1-2019

Ankylosing Spondylitis and Mesenchymal Stromal/Stem Cell Therapy: A New Therapeutic Approach

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Biomedicine & Pharmacotherapy 109 (2019) 1196–1205

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Ankylosing spondylitis and mesenchymal stromal/stem cell therapy: a new therapeutic approach

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ARTICLE INFO

Keywords:
Ankylosing spondylitis
Mesenchymal stem cells
Immunopathogenesis
Therapeutic approach
Inflammation

ABSTRACT

Ankylosing spondylitis (AS) is an inflammatory rheumatoid disease categorized within spondyloarthropathies (SpA) and manifested by chronic spinal arthritis. Several innate and adaptive immune cells and secreted-mediators have been indicated to play a role in AS pathogenesis. Considering the limitations of current therapeutic approaches (NSAIDs, glucocorticoids, DMARDs and biologic drugs), finding new treatments with fewer side effects and high therapeutic potentials are required in AS. Mesenchymal stem cells (MSCs) with considerable immunomodulatory and regenerative properties could be able to attenuate the inflammatory responses and help tissue repair by cell-to-cell contact and secretion of soluble factors. Moreover, MSCs do not express HLA-DR, which renders them a favorable therapeutic choice for transplantation in immune-mediated disorders.

In the present review, we describe immunopathogenesis and current treatments restrictions of AS. Afterwards, immunomodulatory properties and applications of MSCs in immune-mediated disorders, as well as recent findings of clinical trials involving mesenchymal stem cell therapy (MSCT) in ankylosing spondylitis, will be discussed in detail.

Additional studies are required to investigate several features of MSCT such as cell origin, dosage, administration route and, specifically, the most suitable stage of disease for ideal intervention.

1. Introduction

Ankylosing spondylitis (AS) is a chronic progressive spinal inflammatory arthritis and belongs to the spondyloarthropathies (SpA) group. Clinical manifestations usually emerge in the third decade of life [1,2]. AS characteristically affects the sacroiliac joints, axial skeleton, entheses (tendon or ligament attachments to bone), and extra-skeletal sites such as the eye [3], bowel [4] and skin [5] can frequently be affected. Inflammation processes associated with AS can lead to bone erosion, new bone formation, and ankylosis occurring in the spine, which leads to severe pain, a reduction in spinal mobility and stiffness [1]. By region, the average prevalence of ankylosing spondylitis per 10,000 individuals has been reported as 16.7 in Asia, 23.8 in Europe, 31.9 in North America, and 10.2 in Latin America [6]. Also, there is some gender difference in AS patients between continents and countries. Globally, the gender ratio (male: female) is 2.5:1 [7]. The diagnostic approaches for AS include attention to the medical history, physical exam with Bath Ankylosing Spondylitis Metrology Index (BASMI), radiographs of the cervical, thoracic, and lumbar spines, ultrasound and baseline patient-completed outcome questionnaires like Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) [2,8–11] (Table 1).

It has been suggested that cellular elements and cytokine networks, especially the interleukin-23 (IL-23)/ IL-17 pathway [12,13], involved

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https://doi.org/10.1016/j.biopha.2018.10.137
Received 14 August 2018; Received in revised form 22 October 2018; Accepted 24 October 2018

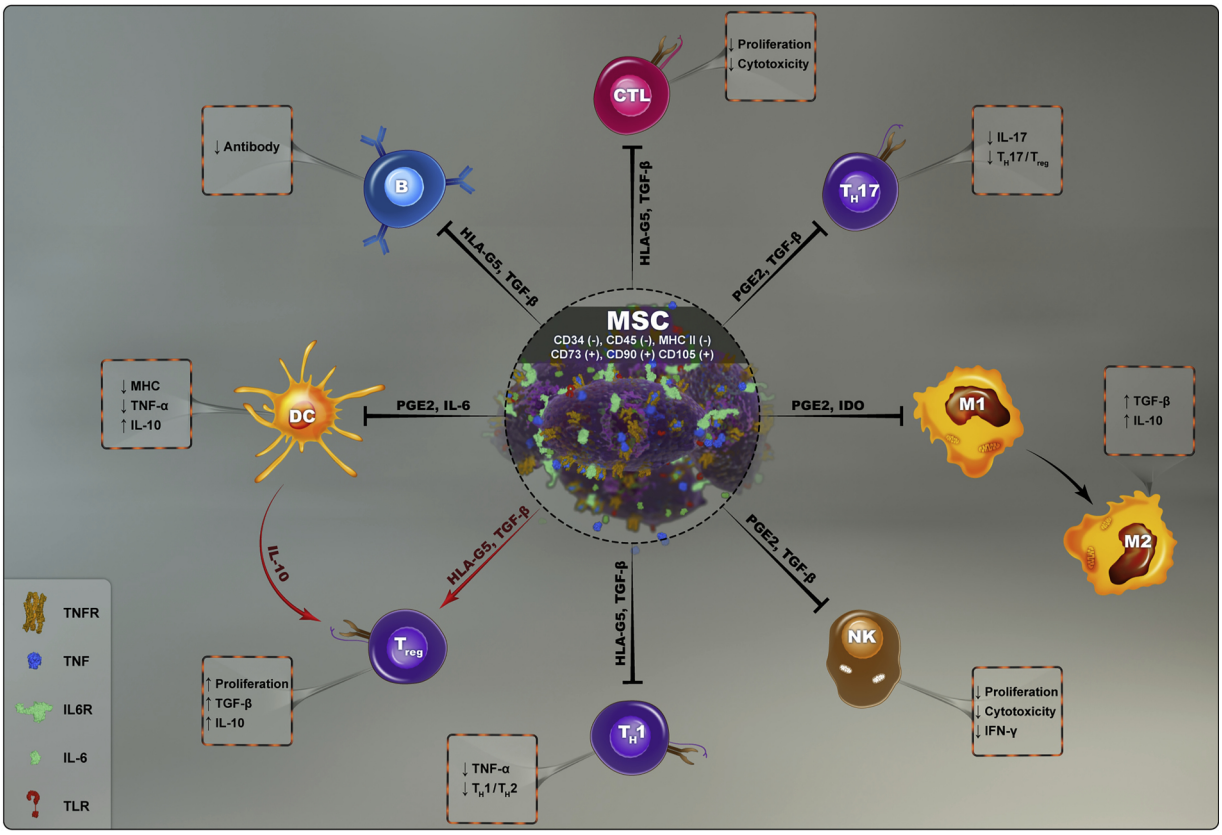

Fig. 1. Mesenchymal stem cells can modulate activation of immune cells involved in the pathogenesis of ankylosing spondylitis.
MSCs express surface molecules such as CD73, CD90, and CD105, but not CD34, CD45, and MHC II, confirmed by flow cytometric analysis. These cells produce many immunomodulatory molecules such as TGF-β, HLA-G5, PGE2, and IDO in response to inflammatory stimulants (IFN-γ, TNF-α, LPS). These stimulants can affect the secretion levels of the immunomodulatory molecules and have subsequent effects on the immune regulation. MSCs with the secretion of PGE2 and TGF-β can decrease proliferation, cytotoxicity, and IFN-γ production activity of NK cells. TGF-β, PGE2, and HLA-G5 are the potent immunomodulatory molecules of MSCs that can suppress the immune system by inhibition of dendritic cell maturation and induction of Treg cell production. On the other hand, MSCs can inhibit the proliferation and activity of effector T cells such as TH1, TH17, and CTL in the pathogenesis of AS. Also, IDO and PGE2 can induce the switch of M1 macrophages to the anti-inflammatory (M2) cells. Therefore, MSC therapy would pave the way for developing efficient methods of cell therapy to improve the treatment of AS in future. MSCs: mesenchymal stem cells; CTL: cytotoxic T lymphocyte; TH: T helper cell; M: macrophage; NK: natural killer cell; Treg: T regulatory cell; DC: dendritic cell; B: B cell; TNF-α: Tumor necrosis factor alpha; TNFR: TNF-α receptor; IL: interleukin; ILR: interleukin receptor; TLR: Toll-like receptor; TGF-β: transforming growth factor β; HLA-G5: human leukocyte antigen G5; PGE2: prostaglandin E2; IDO: indolamine; IFN-γ: interferon gamma.

with innate and adaptive immunity are closely associated with triggering, initiation, and progression of disease inflammation, both acute and chronic [14]. Current drug therapy options are focused on reducing inflammation, stiffness, back pain, and disability. These treatments include non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and biologic agents, including tumor necrosis factor (TNF) and IL-17 A blockers [15,16]. Despite these therapies reducing inflammation and improving clinical manifestations and ankylosing spondylitis quality of life (ASQoL), many patients with ankylosing spondylitis suffer from unresponsive or unbearable side effects from the drugs [17–20] (Fig. 1).

Given that there is no cure for AS, using stem cells has the promise to raise hope as a beneficial treatment option. Mesenchymal stem cells (MSCs) are a kind of stem cells that can revolutionize medicine due to their multipotent capacity and immunomodulatory properties. These cells can migrate chemotactically to the site of inflammation and injury, where they could apply anti-inflammatory and repairing effects [21–23]. Bone marrow is the primary source for harvesting MSCs; furthermore, umbilical cord and adipose tissue are the other main source of these cells. Also, different tissues including lung, periosteum, synovium, tendon, skeletal muscle, deciduous teeth, and peripheral blood can be used [24,25]. However, before exploiting MSCs in the clinic, this new cell-based treatment must be carefully studied for safety and effectiveness.

In this review, we will discuss the ankylosing spondylitis and mesenchymal stem cell therapy (MSCT). The first two sections of the present review cover immunopathogenesis of AS, therapeutic approaches and their restrictions in AS patients. The review then describes the immunomodulatory and regenerative properties and applications of MSCs in different immunological disorders. The final section of this review will cover recent approval of clinical trials of mesenchymal stem cells for treating ankylosing spondylitis.

2. Immunopathogenesis of AS

Considering the inflammatory feature of AS, various cells, cytokines, and genes have been investigated to find any association between AS pathogenesis and immunologic factors.

2.1. HLA-B27

The most studied subject in this context is human leukocyte antigen B27 (HLA-B27), of which 27:02, 27:03, 27:04 and 27:05 subtypes have been indicated as the most relevant molecules susceptible to AS. As a meta-analysis on 8993 AS patients and 19,254 healthy controls showed relative ratios (RR) of 16.02 for HLA-B27, 1.28 for HLA-B*2702 and 1.14 for HLA-B27*04 in ankylosing spondylitis [26].

There are four main hypothesis associating HLA-B27 to AS

pathogenesis, as follows.

The first one is "*arthritogenic peptide,*" which focuses on an aberrant antigen presentation to $TCD8^+$ cells due to the resemblance of microbial peptides as those presented in joints. This phenomenon is probably due to mentioned HLA subtypes' ability to present some intrinsic antigens in two different forms. Therefore, T cell development in thymus would result in less efficient negative selection; as a consequence there would be some autoreactive $TCD8^+$ subtypes in circulation able to recognize HLAB27/autopeptide complexes in the second form of presentation. The problem will occur when these T cells encounter their specific microbial antigens (e.g. pLMP2 of EBV) similar to autoantigens since their attack will be directed toward both foreign and self-antigens.

The second hypothesis is "*misfolding theory,*" which is in favor of unfolded protein response (UPR) as AS etiology and blames unusual conformation and slow folding of the HLA-B27 heavy chain for inflammatory responses in joint. Unfolded heavy chains tend to misfold and accumulate in the endoplasmic reticulum (ER); such accumulation would induce ER stress and activate the UPR, including activation of NF-κB transcription factor. NF-κB triggers pro-inflammatory cytokines production among them IL-23, a major agent involved in AS pathogenesis.

"*Failure in eliminating microbial pathogens*" is the other theory based on HLA-B27 inability to present certain antigens to $TCD8^+$ cells, resulting in microbial survival and sustained inflammation.

Finally "*homodimer effect,*" in which the α heavy chain, after dissociation from the beta-2-microglobulin light chain (B_2m), binds to its homolog molecule and generates a homodimeric HLA-B27 molecule, which is assumed to be a ligand for KIR3DL2 on $TCD4^+$ and natural killer (NK) cells. These cells together with T cells with δγ T-cell receptor (δγ T), T helper 17 (TH17) cells, natural killer T (NKT) cells, $TCD4^-CD8^-$ and mast cells are supposed to produce IL-17, the key player in promoting inflammatory responses in AS. Moreover, KIR3DL2 binding to B27 homodimer inhibits activation-induced cell death (AICD) driven by TCR/NK interactions, promoting the survival of pathogenic Th17 and NK cell subsets in circulation [27,28].

2.2. Cytokines

As mentioned above, IL-23 is a prominent cytokine with elevated serum levels and is involved in chronic inflammation of AS, which triggers IL-22 and IL-17 production. Among IL-23 receptors, rs1004819, rs1495965, and rs2201841 have been demonstrated to be significantly higher in AS patients (p-value < .001, < .001, = .010, respectively) [29,30]. AS pathogenesis is also linked to the proinflammatory cytokines IL-1 and IL-6, as IL-1 SNPs rs2856836, rs17561, rs1894399, rs3811581, and rs1800587 were found to be significantly increased in Europeans with AS [31,32]. Moreover, TNF-α is overexpressed in AS patients' mononuclear cells, and its inhibition has been applied as a therapeutic tool in the clinic which will be discussed later [33].

2.3. B lymphocytes

The contribution of B cells to AS has been defined as highly expressing HLA-B27 antigen presenting cells, as well as autoantibody-producing plasma cells. In addition, decreased number of $CD27^+$ memory B cells and increased proportion of $CD27^-$ naïve B population, together with a higher percentage of $CD86^+$ B cells, have been demonstrated in the peripheral blood of AS patients, suggesting an excessive activation of these cells at least in relapse phase [34]. In another study, it was shown that although $CD24^+CD38^+$ B regulatory (Breg) cells' percentage is similar to healthy controls, their suppressive function is significantly reduced due to defective IL-10 production [35].

2.4. T lymphocytes

T helper 1 (Th1) and Th17 cells have been suggested as playing a considerable role in the pathogenesis of AS. Compared to healthy individuals, ratios of Th1/Th2 and Th17/ T regulatory (Treg) cell are significantly greater in patients with AS. These imbalanced ratios are accompanied by excessive interferon gamma (IFN-γ) and IL-17 A cytokines production [36]. $Foxp3^+$ Treg cells number is also decreased in peripheral blood of AS patients and these cells responsiveness to IL-2 is diminished. Tregs isolated from patients with active AS are not able to inhibit T cells proliferation properly [37].

2.5. Dendritic cells, macrophages, and NK cells

There is a study indicating a significant decrease in circulating myeloid CD1c-expressing dendritic cells in AS patients, whereas $CD14^-$ $CD16^+$ mononuclear cell frequency was increased. The latter group is supposed to augment Th17 cells' inflammatory activities through IL-6 secretion [38].

$CD163^+$ macrophages, $CD68^+$ macrophages, and osteoclasts have also been detected in peripheral arthritis, as well as sacroiliitis lesions of AS patients. In addition, depletion of macrophages has had anti-inflammatory effects in animal models [14].

The $CD56^{dim}$ $CD16^+$ subset of NK cells have increased levels in ankylosing spondylitis patients' circulation; these cells express considerable amounts of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM-1) on their surface, facilitating their tissue entrance. Increased number of NK cells is correlated with BASDAI score of disease [39].

2.6. ERAP

Peptide trimming enzyme, endoplasmic reticulum aminopeptidase 1 (ERAP-1) should be added to the list of immune components involved in AS, owing to the fact that certain SNPs of ERAP-1 are associated with HLA-B27-induced risk of developing ankylosing spondylitis. The SNPs rs30187 (OR = 1.255), rs27044, rs10050860, rs2287987, rs17482078, and rs26653 in a meta-analysis of 19,902 AS patients and 39,750 controls have been demonstrated to increase the susceptibility to AS [40]. Impaired ERAP-1 function in shedding cytokine receptors (e.g. TNFR, IL-1R2, and IL-6) from cell surface has also been demonstrated in AS patients [41,42].

3. AS therapeutic approaches and their restrictions

The major purpose of therapy in patients affected with AS is to attenuate inflammation and relieve progressive back pain, morning stiffness, fatigue, and movement disabilities and as a result, improve ASQoL [43]. Current AS treatments are widely pharmacological interventions.

NSAIDs are still the first line of drugs that alleviate preliminary clinical symptoms of this ailment and dramatically diminish pain and stiffness of active AS patients [44]. Although long-term consumption of NSAIDs, particularly in symptomatic active patients, results in promising effects in slowing spinal radiographic progression [45], some patients have experienced gastrointestinal and cardiovascular difficulties [46]. Continuous consumption of NSAIDs induce upper gastrointestinal ulcers in about one-third of patients, which is diagnosed by endoscopy [47]. In these cases, selective inhibitors of cyclooxygenase (COX)-2, such as celecoxib and meloxicam, which have less serious side effects, should be prescribed [48]. Meanwhile, on the basis of the Massó-González study, coxibs have less relative risk estimate of gastrointestinal bleeding/perforation compared to traditional NSAIDs (OR: 1.88 vs 4.50, respectively) [49].

Cardiovascular disease is stated as the most common cause of mortality in AS patients. The rate of cardiovascular dysfunction in AS patients range from 2 to 10%. In at-risk patients with long-term AS, increased heart morbidity rates are reported [50]. Cardiovascular events comprising of conduction and rhythm disturbances, valve

insufficiency (aortic and mitral), myocardial infarction, stroke, ischemic heart failure, and acute coronary syndrome, are related to the chronic inflammatory pathology of AS [51,52]. The relative risk estimate of cardiovascular events in AS patients ranges from 1.0 to 2.0. Celecoxib-related adverse events increase with high dose regimen of drug and the background risk of patients [53].

Regarding these drawbacks, NSAIDs should be prescribed cautiously. Taking this into account, the previous history of gastrointestinal and cardiovascular risks, the dose and duration of NSAIDs and concomitant use with other drugs can influence the side effects of NSAIDs [47].

Glucocorticoids are the subsequent suggested medication to suppress inflammation and reduce spinal pain in some subjects with a flare-up of AS symptoms. Glucocorticoids can be taken orally or injected into affected joints locally [54]. AS patients with concurrent acute anterior uveitis (AAU) show a good response to this treatment. As a result, both eye inflammation and expression of IL-17 and IL-23 cytokines reduced in active AS patients with AAU [55]. However, the long-term use of glucocorticoids can lead to serious adverse effects, including osteoporosis and increased risk of bone fractures, the occurrence of new infections and weight gain [56,57].

DMARDs are the next group of drugs that have proven to be efficacious for only peripheral joint involvement and some extra-articular manifestations, like uveitis and bowel inflammation [44]. Sulphasalazine (SSZ), a highly effective type of DMARDs, is helpful for dampening symptomatic arthritis in patients with the more active disease but have no significant impact on the axial skeleton [20]. Methotrexate (MTX), another conventional DMARD, seem to be less effective in AS in contrast with RA. Moreover, in some patients with persistent joint involvement, combination DMARDs therapy may be beneficial to manage arthritis [58]. Despite inhibiting IL-1 and TNF- α production, sulphasalazine also induce apoptosis of immune cells. While methotrexate, by inhibiting the enzyme dihydrofolate reductase, is a purine metabolism inhibitor. Therefore, by increasing adenosine, its inhibitory effects are widely applied [59,60]. Also, DMARDs can influence the expression and function of ATP-binding cassette (ABC) proteins in the autoimmune diseases [61].

The recent emerging line of therapies is comprised of biologic agents with beneficial outcomes, particularly anti-TNF-α. TNF-α is a pro-inflammatory cytokine that is predominantly generated by activated macrophages and lymphocytes during immune responses [62]. Previous studies demonstrated the elevated amount of TNF-α in AS subjects, indicating its fundamental role in disease pathogenesis [63].

The use of TNF-α inhibitors is the best choice for patients who poorly respond to former treatments. Four synthetic anti-TNF-α agents, including infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®) and the recombinant receptor etanercept (Enbrel®) [64] are currently used in order to dramatically decrease signs of spinal inflammation and seem to improve imaging outcomes [65]. In addition to axial manifestations, TNF-α inhibitors could improve uveitis, peripheral arthritis and bowel inflammation [66]. Furthermore, TNF-α blockers have shown to down-regulate ESR and serum level of CRP in active AS patients. They can be more beneficial if injected in the early phase of disease development [65].

The most important obstacle is that almost 40% of AS patients are unable to tolerate or respond to conditional medications [67]. In a proportion of patients with inadequate response to first anti-TNF therapy, alternative TNF-α inhibitor will be used. Despite switching TNF-blocking agent, there is still a chance of failure because of drug inefficacy or possible side effects [18,46].

Another substantial risk of the anti-TNF-α appliance is the recurrence of bacterial and fungal infections, especially tuberculosis (TB) and candidiasis, as a result of suppressing immune responses [17,67]. The incidence rate of these serious infections are low but are severe, or even fatal, in some cases. Data from a meta-analysis by XU et al. revealed that relative risk of TB in AS patients receiving anti-TNF agents was 2.42 compared to the control group; however, the ratio was not significant. TB recurrence was mostly correlated with patients receiving infliximab, while those receiving etanercept had the less immunogenic potency to reactivate TB [68]. As about 5–10% of patients with latent TB infection will ultimately develop to active TB, physicians have to perform appropriate screening of patients in a timely manner, in terms of being mycobacteria-infected prior to treatment commencing [69].

In a meta-analysis that carried out in 2016, Wei Liu et al. observed no significant statistical differences concerning efficacy and safety of TNF-α inhibitors [70]. The results of short-term follow-up studies indicate little to no difference in the number of patients dealing with serious infection with various anti-TNF-α drugs compared to subjects who receive a placebo [71].

Furthermore, TNF-α inhibitors do not guarantee long-term remission and cessation of therapy, resulting in AS recurrence [18,19]. Withdrawal of anti-TNF therapy leads to relapse within 6–12 months in almost all patients, requiring re-administration [72].

Unfortunately, TNF-α blockade appears to be unable to halt new spinal bone formation in progressive AS, although it is not clearly characterized whether TNF- α is related to structural progression in the spine of AS patients or not. Several cohort studies proposed that TNF-driven inflammation may be independent from syndesmophyte formation in AS [73].

In addition to these commonly taken medications, several treatments are being investigated in order to obtain approvals. Certolizumab pegol (Cimzia®) is a medicine targeting TNF-α function in phase III axial SpA clinical trial [74,75]. Pathan et al. reported the probable effectiveness of oral phosphodiesterase 4 inhibitor, apremilast (Otezla®), in a double-blind phase II study in AS treatment [76].

Secukinumab, a newly discovered monoclonal antibody against IL-17, is the first approved non-anti-TNF biologic agent and appears to have considerable benefits in patients with weak response to TNF-α blockade [77]. In spite of the fact that patients receiving secukinumab showed improvement rate up to 40%. According to the Assessment of SpondyloArthritis Society (ASAS), administration of this drug resulted in *staphylococcus aureus*-caused abscess in a patient in the secukinumab-treated group [15]. Efficacy, safety, and tolerability of secukinumab are currently undergoing phase 3 clinical trials. In this randomized 3-year study, the risk of candida infections and uveitis were reported, but no occurrence of cardiovascular events, Crohn's disease or ulcerative colitis [78].

With regard to therapeutic limitations in the current AS treatment modalities (those containing NSAIDs, glucocorticoids, DMARDs and biologic drugs), deciphering new medicinal approaches without these adverse events is essential for efficacious anti-inflammatory therapies. A promising therapeutic approach for inflammatory disorders and tissue injuries seems to be mesenchymal stem cell therapy [54,79–81]. Respecting immunomodulatory and regenerative properties of mesenchymal stem cells, the beneficial effects of MSCT are demonstrated in several experimental studies [82–84].

4. MSCs; the immunomodulatory and regenerative properties

Mesenchymal stromal or stem cells were first described in 1976. They are multipotent stromal cells and have a self-renewal proficiency to differentiate into various cell types, including osteoblasts, chondrocytes, and adipocytes [85–87]. MSCs can be acquired from bone marrow, adipose tissue, umbilical cord, molar cells, amniotic fluid and peripheral blood [86,88–90]. The frequency ranges of MSCs have been reported in the previous reports based on CFU-F (fibroblast colony-forming unit) measurement. The CFU-F assay is used for measurement of MSC frequency in different tissues and sites. According to the CFU-F/10^6 nucleated cells, the mean value of MSCs originated from bone marrow, adipose tissue, dermis, umbilical cord blood, peripheral blood, synovial fluid, and amniotic fluid are 46, 25602, 115500, 0.01, 1, 126, 4.6 respectively [91,92]. These cells express CD29, CD44, CD73, CD90, CD105, CD106, and CD166, but not CD11b, CD14, CD34, CD45 nor HLA-DR, confirmed by flow cytometric analysis in vitro [86,93,94]. MSCs have antioxidative, angiogenic and anti-inflammatory properties [90,95,96]. These cells can be isolated easily and are very proliferative in vitro. Additionally, neither local transplantation nor systemic administration can induce immunoreactivity in the host [97,98].

Table 1
Advantages and disadvantages of MSCs as a therapeutic option in ankylosing spondylitis.

Advantages	Disadvantages
Accessibility (Bone marrow, Adipose, Umbilical cord, …)	Limited application for aging MSCs
Easy to harvest and expand in tissue culture	The possibility for malignant transformation
Immunosuppressive effects (Cell contact, soluble factors secretion)	Poor differentiation and short-term activity in vivo
Multi lineage differentiation (Regenerative effects)	Limited engraftment
Favorable therapeutic choice for transplantation (HLA-DR$^-$)	Possibility of contamination
Possibility of autograft application	

Secreted molecules from these cells include hepatocyte growth factor-1 (HGF-1), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), tumor necrosis factor-stimulated gene-6 (TSG-6), prostaglandin E2 (PGE2), galectin 1 and 9, as well as MSC-derived microvesicles that play different roles in the host [90,94,99].

4.1. Immunomodulatory effects of MSCs

MSCs induce a positional inhibitory environment through inhibition by cell-to-cell contact and soluble factor secretion. Numerous studies have shown that MSCs possess immunomodulatory effects. Secretion of many biological molecules and mediators, such as cytokines, from these cells plays an important role in this process. Human MSCs avoid allorecognition, prevent the dendritic cell, T-cell and microglia function, and proliferation. In this process, MSCs can modulate the cytokine secretion of dendritic cells, macrophages, and monocytes. Secreted cytokines and factors can induce the switch of M1 macrophages to the anti-inflammatory cells that in this path, the role of indolamine (IDO) and PGE2 have been identified. MSCs can prevent the reactive oxygen species production by neutrophils in inflammatory conditions. Furthermore, MSCs have low immunogenicity due to the absence of cell surface HLA- DR and co-stimulatory molecules such as CD40, CD80, and CD86. In this way, MSCs can affect immune function of cells and exert the immunosuppressive effects, and these properties can confer many therapeutic benefits of MSC transplantation in diseases [85,98,100–102].

MSCs produce many molecules in response to various stimulants, such as hypoxia, and inflammatory stimulants (IFN-γ, TNF-α, LPS). These stimulants can affect the secretion levels of these molecules and have subsequent effects on the immune regulation [99,102].

4.1.1. The effect of MSCs on NK cells

MSCs can decrease the activity of natural killer cells. NK cells have important roles in the innate immune response, and the immunomodulatory effects of MCS transplantation have been demonstrated in acute myocardial infarction (AMI) by a decrease of infarct lesion size [96]. Secretion of PGE2 by MSCs can decrease the proliferation and cytotoxicity activity of NK cells as well as affect CD56 marker expression in these cells [103].

4.1.2. The effect of MSCs on dendritic cells, neutrophils, B and T cells

TGF-β is the potent cytokine to suppress the immune system by inhibition of dendritic cell maturation and induction of Treg cell production [99]. On the other hand, TSG-6 can neutralize the inflammatory effects of TNF-α and IL-1. PGE2 has suppressive roles in the immune system, including inhibiting proliferation and activity of T cell [94,99].

MSCs can inhibit the T cell and B cell activity by direct contact [94], as well as by having an inhibitory effect on the Tregs through the action of HLA-G5 and TGF-β secretion [102]. On the other hand, MSCs can affect the tissue migration of neutrophils by the effect of IDO, TGF-β and IL-6 secretion [104].

4.2. Regenerative properties of MSCs

MSCs have regenerative roles in many tissues and organs, can differentiate into different cell groups including mesodermal, ectodermal, or endodermal cells, and also have a key role in the tissue repair. It is believed that multilineage-differentiating stress enduring (Muse) cells in mesenchymal tissues of adults play an important role in this regard [105]. On the other hand, MSCs can migrate to the injured tissues and increase the survival of damaged cells by inhibition of proinflammatory cytokines secretion. These properties and benefits of MSC transplantation (MSCT) have been demonstrated in many diseases, such as idiopathic pulmonary fibrosis (IPF), cerebral ischemia, acute renal failure, myocardial infarction, acute lung injury and Alzheimer's disease [80,98,106,107].

5. Applications of MSCs in immune-mediated disorders

MSCs have been introduced as a population of adult multipotent cells that have great potential in immunomodulation and alleviating multiple kinds of immunological dysfunctions [108]. On the other hand, the treatment based on MSCs transplantation has a powerful therapeutic potential for immune-mediated disorders [109]. It is fortunate that the patients did not show side effects after the MSC infusion [110,111]. Herein, we summarize some of the clinical trials of MSC therapy in different immunological disorders (Table 2).

Recent findings support that MSCs are a promising tool for ameliorating the immune dysregulations in patients who are suffering from immunologic disorders [135]. There is an agreement that MSCs can be cultured in vitro with no risk of transformation, whereas a few studies have shown that administered MSCs may have adverse effects [136].

Therefore, the safety profile of this procedure and possible long-term adverse effects, including uncontrolled proliferative processes and development of neoplasms, require further thorough examinations [137]. It seems MSCs can pave the way for future developments of a successful stem cell therapy for several immune disorders in humans [138].

6. MSC: MSC therapy in ankylosing spondylitis

The safety and therapeutic potency of MSC therapy have been shown in many types of research, and also in other disorders such as SLE, MS and autoimmune diseases [79,102]. Many clinical trials are in progress about MSC transplantation in related disorders, such as phase I/II clinical trial to assay the safety and clinical effects of MSC transplantation in AS patients [102,139–141]. As mentioned previously about MSCs roles in the immune modulation, the transplantation of these cells is a therapeutic choice in AS patients that cannot tolerate the anti-inflammatory drugs [139]. In the previous reports, it has been shown that the number of Treg cells in AS patients are low, as well as low levels and abnormal function of B cells, with the resulting autoantibodies being involved in AS pathogenesis. Additionally, MSCs can differentiate T cells to the Th2 phenotype and decrease cytokine levels of Th17 cells due to inhibition of differentiation of these cells, and therefore, MSC therapy has many benefits for AS patients [140].

Table 2
Clinical trials of mesenchymal stem cell therapy in immune-mediated disorders.

	Donor source of MSC	Dose	Number of patients	Phase	Treatment response rate	Outcome	Side effect	References
MSCs treatment for GVHD								
GVHD grade II- III	Bone marrow	2×10^6/kg	14	I/II	92.9 %	Improved	N	[112]
GVHD grade III-IV	Allogeneic placenta	$(0.9 - 2.8) \times 10^6$/kg	9	–	75 %	Improved	O	[113]
GVHD grade III-IV	Bone marrow	$(0.9 - 3) \times 10^6$/kg	37	–	65%	Improved	N	[114]
cGVHD grade -	Bone marrow	$(1.3 - 2.7) \times 10^6$/kg	7	–	57%	Improved	N	[115]
aGVHD grade II-IV	Bone marrow	$(1.3 - 2.7) \times 10^6$/kg	12	–	91.6%	Improved	N	[115]
MSCs prophylaxis for GVHD								
Aplastic anemia	Allogeneic umbilical cord	5.0×10^5/kg	21	–	100%	Improved	N	[116]
Aplastic anemia	Allogeneic umbilical cord	$(2.87 - 10) \times 10^6$/kg	17	–	88.2%	Improved	N	[117]
Hematologic malignancy	Allogeneic umbilical cord	5.0×10^5/kg	50	–	66%	Improved	N	[118]
Hematologic malignancy	Bone marrow	$(1 - 5) \times 10^6$/kg	46	I	53%	Improved	N	[119]
Hematologic malignancy	Bone marrow	$(0.9 - 1.3) \times 10^6$/kg	37	II	83.3%	Improved	N	[120]
Autoimmune diseases								
Multiple sclerosis	Allogeneic bone marrow	63.2×10^6 cells/patient	15	I/II	79%	Mixed	O	[121]
Multiple sclerosis	Allogeneic bone marrow	$3- 5 \times 10^7$ cells/patient	10	I	50%	Mixed	O	[122]
Multiple sclerosis	Allogeneic bone marrow	$1-1.5 \times 10^6$ cells/patient	10	I	60%	Mixed	N	[106]
Multiple sclerosis	Autologous bone marrow	$1–2 \times 10^6$/kg	15	II	–	Improved	N	[123]
Crohn's disease	Allogeneic bone marrow	2×10^6/kg	16	II	80%	Improved	N	[124]
Crohn's disease	Human placenta	$2–8 \times 10^8$/person	12	I	–	Improved	O	[125]
Crohn's disease	Autologous bone marrow	$1–2 \times 10^6$/kg	9	I	30%	Improved	O	[126]
Crohn's disease	Autologous adipose	$3–30 \times 10^6$/person	5	I	–	Mixed	N	[127]
Diabetes	Allogeneic placenta	1.35×10^6/kg	10	I	40%	Improved	N	[128]
Diabetes	Autologous bone marrow	Not clear	41	–	100%	Improved	N	[129]
Systemic lupus erythematosus	Allogeneic bone marrow	1×10^6/kg	2	–	–	No change	N	[130]
Systemic lupus erythematosus	Allogeneic umbilical cord blood	1×10^6/kg	1	I	–	Improved	N	[131]
Systemic lupus erythematosus	Allogeneic umbilical cord blood	1×10^6/kg	16	I	100%	Improved	N	[132]
Systemic lupus erythematosus	Allogeneic bone marrow	1×10^6/kg	15	I	86%	Improved	N	[133]
Osteoarthritis	Autologous bone marrow	$8-9 \times 10^6$	4	–	75%	Improved	N	[134]

aGVHD: acute graft versus host disease, cGVHD: chronic graft versus host disease, N: not observed, O: observed.

Previous studies have shown that MSC infusion in AS patients is a safe and beneficial choice with no severe side effects, and is effective in decreasing the related clinical symptoms and severity of the disease [139,140]. Wang et al. demonstrated that intravenous infusion of allogeneic mesenchymal stem cells is an effective and safe treatment in active ankylosing spondylitis patients [139]. Also, in a study conducted by Ai Li et al., the intravenous transfusion of umbilical cord mesenchymal stem cells (UC-MSCs) shows beneficial outcomes such as safety and decrease of clinical symptoms in the AS patients [140]. However, more studies are necessary regarding the effectiveness of MSC therapy and the systemic adverse effects of its intravenous injections for curing of AS patients in the future [139–141]. For this purpose, it is necessary to study a larger number of patients. Recent studies have been conducted on a smaller number of patients due to the low number of AS cases, especially in Asia [139,140].

At present, many clinical trials are in progress for curing AS patients with MSCs (Table 3). In summary, in phase 1 of a clinical trial (Identifier: NCT01420432), application of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) was assessed and repeated after 3 months, along with DMARDs were given to the patients [142]. Another clinical trial, (Identifier: NCT01709656) involved IV infusion of human mesenchymal stem cells plus NSAIDs in AS patients [143]. Other clinical trials, including phase 2 of a clinical trial (Identifier: NCT02809781) for evaluation of human bone marrow-derived MSCs application in AS patients [144] and clinical trial phase I/II, registration number: ChiCTR-TRC-11001417 for safety evaluation of MSC transplantation in AS are in progress [145]. The results of these can help us to cure AS patients in the future.

7. Conclusion and future perspective

Despite considerable achievements in the treatment of ankylosing spondylitis using NSAIDs, glucocorticoids, DMARDs and biologic drugs, a highly efficient therapeutic modality without side effects has not yet been established. Mesenchymal stem cells with substantial immunomodulatory and regenerative properties are a favorable therapeutic choice in treating immune-mediated disorders such as AS. MSCs can modulate the activation of immune cells associated with the pathogenesis of ankylosing spondylitis and can promote regeneration process in subsequent tissue damage. The findings of previous studies demonstrate that injection of MSCs might be beneficial in alleviating AS signs and symptoms. Nonetheless, further studies are required to investigate several features of mesenchymal stem cell therapy, such as cell origin, dosage, administration route and especially the most ideal stage of disease (early or end) for intervention. Currently, there are several ongoing clinical trials evaluating the efficacy and safety of MSCT in AS patients. The results of these studies would pave the way for developing efficient methods of cell therapy to improve the treatment of AS in future.

Table 3
The list of recent clinical trials for curing of ankylosing spondylitis.

Title of the study	Study start Year/ Identifier	Site of research	Intervention	status/number of participants	Reference
"Safety and Efficacy Study of Umbilical Cord/Placenta-Derived Mesenchymal Stem Cells to Treat Ankylosing Spondylitis (AS), phase I of the study"	2011/ NCT01420432	Shandong University	Transplantation of the human umbilical cord-derived MSCs at a dose of 1.0E + 6 MSC/kg, repeated after three months along with DMARDs including sulfasalazine, methotrexate, thalidomide for 12 months	Completed December 2013/10 participants	[142]
"A Molecule Basic Study of Early Warning of New Pathogenic Risk of Ankylosing Spondylitis"	2012/ NCT01709656	Sun Yat-sen University	Human mesenchymal stem cells,$1 \times 10^{4-6}$ cells/Kg, intravenously on day 1 of each 14-60 day cycle, 1-6 times treatment (for 24 weeks for follow up) along with "celecoxib"	Completed, 2014/120 participants	[143]
"A Pilot Study of MSCs Infusion and Etanercept to Treat Ankylosing Spondylitis, Phase III"	2016/ NCT02809781	Sun Yat-sen University	Human bone marrow-derived MSCs, 1.0E + 6 cells/kg, Intravenously per week in the first 4 weeks and every two weeks in the second 8 weeks Etanercept 50 mg, hypodermic injection, once per week, for 12 weeks	Recruiting/250 participants	[144]
"Clinical study of Mesenchymal Stem Cells transplantation in Ankylosing Spondylitis, Phase I,II"	2011/ ChiCTR-TRC-11001417	Sun Yat-sen University	Group 1: oral sulfasalazine and indomethacin Group2: Mesenchymal Stem Cells (MSC) transplantation	Completed, 2015/80 participants	[145]

Conflicts of interests

There is no conflict of interest to declare.

Acknowledgment

None.

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