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Review

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Role of stem cells in spondyloarthritis: Pathogenesis, treatment and complications

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Abstract

Spondyloarthritis (SpA) is a family of interrelated inflammatory arthritis that includes ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel disease and undifferentiated SpA. The classification, epidemiology, pathogenesis and treatment of SpA have been extensively reviewed in the published literature. Reviews on the use of stem cells in various autoimmune diseases in general are also common. However, a review on the role of stem cells in SpA is currently lacking. This review focuses on the involvement of stem cells in the pathogenesis of SpA and the application of different types of stem cells in the treatment of SpA. It also addresses some of the complications which may arise as a result of the use of stem cells in the treatment of SpA.

Key words: Spondyloarthritis, stem cells, pathogenesis, treatment, complications
1. Introduction

Spondyloarthritis or spondyloarthritis (SpA) is a family of inflammatory arthritis including the prototype ankylosing spondylitis (AS) and several related diseases, namely, psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel disease (enteropathic arthritis) and undifferentiated SpA. These diseases share various common features in their clinical presentation, as well as pathophysiology. To date, its classification [1-3], epidemiology [4-6], pathogenesis [7-12] and treatment [13-15] have been reviewed extensively in the published literature. In addition, there is an increasing interest and an expanding body of research concerning the use of stem cells of various origins in the treatment of autoimmune diseases including SpA. Several reviews have been carried out on the use of stem cells in autoimmune diseases in general [16-20] while reviews on the use of stem cells in inflammatory arthritis [21] or specific arthritic conditions such as rheumatoid arthritis (RA) [22] are also common. However, a specific review emphasising in the role of stem cells in SpA is lacking. Thus, this paper critically reviews and summarises the role of stem cells in SpA from the perspectives of pathogenesis, treatment as well as existing and potential complications arising from stem cell-based therapy.

2. Spondyloarthritis

Spondyloarthritis or spondyloarthropathy (SpA) refers to an interrelated group of rheumatic diseases which share some common features. Several sets of classification criteria used to classify SpA have been reviewed, which include the Assessment of SpondyloArthritis Society (ASAS) criteria, the modified New York criteria for ankylosing spondylitis (AS), the Amor criteria and the European Spondyloarthropathy Study Group
(ESSG) criteria [1-3]. Diseases that are included in the SpA family include AS, reactive arthritis, psoriatic arthritis, enteropathic arthritis and undifferentiated SpA. Variations in the epidemiology of SpA are explained by the application of different sets of SpA classification criteria. Dean et al estimated that there were 1.30 to 1.56 million and 4.63 to 4.98 million cases of AS in Europe and Asia respectively [6]. In the United States, the overall age-adjusted prevalence of definite and probable SpA by the Amor criteria was 0.9%, which corresponded to approximately 1.7 million persons, while the age-adjusted prevalence of SpA by the ESSG criteria was 1.4%, which corresponded to 2.7 million persons [23]. Despite wide variations in the prevalence of SpA geographically, the reported prevalence of SpA between 0.9% and 1.4% may represent an overestimation due to recruitment biases. Some studies have reported an overall prevalence of SpA as low as 0.3% in France [24, 25], 0.45% in southern Sweden [26] and 0.4% in North America [27].

Although SpA is a class of diseases that share some similarities with rheumatic arthritis (RA), some distinctive features of SpA differentiate it from the latter. In RA, there is symmetrical involvement of the joints of the hands and feet accompanied by the presence of erosions and absence of new bone apposition. Auto-antibodies such as rheumatoid factor (RF) and anti-citrullinated peptide antibody (anti CCOP) are often present in RA [14]. On the other hand, SpA is characterised by human leukocyte antigen (HLA)-B27 association, and asymmetrical, oligoarticular peripheral arthritis that predominantly occurs in the lower extremities. Other features that link the SpA group of diseases include sacroiliitis, spondylitis, dactylitis, enthesitis and an increased susceptibility for inflammatory eye disease [14, 28].
The pathogenesis of SpA is not fully understood. Inflammation and new bone formation, especially in the spine, are two central themes of the disease [29]. Several factors and mediators have been associated with the disease. For example, HLA-B27, a major histocompatibility complex (MHC) class I molecule encoded on chromosome 6p, was first described to be associated with AS in 1973 [30]. Several earlier studies have shown that more than 90% of patients with AS were HLA-B27 positive [31, 32] whereas reactive, psoriatic and enteropathic arthritis were less frequently associated with HLA-B27 [32, 33]. However, not all HLA-B27 positive persons in the general population will eventually develop AS. HLA-B27 positive individuals in the general European population had a 16-fold lower risk (1.3%) of developing AS when compared to those who were HLA-B27 positive relatives of HLA-B27 positive patients with spondylitis (21%) [31]. The multiple HLA-B27 related mechanisms and theories involved in the pathogenesis of SpA have been reviewed by Colbert et al [8] and Chatzikyriakidou et al [7]. Other players in the pathogenesis of SpA include inflammatory cytokines such as tumour necrosis factor alpha (TNF-α) [34, 35], interleukin (IL)-1 [36], IL-6 [34, 37], IL-7 [38], IL-17 [39] and IL-23 [39, 40]. The role of inflammatory cytokines and biomarkers in the pathogenesis of SpA has been reviewed by Keller et al [9], Maksymowych [10] and Hreggvidsdottir et al [11], while their role in the structural remodeling in peripheral SpA by Vandooren et al [12].

Despite new advances, novel approaches and discoveries, the treatment of SpA is largely dependent on pharmacological agents. Non-steroidal anti-inflammatory drugs (NSAIDs) remain the first-line drugs, while traditional disease-modifying drugs (DMARDS) such as sulphasalazine and methotrexate and intra-articular injections of corticosteroids in local disease, are commonly and conventionally used in the treatment of SpA whereas newer approaches such as tumour necrosis factor (TNF)-α blockers (e.g. infliximab, etanercept, adalimumab and
golimumab) have been used in the treatment of SpA (reviewed by Braun & Sieper; Papagoras & Drosos; Keith) [13-15]. Other supportive measures that play an important role in the management of SpA include patient education and exercise [41, 42], as well as physical therapy, rehabilitation, surgical referrals, patient associations and self-help groups [41].

3. Role of stem cells in the pathogenesis of spondyloarthritis

Several studies have pointed to the involvement of stem cells in the pathogenesis of SpA, with a majority of them involving the mesenchymal stem cells (MSCs) (Figure 1), which are multipotent cells capable of differentiating into osteoblasts, adipocytes and chondroblasts [43]. In one study, the bone marrow-derived MSCs (BMSCs) from 51 AS patients were studied [44]. Although BMSCs obtained from AS patients were shown to demonstrate normal proliferation, cell viability, surface markers and multiple differentiation characteristics, their immunomodulatory potential were significantly reduced when compared to that of BMSCs from healthy donors. In addition, there was an increase in the frequencies of Treg and Fox-P3+ cells in the peripheral blood nuclear cells (PBMCs) of these patients, with an increase in CCR4+CCR6+ Th cells in comparison with healthy donors. The study concluded that the reduced immunomodulatory potential of BMSCs played a crucial role in the pathogenesis of AS as it induced CCR4+CCR6+ Th/Treg cell imbalance in peripheral blood [44].

Other than being functionally abnormal and contributing to CCR4+CCR6+ Th/Treg cell imbalance, the MSCs have also been found to affect bone mineralisation by influencing the activity of tissue-nonspecific alkaline phosphatase (TNAP), an enzyme encoded by the ALPL gene [45] which has been reported to play a role in bone mineralization [46]. Ding et al examined the effects of TNF-α and IL-1β on osteoblast differentiation and mineralisation in
cultured human MSCs (hMSCs) in search of a possible explanation for the differences in bone changes observed in RA and SpA. Interestingly, it was demonstrated that TNF-α and IL-1β inhibited collagen expression and stimulated TNAP activity. The differential effects of these cytokines on collagen expression and TNAP activity in turn, may help explain why in RA, inflammation is associated with bone erosion but leads to new bone formation in SpA [47]. In addition, a more recent study further supported the role of TNF-α in osteoblastic function and excessive bone formation by demonstrating autocrine stimulation of osteoblast activity by Wnt5a in response to TNF-α in human MSCs. TNF-α was shown to significantly increase the levels of Wnt10b and Wnt5a, accompanied by stimulation of TNAP and mineralisation, an effect which could be mimicked by activating the canonical β-catenin pathway [48], suggesting the effects of inflammation on bone formation may potentially be mediated by Wnt5a. This may help explain partly why anti-TNF-α therapy is inefficient in preventing excessive bone formation in AS as the process involves indirect stimulation of ossification via the MSCs.

The effects of activated monocytes or macrophages on MSCs with respect to matrix mineralisation and osteogenesis were studied by Guihard et al [49]. It was demonstrated that the induction of osteogenesis in MSCs by monocytes or macrophages relied on oncostatin M (OSM), a cytokine belonging to the IL-6 family. Bone formation was induced by OSM via the recruitment of MSC type II receptor, activating the transcription factor STA3 and resulting in osteoblastic differentiation. It was, therefore, proposed that during bone inflammation, injury or infection, this IL-6 family signaling network is responsible for osteogenesis and bone formation. This was further supported by earlier evidence that over-expression of OSM in the joints of mice led to periosteal bone formation, suggesting its role in bone apposition in RA, juvenile arthritis and SpA such as psoriatic arthritis and AS [50,51].
MSCs have been isolated, localised and characterised in ossified spinal ligaments [52, 53]. Besides their involvement in osteogenesis and excessive bone formation in SpA, it is believed that MSCs may play a role in abnormal osteoblastic differentiation that leads to enthesial ossification in diffuse idiopathic skeletal hyperostosis (DISH), which share similarities with some forms of AS. Such a belief has led to the inference of the possible contribution of MSCs in the pathogenesis of enthesal abnormalities observed in SpA. The role of mesenchymatous cells in the pathogenesis of hyperostosis has been reviewed by Berthelot et al [54].

Additionally, MSC-derived adipocytes may also play a role in SpA pathogenesis due to deranged regulatory functions. The role of adipose tissue as a potent source of inflammatory cytokines is not an uncommon phenomenon in autoimmune diseases [55]. Such adipocyte dysfunctions have been demonstrated in AS patients showing an increased level in resistin (an adipokine primarily defined in human adipocytes) [56], suggesting a role played by the adipocytes in SpA. Resistin has been linked to increased expression of several pro-inflammatory cytokines such as IL-12 and TNF-α in an NF-κB-dependent manner [57]. In AS patients, resistin has been correlated to inflammatory markers whereas visfatin (a proinflammatory adipokine) was correlated to worsening of the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) in one study. It was also shown to be predictive of subsequent radiographic spinal progression and syndesmophyte formation/ progression [58]. Other adipokines that may be involved in AS include leptin, adiponectin and apelin. However, some conflicting opinions exist in the published literature regarding the role of these substances in AS (reviewed by Genre et al) [59].
Although stem cells have been shown to contribute to the pathogenesis of SpA, some studies have reported their protective effects in the bone marrow both in vitro and in vivo. The interplay of MSCs and regulatory T (Treg) cells within the bone marrow may play a protective role in the pathogenesis of spondyloarthritis, given the bone marrow’s close proximity with the entheses. As SpA is a chronic inflammatory disease affecting the musculoskeletal system, the outcome of the disease depends not only on immune changes but also bone tissue homeostasis and remodeling [60]. In addition, a balance between T helper 17 (Th17) cells and Treg cells have been implicated in autoimmune bone related diseases [61]. In animal studies, it has been demonstrated that defects in Th17 cells played a proinflammatory role whereas Treg cells are anti-inflammatory [62, 63]. Luz-Crawford et al demonstrated that MSCs were capable of suppression of the proliferation, activation and differentiation of CD4+ T cells induced to differentiate into Th1 and Th17 cells, which was accompanied by an increase in the percentage of functional induced CD4+CD25+Foxp3+ Treg cells and increased IL-10 secretion. The study further demonstrated suppression of Th17 cells and an increase in the percentage of CD4+CD25+Foxp3+ Treg cells following MSC injection in mice [64].

Besides their interactions with MSCs, Treg cells have also been found to provide immune privilege to the haematopoietic stem-cell niche. Fujisaki et al demonstrated the persistence of the haematopoietic stem/progenitor cells (HSPCs) from allogeneic donor mice (allo-HSPCs) in non-irradiated recipient mice, which was lost if the FOxP3 Treg cells were depleted. It was also demonstrated that HSPCs co-localised with Treg cells on the endosteal surface in the calvarial and trabecular bone marrow suggesting the role of Treg cells in allo-HSPC persistence. Hence such interactions between bone marrow HSPCs and the Treg cells may play a role in providing a
relative sanctuary from immune attack as the accumulation of Tregs in the HPSC niche shield endogenous HSPCs from autoimmunity or excessive inflammation [65].

4. Role of stem cells in the treatment of spondyloarthritis

The co-existence of an autoimmune disease and a haematological disease in some patients often provides a good opportunity to examine the effects of bone marrow or haemtopoietic stem cell transplantation (BMT/HSCT) on autoimmune diseases in these patients. Hence, reports on the effects of BMT or HSCT on autoimmune diseases are not uncommon and may be dated back a few decades ago [66]. There have also been incidences where HSCT was used for the treatment for severe autoimmune diseases in the absence of a haematological disease [16]. Both autologous and allogeneic transplant, and both myeloablative and non-myeloablative approaches have been reported. Other than the haematopoietic stem cells (HSCs), MSCs have also been used widely in the treatment of autoimmune diseases in various reports with variable outcomes. Both HSC- and MSC-based therapy in a wide range of autoimmune disease including RA, systemic lupus erythematosus (SLE), multiple sclerosis (MS), scleroderma etc. have been extensive reviewed in published literature [16-20, 66]. However, much fewer studies have been carried out on stem cell-based therapy on SpA. There have been several reports on the beneficial effects of HSCT on SpA in which a majority involving HSCT as a treatment for a haematological disease in patients with concomitant SpA. While reports on the HSCT effects on psoriasis in general are abundant [67-69], there are relatively fewer reports that focus specifically on psoriatic arthritis, ankylosis spondylitis or other forms of SpA.

Slavin et al observed graft versus autoimmunity effects following allogenic myeloablative blood stem cell transplantation (STC) in a patient with chronic myelogenous
leukaemia (CML), severe systemic psoriasis and psoriatic polyarthritis [70]. In 2006, Woods and Mants described a case of aplastic anemia with concomitant psoriatic arthritis in which the patient achieved amelioration of severe psoriasis and psoriatic arthritis for twenty years after allogeneic HSTC [71]. The patient had a brief remission followed by a long chronic disability-free period post HSTC. Another patient with psoriatic arthropathy achieved complete remission of psoriatic arthropathy after autologous HSCT for multiple myeloma [72]. The patient was reported to have a 15-year history of arthralgias and oligoarticular SpA. Following myeloablation and autologous HSCT, complete regression of his psoriatic arthropathies and skin lesions was observed, although he eventually had a relapse of his myeloma.

It is worth mentioning that although the presentation of AS can be severe, it is usually not life-threatening. Therefore, HSCT is rarely used in these patients. For those who did receive HSCT as a treatment for AS, a majority of these patients did so because they also had a concomitant haematological disease. Jantunen et al reported a case of autologous stem cell transplant (ASCT) in a patient with lymphoma and a long history of AS [73]. The patient underwent chemotherapy and ASCT for the treatment of lymphoma and successfully achieved clinical remission for both the lymphoma and AS. The first autologous HSCT for the intentional treatment of AS was reported recently in 2012 [74]. In this case, a HLA-B27 positive man received high-chemotherapy and autologous HSCT at the age of 46 years. The patient achieved complete clinical remission throughout the entire two-year follow up period. In another case report, a 39-year-old man with active AS and concomitant acute myeloid leukaemia (AML) was given pre-transplantation total body irradiation and cyclophosphamide followed by allogeneic peripheral blood SCT. He experienced clinical remission and partial radiological regression of
cervical spine syndesmophytes, and remained medication- and symptom-free for three years after the transplantation [75].

More recently, other than stem cells of haematopoietic origin, MSCs have also caught the attention of researchers. For instance, Huang et al [76] have investigated the inhibitory effects of human umbilical cord derived MSCs (hUCMSCs) on peripheral blood T cells from patients with SpA in vivo in search of their therapeutic potential. It was found that co-culturing of peripheral blood mononuclear cells (PBMNC) with hUCMSCs significantly reduced IL-17 production from peripheral blood T cells, suggesting that MSCs may be a good candidate for the treatment of SpA. On the other hand, Wang et al investigated the effects and safety of intravenous infusion (IVI) of allogenic MSCs in patients with AS who have failed non-steroidal anti-inflammatory drugs in a 20-week clinical trial [77]. In the study, 31 AS patients received four IVI of MSCs on days 0, 7, 17 and 21. It was reported that the percentage of Assessment in Ankylosing Spondylitis Response Criteria (ASAS 20) responders reached 77.4% at the end of 4th week with a mean response duration of 7.1 weeks. There was a reduction of the Ankylosing Spondylitis Disease Activity Score Containing C-reactive Protein (ASDAS-CRP) from 3.6±0.6 to 2.4±0.5 at the 4th week, followed by an increase to 3.2±0.8 at the 20th week. There was also a significant reduction in the average total inflammation extent (TIE) detected by MRI, while no adverse effects were noted. The study concluded that IVI of MSCs was safe, feasible and promising for the treatment of AS [77]. However, it is worth mentioning that the difference in ASDAS-CRP between baseline (3.6±0.6) and 4 weeks (2.4±0.5) could be explained by regression to the mean and that a controlled study will better demonstrate the effectiveness of IVI MSCs in SpA.

In addition, there are several registered clinical trials that involve the use of stem cells in SpA. Two clinical trials have been identified at www.clinicaltrial.gov (a registry and results
database of publicly and privately supported clinical studies of human participants conducted around the world). The first is titled “Safety and Efficacy Study of Umbilical Cord/Placenta-Derived Mesenchymal Stem Cells to Treat Ankylosing Spondylitis” [78]. This is a phase I clinical trial lasting two to three years in which the patients in the experimental group will receive MSC transplant with disease modifying drugs (DMARDs) and patients in the control group will receive DMARDs alone. The second is titled “A Molecule Basic Study of Early Warning of New Pathogenic Risk of Ankylosing Spondylitis” [79], in which the investigators will inject human MSCs into active AS patient and study the gene expression profiles of their PBMCs and related pathogenesis before and after treatment. A third phase I/II clinical trial was retrieved at the Chinese Clinical Trial Registry titled “Clinical Study of Mecenchymal Stem Cells Transplantation in Ankylosing Spondylitis” [80] in which the investigators study the safety and the clinical effects of MSC transplantation in AS patients. The use of stem cells in SpA is summarised in Table 1.

5. Complications of the use of stem cells in autoimmune diseases

To date, despite past success and promising results from various studies, stem cell-based therapy is still not the treatment of choice in SpA or other types of autoimmune diseases except in very severe diseases or where there is failure of traditional treatment options. Although evidence of complications of stem cell therapy in SpA is not abundant due to scarcity of the published literature, lessons can be learnt from complications of HSCT and other stem cell-based therapy in other diseases, particular autoimmune diseases. Some of the complications of HSCT in the treatment of autoimmune diseases have been reviewed [81], which include treatment-
related mortality, infectious complications, treatment-associated toxicity, endocrinological complications, and secondary autoimmune diseases and malignancies after HSTC.

Like a double-edged sword the use of stem cells to treat autoimmune diseases have been shown to give rise to the development of secondary autoimmune diseases and inflammatory arthritis. Autoimmune phenomenon of haematological, endocrinological, neurological and rheumatological nature has been reported. The wide range of secondary autoimmune conditions developed post HSCT includes arthritis, SLE, vasculitis, eosinophilic fasciitis, antiphospholipid antibody syndrome, thyroiditis, autoimmune haemolytic anaemia, pancytopenia scleroderma etc. [81-84]. This has led researchers to turn their attention to other types of stem cells such as the MSCs. However, MSC-based treatments are not without their complications. The immunosuppressive and immunomodulatory properties of MSCs make them promising therapeutic agents in autoimmune diseases [85]. Nevertheless, MSCs have been reported to be involved in leukaemogenesis and to support tumour growth in various types of cancers (reviewed by Wong; Wong & Cheong) [86, 87].

Interestingly, there have been several sporadic reports on the development of SpA after BMT or SCT. In 1997, after receiving syngeneic bone marrow from a psoriatic donor, a patient was reported to develop psoriasis. Recurrence of the psoriasis with arthropathy was observed after a second syngeneic BMT [88]. Similarly, a HLA-B27 negative patient with CML developed psoriasis and psoriatic arthritis after receiving bone marrow from his HLA-identical brother, who had psoriatic skin lesions [89]. In 2000, a case report described the first manifestations of seronegative SpA following autologous SCT in three HLA-B27 positive patients, in which two were male patients with non-Hodgkin lymphoma and one, female patient with AML. Two of the three patients had X-ray evidence of sacroiliitis. All three patients had
enthesopathy and were subsequently tested positive for HLA-B27. The development of these SpA manifestations took between 4 and 15.5 years after SCT [90]. In 2010, another case report described the development of undifferentiated SpA in a 26-year-old male patient following allogeneic SCT. The patient was diagnosed with acute pre-B lymphocytic leukaemia at 10 years of age and had received allogeneic SCT from his father. The patient developed signs of SpA 10 years after SCT and showed signs of axial disease with dactylitis insidiously [91].

6. Conclusion

Several points can be concluded concerning the role of stem cells in SpA:

- **The role of stem cells in the pathogenesis is not fully understood**
  Further explorations on how stem cells, especially the MSCs contribute to the pathogenesis of SpA are necessary. It is also beneficial to elucidate the mechanisms of secondary autoimmune disease and SpA manifestations after HSCT.

- **There is insufficient data to support the role of stem cells in the treatment of SpA**
  Data currently available is inconclusive to suggest whether stem cells can cure or significantly improve SpA symptoms. Most published clinical studies are short-term, involving a small number of patients or are mostly case reports. There may be publication biases in the relief of symptoms in some SpA patients as only striking improvements following STC or HSCT were being reported whereas those cases with poor outcomes may have been excluded from publication.
• Larger studies with longer follow-up periods are needed to support the use of stem cells in the treatment of SpA

Clinical trials with a large sample size and long-term follow-ups are crucial to prove the safety and efficacy of stem cell use in SpA treatment. This can provide insights into the sustainability of treatment, relapse of disease after treatment, as well as the long-term complications of stem cell-based therapy.

• Not all stem cell types can be used in the treatment of SpA

So far, the effects of stem cells of haematopoietic origin and the MSCs have been reported in the treatment of SpA. Literature on the use of other types of stem cells in the treatment of SpA is scarce.

• Stem cells therapy for SpA may not be suitable for all types of patients

The careful choice of patients is important as not all patients are suitable candidates of stem cell therapy. Only those with very severe diseases who are not responsive to conventional treatment should be considered for such treatment.

• The use of stem cells is not without risks and complications

The benefits of the treatment must outweigh the risks as stem cell therapy is not without disadvantages. The complications caused by each type of stem cells have to be thoroughly studied before they become commonly used in SpA treatment.
References


**Figure legends**

Figure 1 Role of stem cells in the pathogenesis of spondyloarthritis. (AS= ankylosing spondylitis; HSPCs= haematopoietic stem/progenitor cells; IL= interleukin; MSCs= mesenchymal stem cells; SpA= spondyloarthritis; Th cells= T helper cells; TNF= tumour necrosis factor; TNAP= tissue non-specific alkaline phosphatase; Treg cells= Regulatory T cells)

Figure 2 (A) Complications of stem cell-based therapy in autoimmune disease or in general. (B) Development of SpA after bone marrow or stem cell transplantation.
Patients with SpA had MSCs with reduced immunomodulatory potential. MSCs played a role in induction of CCR4+CCR6+ Th/Treg cell imbalance in peripheral blood [44].

MSCs may play a role in abnormal osteoblastic differentiation that led to entheseal ossification in diffuse idiopathic skeletal hyperostosis, which share similarities with some forms of AS [52-54].

TNF-α and IL-1β inhibit collagen expression and stimulated TNAP activity leading to new bone formation in SpA [47].

Autocrine stimulation of osteoblast activity by Wnt5a in response to TNF-α in human MSCs led to excessive bone formation [48].

Induction of osteogenesis in MSCs by monocytes or macrophages relied on oncostatin, a cytokine belonging to the IL-6 family [49].

Adipocytes are a rich source of pro-inflammatory apokines. Increased levels of resistatin, visfatin, leptin, apenectin and apelin in AS patients have been reported [55-59].

Suppression of the proliferation, activation and differentiation of CD4+ T cells induced to differentiate into Th1 and pro-inflammatory Th17 cells [64].

In vitro
Increased percentage of functional induced anti-inflammatory CD4+CD25+Foxp3+ Treg cells and increased IL-10 secretion [64].

In vivo
Increased percentage of CD4+CD25+Foxp3+ Treg cells following MSC injection in mice [64].

HSPCs co-localised with Treg cells on the endosteal surface in the calvarial and trabecular bone marrow. Interactions between bone marrow HSPCs and the Treg cells may play a role in providing a relative sanctuary from immune attack [65].

In increased osteoblast activity and bone formation

Co-localisation of HSPCs and Treg cells in bone marrow

MSC-derived adipocytes

Harmful effects

Th cells

MSCs

Increased osteoblast activity and bone formation

HSPCs co-localised with Treg cells on the endosteal surface in the calvarial and trabecular bone marrow. Interactions between bone marrow HSPCs and the Treg cells may play a role in providing a relative sanctuary from immune attack [65].
Complications of stem cell-based therapy in autoimmune disease or in general

- Treatment-related mortality
- Infections complications
- Support leukaemogenesis
- Support tumour growth in various types of cancers
- Secondary malignancies
- Secondary autoimmune disease
- Endocrinological complications

Complications related to bone marrow or haematopoietic stem cell transplantation in autoimmune disease [83-85]
Complications related to the use of mesenchymal stem cells in general [86,87]

BMT: Bone marrow transplantation
SpA: Spondyloarthritis
SCT: Stem cell transplantation

A

Transmission of psoriasis after first syngeneic BMT. Recurrence of psoriasis with arthropathy after a second syngeneic BMT [88].

Development of SpA and psoriatic arthritis after receiving bone marrow from HLA-identical donor with psoriatic skin lesions [89].

Development of seronegative SpA manifestations including sacroiliitis and enthesopathy after autologous SCT [90].

Development of signs of SpA including signs of axial disease and dactylitis after allogeneic SCT [91].

B
<table>
<thead>
<tr>
<th>Disease</th>
<th>Stem cell type</th>
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<tr>
<td><strong>Severe psoriasis with psoriatic polyarthritis</strong></td>
<td>Allogenic myeloablative blood stem cell transplantation</td>
<td>The patient had concomitant chronic myelogenous leukaemia. Graft versus autoimmunity effects were observed following allogenic myeloablative blood stem cell transplantation</td>
<td>[68]</td>
</tr>
<tr>
<td><strong>Severe psoriasis and psoriatic arthritis</strong></td>
<td>Allogeneic haematopoietic stem cell transplantation</td>
<td>The patient had concomitant aplastic anemia. He experienced a brief remission followed by a long chronic disability-free period post HSTC</td>
<td>[71]</td>
</tr>
<tr>
<td><strong>Psoriatic arthropathy and psoriasis vulgaris</strong></td>
<td>Autologous myeloablative haematopoietic stem cell transplantation</td>
<td>The patient had concomitant multiple myeloma. He had complete regression of his psoriatic arthropathies and skin lesions and an eventual relapse of his myeloma</td>
<td>[72]</td>
</tr>
<tr>
<td><strong>Ankylosing spondylitis</strong></td>
<td>Autologous stem cell transplantation</td>
<td>The patient had concomitant lymphoma and underwent chemotherapy and ASCT for the treatment of lymphoma. Successful achievement of clinical remission for both lymphoma and AS.</td>
<td>[73]</td>
</tr>
<tr>
<td><strong>Ankylosing spondylitis</strong></td>
<td>Allogeneic peripheral blood stem cell transplantation</td>
<td>The patient also had concomitant acute myeloid leukaemia. He was given pre-transplantation total body irradiation and cyclophosphamide. He experienced clinical remission and partial radiological regression of cervical spine syndesmophytes.</td>
<td>[74]</td>
</tr>
<tr>
<td><strong>Ankylosing spondylitis</strong></td>
<td>Autologous haematopoietic stem cell transplant</td>
<td>The first reported case of intentional autologous HSCT for AS. A HLA-B27 positive man received high-chemotherapy and autologous HSCT and achieved complete clinical remission throughout the entire 2-year follow up period.</td>
<td>[75]</td>
</tr>
<tr>
<td><strong>Ankylosing spondylitis</strong></td>
<td>Intravenous infusion of allogeneic mesenchymal stem cells</td>
<td>20-week clinical trial involving 31 AS patients who have failed NSAIDs. The percentage of ASAS 20 responders reached 77.4% at the 4th week with a mean response duration of 7.1 weeks. A reduction in ASDS-CRP and TIE was observed. No adverse effects noted.</td>
<td>[77]</td>
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**Registered clinical trials**

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<td>[78]</td>
</tr>
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<td><strong>Ankylosing spondylitis</strong></td>
<td>Human mesenchymal stem cells</td>
<td>Human MSCs injection into active AS patient to study the gene expression profiles of their PBMCs and related pathogenesis before and after treatment.</td>
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</tbody>
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Ankylosing spondylitis Mesenchymal stem cells A phase I/II clinical trial to study the safety and clinical effects of MSC transplantation in AS patients. [80]

AS= Ankylosing spondylitis; ASAS 20= Assessment in Ankylosing Spondylitis Response Criteria; ASCT= Autologous stem cell transplantation; ASDAS-CRP= Ankylosing Spondylitis Disease Activity Score Containing C-reactive Protein; DMARD= Disease-modifying drugs; MSC= Mesenchymal stem cells; NSAID= Non-steroidal anti-inflammatory drug; PBMC=Peripheral blood mononuclear cell; TIE= total inflammation extent