

Conclusion
Although it is well known that many systemic autoimmune diseases are characterized by activation of autoreactive immune clones of both T and B lymphocytes, little is known about the contribution of MSCs and HSCs to the development of autoimmune pathology. In autoimmune diseases, these cells show quantitative, phenotypic and functional changes. On the other hand, in the last 40 years, transplant of stem cells has been widely performed in many different systemic autoimmune disease, with encouraging results. Although many aspects in this field are still poorly understood, the scientific bases for autologous HSCT in autoimmune diseases seem to be both the ablation of an aberrant or self-reactive immune system by chemotherapy, and the regeneration of a new and hopefully self-tolerant immune system from the transplanted HSCs.

The correct and optimal application of stem cell transplant in the management of refractory autoimmune rheumatic disease remains an area of active investigation. Consensus statements from EULAR and the EBMT indicate a preference for autologous more than allogeneic transplants, owing to the lower overall risk of severe toxicity with autologous transplant, largely due to the elimination of severe refractory GvHD [80]. At present, HSCT should be reserved for patients showing an irreversible disease, refractory to standard therapies, or with an higher risk of mortality rate, and that have not still developed extensive, irreversible organ damage [22,78–81].

Future perspective
Our knowledge of biology of stem cells therapy is still limited. At present, duration of engraftment, impact on normal tissues and organs, and phenotypic changes occurring in stem cells exposed to inflammatory and/or ischemic target tissue are still matter of debate. Larger, randomized, double-blind clinical trials, including biological studies are needed to improve our body of knowledge and better understand the clinical use of stem cell therapy.

Stem cell therapy has demonstrated promising prospect for its clinical application in autoimmune diseases, both in experimental models and in preliminary clinical studies. Up to now, there are many clinical trials concerning stem cells transplant, registered at ClinicalTrial.gov [21]. We believe that a better knowledge of stem cells biology will play an important role in improving the treatment of many severe autoimmune refractory diseases. Future larger-scale, multicenter, prospective, randomized HSCT clinical trials, specifically designed for autoimmune patients, need to definitively assess the safety and efficacy of MSCs versus HSCs, allogeneic versus autologous cell sources, and myeloablative versus nonmyeloablative conditioning regimens.

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Executive summary

- Autoimmune diseases represent the failure of normal immune regulatory processes characterized by activation and expansion of immune cell subsets in response to nonpathogenic stimuli.
- The rationale for hematopoietic stem cell (HSC) transplantation in autoimmune diseases is the ablation of an aberrant, self-reactive immune system by chemotherapy, and regeneration of a new and self-tolerant immune system from by HSCs.
- Many patients worldwide received HSC transplantation, mostly autologous, as treatment for refractory, severe autoimmune disease with encouraging results.
- Further studies and multicenter prospective randomized HSC transplantation clinical trials, specifically designed for autoimmune patients, still need, in order to assess the safety and efficacy of stem cells transplant in these clinical conditions.
- In the last few decades, many evidence provided new and fascinating in vitro and in vivo results on the immunosuppressant properties of mesenchymal stem cells supporting their potential therapeutic use as a suitable option to treat refractory autoimmune disease.
- Although the available data are not homogeneous, therapies with both autologous and allogenic mesenchymal stem cells demonstrated promising and encouraging results in rheumatic patients.

References

Papers of special note have been highlighted as:

• of interest;  • of considerable interest

• First evidence of mesenchymal stem cells therapeutic role in autoimmune animal model.
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Potential of stem cells in the treatment of rheumatic disease  Review

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** Excellent review of stem cell transplantation in autoimmune disease.
** Excellent review of hematopoietic stem cell transplantation (HSCT) use in autoimmune disease.
• Demonstrates the regeneration of a new, naive T-cell repertoire emerging from the thymus of patients with autoimmune disease after autologous HSCT.
• Long-term results to evaluate the safety and efficacy of HSCT.
• Long-term data to evaluate the outcome of transplanted patients affected by autoimmune diseases.


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