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Stem cell-based therapy for systemic lupus erythematous

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ABSTRACT

Systemic lupus erythematosus (SLE), an autoimmune disease, is among the most prevalent rheumatic autoimmune disorders. It affects autologous connective tissues caused by the breakdown of self-tolerance mechanisms. During the last two decades, stem cell therapy has been increasingly considered as a therapeutic option in various diseases, including parkinson's disease, alzheimer, stroke, spinal cord injury, multiple sclerosis, inflammatory bowel disease, liver disease, diabete, heart disease, bone disease, renal disease, respiratory diseases, and hematological abnormalities such as anemia. This is due to the unique properties of stem cells that divide and differentiate to the specialized cells in the damaged tissues. Moreover, they impose immunomodulatory properties affecting the diseases caused by immunological abnormalities such as rheumatic autoimmune disorders.

In the present manuscript, efficacy of stem cell therapy with two main types of stem cells, including mesenchymal stem cell (MSC), and hematopoietic stem cells (HSC) in animal models or human patients of SLE, has been reviewed. Taken together, MSC and HSC therapies improved the disease activity, and severity in kidney, lung, liver, and bone (improvement in the clinical manifestation). In addition, a change in the immunological parameters occurred (improvement in immunological parameters). The level of autoantibodies, including antinuclear antibody (ANA), and anti-double-stranded deoxyribonucleic acid antibodies (dsDNA Abs) reduced. A conversion of Th1/Th2 ratio (in favor of Th2), and Th17/Treg (in favor of Treg) was also detected.

In spite of many advantages of MSC and HSC transplantations, including efficacy, safety, and increased survival rate of SLE patients, some complications, including recurrence of the disease, occurrence of infections, and secondary autoimmune diseases (SAD) were observed after transplantation that should be addressed in the next studies.

1. Introduction

In the last two decades, stem cell therapy has been increased due to the unique properties of these cells. After dividing, stem cell generates a new stem cell and differentiate to a specialized cell. Moreover, it has been shown stem cell therapy is a safe and feasible therapeutic method [1,2].

There are several types of stem cells such as mesenchymal stem cell (MSC), hematopoietic stem cell (HSC). Herein, MSC transplantation (MSCT), and hematopoietic stem cell transplantation (HSCT) in systemic lupus erythematous (SLE) will be reviewed [3].

2. MSC

MSCs introduced by Friedenstein. et al. for the first time. Herein, the cells were appeared like Cd44, CD49b, CD87, CD95, Ly-6C cancer associated fibroblasts, and derived from the bone marrow (BM). MSC, and mesenchymal stromal cell like, another type of stem cell, could be found in the other tissues, including umbilical cord MSC (UC-MSC), endometrial polyps, menses blood, and adipose tissue. These cells express cluster of differentiation (CD)73, CD90, and CD105, while they are negative for CD34, CD45, CD14, CD11b, CD79 alpha, CD19, and human leukocyte antigen (HLA)-DR [4–7].

MSC characteristics that given them advantages for the treatment of autoimmune diseases include [8].

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- MSC isolation and expansion is not complex [9].
- MSC is capable of migration into injured tissues for their repair [10].
- MSC has low immunogenicity, because they do not express major histocompatibility complex (MHC)-II, co-stimulatory molecules, including B7-1, B7-2, and CD40. Therefore, they are not recognized by T cells and are not rejected after allogeneic transplantation [4,11].
- MSC suppresses CD3+T cells proliferation and secretion of cytokine MSC suppresses T cells proliferation and secretion of cytokine [12,13].
- MSC prevents $CD19^+$ B cells proliferation and autoantibody production [14].
- MSC inhibits $CD45^+$,MHC-II+,CD1+/CD3-,CD19-,CD14-,CD56-CD66b-dendritic cells (DCs) maturation and prevents cytotoxicity of $CD56^+$ NK cells [15,16].

Notably, the multiplication power and differentiation capacity of MSC varies and depends on the type of tissues that MSC has been originated. For example, UC-MSC has higher capacity in multiplication power and differentiation capacity to various cells than BM-MSCs [17].

3. HSC

HSC is a pluripotent stem cell that differentiate into multiple blood cells lineages. HSC is commonly characterized by the absence of lineage-specific markers of blood cells. Human HSC is detected as $CD34^+$, $CD59^+$, CD90/Thy1+, CD38low/-, c-Kit-/low, and Lin-. Mouse HSC is considered as CD34low/-, SCA-1+, Thy1+/low, $CD38^+$, c-Kit+, and Lin- [18,19].

HSCT was first introduced in the middle of 1950 in a mouse model of leukemia/lymphoma. Allogeneic injections of healthy BM components to mice and X-ray conditioning regimen increased survival of mice. Thomas. et al. performed the first HSCT in children, and adults with leukemia that had promising results [20].

HSCT, bone marrow transplantation (BMT) is now used as a treatment for malignant diseases such as leukemia, myeloma, lymphoma, as well as non-malignant diseases such as immunodeficiency disorders, hemoglobinopathy, and autoimmune rheumatic diseases. MSCT or HSCT could be an effective therapeutic option in autoimmune rheumatic diseases patients that are resistant to the conventional therapies (refractory autoimmune diseases) [21].

In autoimmune diseases, HSCT helps to re-establish the immune system tolerance after removal of autoreactive CD27+memory cells through conditioning regimen. Indeed, the adaptive immune system is re-adjusted so that it do not recognize self-antigens and is tolerant to self-antigens [22].

4. Stem cell therapy (SCT) in SLE

SLE is a chronic inflammatory autoimmune disease in which break down of T and B lymphocytes tolerances to nuclear antigens leads to the production of cytokines, and autoantibodies against nuclear components. These results accompanied by activation of complement system on immune complexes that deposited in tissues and capillaries followed by inflammation, tissue dysfunction, and damage. The disease is differentially manifested depending on the type of the tissues involved, clinical manifestations, the amount of immune complexes sedimented in tissues, and vessels, and severity of the disease. The organs and tissues involved include kidney, stomach and intestine, lung, cardiovascular system, and skin. Other pathological conditions include hematological, endocrine, obestric, and ocular manifestations [23,24]. Results of SCT, including MSCT, and HSCT in SLE animal models or human patients will be reviewed in the next sections (Table 1, Fig. 1).

Table 1
Results of stem cell therapy (SCT) in SLE animal models/human patients in different studies.

	Type of stem cell	Results of SCT	Animal model/ human	Reference number
1	MSCs	➢ Improvement in the kidney function ➢ Improvement in liver function ➢ Improvement in osteoporosis	SLE mouse model	[27,28,120]
2	MSCs	➢ Decrease in anti-dsDNA antibody ➢ Decrease in ANA	SLE mouse model	[27,121,122]
3	MSCs	➢ Decrease in plasma cells	MRL-Fas lpr/J mice	[27,39,123,124]
4	MSCs	➢ Reduction in proinflammatory cytokines, including TNF-α, IL-6, IL-12	NZB/W F1 mice	[33,125]
5	MSCs	➢ Reduction in the disease severity ➢ Conversion of Th1/Th2 ratio	SLE mouse model SLE patients	[34]
6	AD-MSCs	➢ Increase in IL-4	SLE mouse model	[35,126]
7	Engineered MSCs- IL-37	➢ Reduction in splenocyte proliferation ➢ Reduction in the production of proinflammatory cytokines by PBMCs ➢ Reduction in the production of anti-dsDNA antibody	MRL/lpr mice	[37]
8	UC-MSCs	➢ Increase in apoptosis of CD4+T cells	SLE mouse model	[127]
10	MSCs	➢ Improvement in the renal function, including decrease in glomerulonephritis, renal excretion of proteins, serum creatinine and BUN, and albumin ➢ Improvement in GFR ➢ Improvement in the immunological parameters, including decrease in anti-dsDNA antibody, complement C3, and a slightly increase in complement C4	4 SLE patients (27th ref) 40 SLE patients (44th ref)	[27,44]
11	MSCs	➢ Improvement of hematologic complications, including leukocytopenia, thrombocytopenia, and anemia	81 SLE patients	[41]
12	UC-MSCs	➢ Upregulation of FLT3L level ➢ Improvement in the number and function of tolerogenic DCs ➢ Improvement in Treg/Th17 balance (increase in Treg and decrease in Th17) ➢ High level of TGF-β	166 SLE patients (53rd ref) 30 SLE patients (54th ref) 166 SLE patients (129th ref)	[53,54,128,129]
13	MSCs	➢ Increased production of FoxP3+$CD4^+$CD25+Tregs ➢ Increased production of iTreg ➢ Decrease in Th17s	30 SLE patients (54th ref) PBMCs from SLE patients (55th ref)	[54,55]
14	MSCs	➢ Improvement in the disease course	22 SLE patients	[58]

(continued on next page)

Table 1 (*continued*)

	Type of stem cell	Results of SCT	Animal model/ human	Reference number
15	UC-MSCs	➢ Upregulation of miR-181a expression in T cells	23 SLE patients (60th ref) 20 SLE patients (61st ref) 100 SLE patients (62nd ref) 24 SLE patients (63rd ref)	[60–63].
16	BM-MSCs	➢ Suppression of MEK/ERK signaling pathway ➢ Inhibition of PBMCs activation ➢ Downregulation of genes, including CD70, ITGAL, selectin-l, and IL-13	PBMCs from SLE patients	[130]
17	HSCs	➢ Long-term recovery from the disease ➢ Low mortality	A 46 year woman with severe long-lasting SLE	[79]
18	HSCs Autologous	➢ 5-years survival rate of 91 %	22 SLE patients	[75]
19	Autologous HSC	➢ 7-years disease-free survival of 64.7 %	17 SLE patients	[77]
20	Autologous PBSCs	➢ 10-years overall survival rate of 86 %	24 SLE patients	[80]
21	Autologous HSCs	➢ 5-years disease-free survival rate of 29 %	28 SLE patients	[131]
22	Autologous HSCs	➢ Improvement in the quality of life of patients based on the SF-36 score after 5-years of HSCT	50 SLE patients (81st ref)	[81,84]
23	Autologous HSCs	➢ Improvement in SLEDAI, including clinical manifestation, and immunological parameters	22 SLE patients (75th ref) 22 SLE patients (76th ref) 7 SLE patients (86th ref)	[75,76, 86]
24	Autologous HSCs	➢ Improvement in nephritis with a 5-years survival of 86 % for kidney	22 SLE patients	[75]
25	Autologous HSCs	➢ Improvement in pulmonary function ➢ Improvement in carbon monoxide diffusion lung capacity corrected for hemoglobin	34 SLE patients	[82]
26	Autologous HSCs	➢ Improvement in cardiac disorders	55 SLE patients	[88]
27	Autologous HSCs	➢ Affecting immune system: ➢ Neutrophil increase ➢ Reduction in autoantibodies level such as anti-dsDNA antibodies ➢ Reduction in antibodies against infectious agents ➢ Increase in $CD4^{+}CD25^{+}FoxP3^{+}$T cells ➢ Increase in $CD8^{+}$ $FoxP3^{+}$ Treg ($CD28^{+}$ or $CD28^{-}$) cells containing LAP, CD103, PD-1, PD-L1, CTLA-4, and TGF-β	7 SLE patients (86th ref) 30 SLE patients (132nd ref) 46 SLE patients (133rd ref)	[86,132, 133]
28	Autologous HSCs	➢ Reduction in autoantibodies, including anti-dsDNA antibodies, and anti-phospholipid antibodies ➢ No requirement for the consumption of anti-coagulant	46Patients with both SLE and APS (133rd ref)	[101,133]
29	Autologous HSCs	➢ Reduced incidence of pregnancy-related complications, including high blood pressure, lupus nephritis, and lupus flare in postpartum	11 pregnant SLE women	[103]
30	Allogeneic BM-HSCs	➢ Engraftment functionality 5.5 years after BMT ➢ Improvement in SLEDAI score ➢ Normal ratio of urine protein to creatinine	SLE woman	[117]
31	Allogeneic HSCs	➢ Compensation of the reduced level of complement C1q	5 SLE patients with C1q deficiency	[119]
32	Haplo mismatched allogeneic HSCs	➢ Decreased incidence of the disease symptoms ➢ Increase in overall survival rate ➢ Reduced autoantibody production ➢ Reduced proteinuria ➢ Reduce accumulation of B cells in thymus	NZB/W F1 mice	[134]

4.1. MSCT in animal models of SLE

Generally, implication of MSCs in animal models of SLE (MRL/lpr, C3.MRL-Fas lpr/J, and NZB/W F1) demonstrated an increase in the survival of mice. MSCT restored renal function in the mice model of SLE. These dysfunctions include kidney damage, inflammation of nephrons, and infiltration of $CD3^{+}$ cells followed by deposition of complement components and antibodies in the kidney tissue [25]. MSCT also ameliorated liver function and osteoporosis activity of bone in mice model of SLE [26–29]. In another study of the mouse model of lupus, circulating autoantibodies, especially anti-double stranded DNA (anti--dsDNA) IgG and IgM antibodies, and antinuclear antibodies (ANA) IgG1, IgG2a, IgG2b, and IgM autoantibodies decreased after MSCT [27]. In addition, MSCT in MRL-Faslpr/J mice was associated with a significant reduction in CD138 expressed on plasma cells. Indeed, a decrease in CD138+ plasma cells resulted in the reduction of autoantibodies [3,27, 30,31]. In addition, MSCT in NZB/W F1 mice reduced pro-inflammatory cytokines levels, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and IL-12 which have an undeniable role in the development of SLE [32,33]. Actually, MSCT could invert STAT4+ and T-bet + Th1/STAT5+, STAT6+, and GATA-3+Th2 ratio observed in lupus patients and reduced the severity of the disease in the mice [34]. Accordingly, an increase in serum IL-4, and IL-10 levels was detected following adipose tissue-derived mesenchymal stem cell transplantation (AD-MSCT) in lupus mice [33,35]. Notably treatment of MRL\lpr mice with MSC was more effective in the early stages of the disease and at the optimal dose compared to the higher or lower doses [35]. Results of Yu et al. demonstrated that the nucleotide binding oligomerization domain-like receptor 3 (NLRP3) inflammasome was activated in $CD14^{+}$, CD16+,CD64+,CD68+,CD71+, and CCR5+ macrophages from MRL/lpr mice and patients with SLE, correlating with disease activity. After MSC transplantation, the disease severity in MRL/lpr mice was alleviated, and NLRP3 inflammasome activation was inhibited with decreased levels of NLRP3 and caspase-1 in macrophages. Furthermore, lower serum levels of IL-1β and IL-18 were observed in patients with SLE

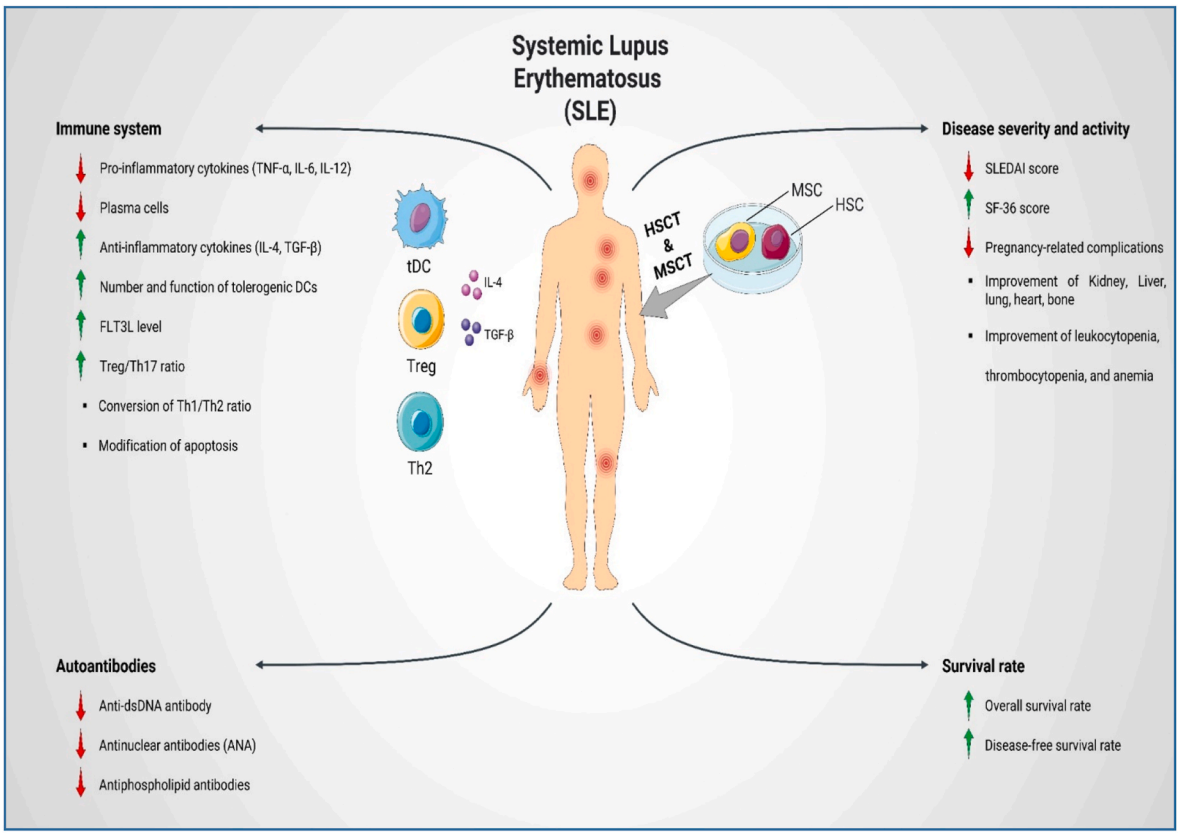

Fig. 1. Disease pathogenesis, severity, and activity of SLE patients.

who underwent MSC transplantation. In vitro and in vivo studies indicated that MSC suppressed NLRP3 inflammasome activation. The findings provide an updated view of inflammasome signaling in SLE. Additionally, MSC ameliorated SLE by inhibiting NLRP3 inflammasome activation [36].

Treatment of MRL/lpr mice with genetically modified MSC overexpressing IL-37, that is an anti-inflammatory cytokine, showed a significantly elevated level of the immunoregulatory properties of these cells. Herein, the immunosuppressive properties of MSC-IL37 or MSCs or IL-37 alone showed immunoregulatory effect of engineered MSC-IL37 is more prominent than MSCs or IL-37 alone. This suggests engineered MSC containing various anti-inflammatory factors/cytokines may be more effective than MSCs alone in MSC therapy of autoimmune diseases [37].

Allogenic BM-MSCT is associated with secretion of interferon gamma (IFN-γ), and IL-10; as well as up regulation of TGF-β in lupus mice. Moreover, reduced level of serum and peripheral BAFF expression was detected. These alterations result in the down regulation of B cell population and reduced autoantibodies and 24 h proteinuria [38].

Park et al. showed MSCT induced expansion of B cells produceing IL-10, and a significant increase in the number of CD4+FoxP3+ cells (Treg) leading to improvement of autoimmunity in the murine model [39].

Z Gu et al. showed the expression level of monocyte chemotactic protein-1 (MCP-1) and high-mobility group box 1 (HMGB-1) was increased in the kidney of MRL/lpr mice after UC-MSCT, resulting in the amelioration of lupus nephritis [40].

4.2. MSCT in SLE human patients

Evaluation of MSCT in SLE patients showed minimum side effects, while it increased patient survival rate and reduced disease activity expressed in term of systemic lupus erythematosus disease activity index (SLEDAI) [29,41–43]. A multicenter study evaluating the safety and efficacy of MSCT in SLE patients showed MSCT is safe and effective especially if MSCs were reinjected six months after the first MSCT [44–47]. Interestingly, allogeneic MSCT is more effective in amelioration of SLE than autologous MSCT. This could be due to dysfunctionality of MSCs in SLE patients in both proliferation and immunoregulation. Accordingly, SLE MSCs were also phenotypically senescent [48,49].

MSCT in human patients significantly improved renal function, including decreased glomerulonephritis, decrease in renal excretion of proteins, reduced level of serum creatinine, decreased level of blood urea nitrogen (BUN), and decreased level of albumin. Decreased level of albumin is detected in patients with SLE in which renal dysfunction causes proteinuria from the kidney. On the other hands, glomerular filtration rate (GFR) improved. A change in immunological parameters, including decreased anti-dsDNA antibodies especially pathogenic IgG isotypes, decrease in serum complement C3 level, a slightly increase in complement C4 component were also detected after MSCT in patients [29,41,44,50,51]. All these show a slightly improvement in immune system function. Accordingly, MSCs suppress T lymphocytes through various mechanisms, including the production of transforming growth factor-beta (TGF-B), prostaglandin E2 (PGE2), nitric oxide (NO), and indolamine 2 and 3-oxygenase (IDO). In addition, MSCs inhibit the production of their autoantibodies by inhibiting the differentiation of lymphocytes. The production of autoantibodies against nuclear antigens is an important feature of SLE. On the other hand, MSCs inhibit antigen delivery by antigen-presenting cells (APCs) to T lymphocytes [52].

Long-Term follow-up of SLE patients after MSCT showed MSCT could improve the hematologic complications of lupus patients such as leukocytopenia, thrombocytopenia, and anemia [29,41].

FMS-like tyrosine kinase 3 ligand (FLT3L) is an inducer cytokine, contributing to the progression of SLE and its decline is associated to a defect in the production and differentiation of IL-10+,TGF-β+,MHC-II-, CD80/CD86-, and CD40^{-}tolerogenic DC. FLT3L has immunoregulatory properties and its reduction has been detected in SLE patients.

Transplantation of allogeneic UC-MSCs significantly upregulated FLT3L level, and number, and function of tolerogenic DCs in patients with SLE [53]. In SLE patients, FoxP3+CD4$^+$CD25+Treg/STAT3+, and ROR-gamma t + Th17 balance that is disrupted, returns to the normal level after MSCT. Actually, the number of Treg increased, and TH17 decreased. Moreover, in serum of patients, higher level of anti-inflammatory cytokine (transforming growth factor Beta (TGF-β)) was detected [54]. It has been shown TGF-β released by MSCs, increases production of FoxP3+CD4$^+$CD25+Treg cells, and inducible Tregs (iTreg) in SLE patients [55]. On the other hand, decrease in Th17, was due to the production of TGF-β and prostaglandin E2 (PGE2) levels [54,56].

Higher level of interferon gamma (IFN-γ) was detected in the serum of people with SLE and is directly related to the progression of the disease. In addition, the level of IFN-γ predicts the outcome of MSCT. The higher the level of IFN-γ, the greater the effectiveness of MSCT. This can be explained by T CD8$^+$ effect on MSCs. CD8+T that is a major producer of IFN-γ, induces the production of IDO by MSC that in turn inhibits T cell proliferation [44].

Cao et al. found that repeated IL-2 administration and one single injection of UC-MSCs are comparable in upregulating serum IL-2 and alleviating SLE manifestations short after treatment. One single injection of UC-MSCs provides sustained alleviation of SLE manifestations, especially in renal pathology, compared with repeated IL-2 administration. Therefore, UC-MSCs alleviate SLE manifestations through sustained upregulation of serum IL-2, overcoming the disadvantage of repeated IL-2 administration [57].

Apoptosis has a pathogenic role in SLE. Results of a study performed by Zhang. et al. showed MSCT reduced apoptosis resulting in an improvement in SLE patients [58].

Apoptosis of CD4+T cells was reduced in the peripheral blood of lupus-prone mice. Huang. et al. showed that UC-MSCT increased the apoptosis of CD4 T cells in both in vivo and in vitro conditions in SLE-prone mice [59].

Interestingly, micro ribonucleic acids (RNAs) that have roles in various developmental stages of B, and T lymphocytes, showed changes in SLE patients. For example, it has been shown that microRNA 181-a has decreased in SLE patients. Co-culture of UC-MSCs and T cells isolated from patients with SLE showed an up-regulation in the expression of microRNA 181-a in T cells from patients with SLE [60–63].

Mitogen-activated protein kinase kinas (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway of lymphocytes has defect in SLE patients and contributes to the pathogenesis of SLE. Co-culture of BM-MSCs with peripheral blood mononuclear cells (PBMCs) from SLE patients attenuated the lymphocyte activation with suppressing signaling of this pathway. Suppressing this pathway suppressed activation of PBMCs through downregulation of pathological genes such as CD70, integrin alpha L chain (ITGAL), selectin-l, and IL-13 [64,65].

4.3. HSCT in SLE human patients

4.3.1. HSCT preparation

For HSCT, the patient initially receives a high dose of chemotherapy and/or radiotherapy. In the second step, HSCs are separated from BM, peripheral blood (PB) or umbilical cord blood (UCB) [21].

HSCT could be autologous or allogeneic. In autologous HSCT, HSCs are isolated from the BM or PB of the own patient. Typically, in autoimmune diseases, HSCs are obtained from BM or PB of the own patient called autologous stem cell transplantation (ASCT). Allogeneic HSCT has been less studied as a treatment option compared to the autologous one, because it can cause graft-versus-host disease (GVHD) in the patients [66,67].

The patients receive a preparative regimen known as conditioning regimen. The choice of conditioning regimen is very important, as it can affect the success of the transplantation and consequently the disease improvement. In autoimmune diseases, non-myeloblablative regimen (anti-thymocyte globulin (ATG) or anti-CD52 and cyclophosphamide) more commonly used than the myeloblablative regimen (total body irradiation (TBI) and cycliphosphamid or busulfan) [68].

4.3.2. HSCs separation from BM in ASCT

To collect BM HSCs, granulocyte colony stimulating factor (G-CSF) is injected to patients to increase the number of CD34$^+$ stem cells. Thereafter, under general anesthesia, a posterior superior iliac crests BM sample is taken from the patient and CD34$^+$ stem cells are separated from the sample [69].

4.3.3. HSCs separation from PB in ASCT

Normally, a small number of HSCs enter into the PB from BM. To isolate HSCs from PB, two doses of G-CSF (subcutaneous injection) and cyclophosphamide (intravenous injection) are injected to the patients to increase the recruitment of HSCs from BM to the periphery. The net result is an increase in the number of HSCs in PB. Thereafter, CD34$^+$ stem cells are isolated by leukopheresis. This procedure resulted in the lower damage to the isolated cells. The minimum required number of CD34$^+$ stem cells needed for HSCT is 2.0*1000000 CD34$^+$ stem cells/kg of recipient. HSCs could be frozen until the HSCT time [70,71].

4.3.4. Autologous HSCT in SLE

Despite the altered function of HSCs in SLE-prone mice and SLE individuals that contributes to clinical manifestations of SLE, HSCT is a salvage treatment usually recommended for refractory SLE [72–74]. According to the studies, it is a safe therapeutic method and could lead to a long-term remission in the adult and pediatric patients [75–78].

The autologous HSCT method in SLE patients who did not respond to routine treatments was first performed by Marmont, AM. et al., in 1997. The results of the study were promising and were associated with a long-term recovery from disease and low mortality among patients. HSCT efficacy is determined based on several parameters, including patient survival, clinical manifestations (organ function), and laboratory parameters [79].

4.3.4.1. Patients survival. Though patient survival rate reported after HSCT is not similar in different studies, but the results are promising. A study in 2019 on patients with refractory lupus nephritis showed a 5-years survival rate as high as 91 % [75]. In another study, a 7-years disease-free survival was reported as 64.7 % in patients treated with HSCT, which was significantly higher than the conventional treatments in patients [77]. Results of Leng, XM. et al., demonstrated after treatment of SLE patients with high-dose immunosuppressive drugs and autologous PBSCT, 10-years overall survival rate and 10-year remission survival rate were both 86.0 % [80]. However, in most studies, overall survival and disease-free survival rates were lower, including 80 % and 50 %, respectively [81–83]. On the other hands, Alchi, B. et al. Showed overall survival and 5-years disease-free survival rate was 81 % and 29 %, respectively [83]. Altogether, these results suggest autologous HSCT increases overall survival rate and disease-free survival.

Numerous studies have shown that quality of life of SLE patients is lower than healthy people. Burt, RK. et al. reported an improvement in the quality of life of patients, including physically and mentally improvement after 5-years of HSCT based on the 36-Item short form survey (SF-36) score [81,84]. SF-36 is a questionnaire that is used to assess the quality of life of healthy people and people with a disease in the general population [85].

4.3.4.2. Clinical manifestations (Organ function) and laboratory parameters. After autologous HSCT, an improvement in systemic lupus erythematosus disease activity index (SLEDAI) index occurs. SLEDAI measures disease activity in SLE patients based on the clinical manifestation such as arthritis, vasculitis, inflammatory-type rash, myositis, and neurological symptoms as well as immunological parameters such

as autoantibodies titers, including ANA, anti-dsDNA antibody, anti-Smith (Sm) antibody, complement component level, and number of leukocytes, platelets, and red blood cells (RBCs). Moreover, the levels of urinary proteins, and serum albumin were also improved after autologous HSCT [75,76,86].

Kidney is an organs that is severely affected in 40–60 % of SLE patients. Kidney function could be determined by measuring creatinine clearance and biopsy. Though creatinine clearance remains constant before and after HSCT, but comparison of biopsies before and after HSCT showed an improvement in nephritis with an overall 5-years survival of 86 % for kidney [75,87]. After HSCT, pulmonary function was greatly improved as measured by carbon monoxide diffusion lung capacity corrected for hemoglobin [82]. Cardiac dysfunction is associated with 70 % prevalence in patients with SLE. The results of a study in SLE patients with cardiac disorders after autologous HSCT were promising suggesting this method could improve cardiac symptoms [88]. Altogether, autologous HSCT could improve organs functions and affect laboratory parameters towards the improvement of the disease.

4.3.4.3. HSCT effect on immune system. Injection of non-myeloablative conditioning regimen (immunoablative) to the SLE patients before HSCT that is commonly consists of ATG leads to the depletion of immune cells, including T cells, B cells, plasma cells, regulatory T cells, natural killer (NK) cells, and dendritic cells [89]. ATG is a polyclonal antibody against thymocyte antigens that depletes leukocyte in blood, lymphoid organs, and tissues through complement-dependent lysis or activation-associated apoptosis [90,91].

A few weeks after HSCT, CD15+CD16+/CD14-neutrophil count increases and a recovery in the disease occurs. This is due to the removal of autoimmune cells and induction of tolerance in new generated immune cells [86]. After removal of autoimmune cells by non-myeloablative regimen, HSCs recruit into the BM and differentiate to various immune cells. The precursors of T lymphocytes migrate from the BM to the thymus, where they continue the developmental stages. Therefore, a new auto-tolerant T cells are generated that are not autoreactive and are tolerant to autoantigens. A number of progenitor cells migrated to the thymus also differentiate to regulatory T lymphocytes. Finally, differentiated to non-autoreactive immune cells entering to the blood [92–94].

It is notable a reduction in autoantibodies levels (particularly anti-dsDNA antibodies), and antibodies against infectious agents (mumps, measles, tetanus, and diphtheria) is detected in the plasma of individuals after conditioning regimen. This suggests destruction of $CD27^{+}$,CD23-, CD138-memory B cells, and plasma cells located in the bone marrow [86]. Notably, if autoreactive plasma cells are not completely removed, the patient may experience a diseases relapse. Indeed, the long-term recovery of the disease without any relapse after HSCT, depends on the complete destruction of long-lived plasma cells in the bone marrow [86,95].

After HSCT, the number of $CD4^{+}CD25^{+}FoxP3^{+}$T cells increases and reaches to the normal level; however, the cells have little suppressive activity [86]. The number of $CD8^{+}FoxP3^{+}$Treg ($CD28^{+}$ or $CD28^{-}$) cells also increases after HSCT. These regulatory cells assist in the suppression of autoreactive $CD4^{+}$T cells by the high expression of latency-associated peptide (LAP), CD103, programmed death-1 (PD-1), programmed death-ligand 1(PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and TGF-β [96].

4.3.4.4. Efficacy of HSCT in SLE patients by post-conditioning regimen. Burt. et al. evaluated the effect of post-HSCT conditioning regimen on the disease recovery. In this study, the patients were re-injected by PB stem cells and divided into two groups receiving two different types of post-conditioning regimen. One group received ATG, cyclophosphamide, and rituximab (anti-CD20). Another group received cyclophosphamide, and alemtuzumab (anti-CD52). The Second group did not show improvement in the disease, but the group that received ATG had a remission of 64 % at 5-years after transplantation. Post-HSCT conditioning regimen also affected immunoregulatory and anti-inflammatory properties of HSCs. Therefore, post-conditioning regimen could contribute to the disease improvement [81,97].

4.3.5. HSCT in SLE patients with anti-phospholipid syndrome (APS) and pregnant SLE women

The studies have shown HSCT is also efficient in people with SLE and APS. APS is an autoimmune disease in which the pathogenic autoantibodies result in the venous and arterial thrombosis, and pregnant morbidity in both mother and fetus. The presence or absence of SLE can alter the clinical and serological manifestations. Therefore, the disease is tightly associated with SLE [98,99].

A review of people with both diseases (SLE and APS) that were transplanted with HSCs showed HSCT is associated with a reduction in autoantibodies, including anti-dsDNA antibodies, and antiphospholipid antibodies. Moreover, a great number of patients was not required to consume anti-coagulant drugs [99–101].

Pregnancy in women with SLE is associated with many risks for both mother and fetus [102]. The results of a study showed autologous HSCT in pregnant women with SLE is associated with a reduced incidence of pregnancy-related complications such as high blood pressure, lupus nephritis, and lupus flare in postpartum compared to those who did not receive this treatment [103].

4.3.6. HSCT complications in SLE patients

Considering many advantages of HSCT, including safety, and efficacy in SLE patients, it could be considered as an alternative in SLE treatment especially in refractory SLE patients [83,104]. However, the issues, such as recurrence of the disease, occurrence of infections, and secondary autoimmune diseases (SAD) in autologous HSCT are observed after HSCT (Table 2) [45,105,106].

4.3.6.1. Relapse of SLE in patients after HSCT. In some patients, an increase in the level of autoantibodies, and a decrease in the level of complement components occurs and is considered to be associated with the disease recurrence [107–109], however, evaluation of SLEDAI index and kidney biopsy are more reliable for evaluation of the disease recurrence [109,110]. Though the main reason(s) for the relapse of the disease after HSCT is unknown, long-lived plasma cells that secret autoantibodies may contribute to the disease relapse [75,107].

Table 2
Complications of stem cell therapy (SCT) in SLE animal models/human patients.

	Complication	Manifestation(s)	Cause(s)
1	Recurrence of the disease	➢ An increase in the level of autoantibodies ➢ A decrease in the level of complement components ➢ Reduced SLEDAI ➢ Problem in the kidney function	➢ Long-lived plasma cells secreting autoantibodies
2	Occurrence of infections	➢ Cytomegalovirus (CMV) infection ➢ Sepsis ➢ Bacteremia especially with gram positive bacteria ➢ Fungal infections	➢ Consumption of immunosuppressive drugs ➢ Organ dysfunction ➢ Transplantation-related neutropenia
3	Secondary autoimmune diseases	➢ Thyroiditis ➢ Immune thrombocytopenia (ITP) ➢ Autoimmune hemolytic anemia (AIHA)	➢ Genetic predisposition to autoimmune diseases ➢ Impaired regulation of immune system ➢ Conditioning regimen

4.3.6.2. Infection in SLE patients after HSCT. Typically, patients with SLE are prone to various infections due to the consumption of immunosuppressive drugs, organ dysfunction, and transplantation-related neutropenia [81,108]. Infections in these patients slows down the healing process of the disease [108,111]. The most important infections in SLE patients after transplantation are cytomegalovirus (CMV) infection, sepsis, bacteremia especially with gram positive bacteria, and fungal infections [105,112,113].

4.3.6.3. SAD in SLE patients after HSCT. In some SLE patients treated with HSCT, SAD such as thyroiditis, immune thrombocytopenia (ITP), and autoimmune hemolytic anemia (AIHA) are developed probably due to a genetic predisposition to autoimmune diseases, impaired regulation of immune system, and conditioning regimen [88]. Daikeler. et al. found out younger patients, patients smaller than 62 months, as well as patients who have received $CD34^+$ stem cells, and ATG as conditioning regimen, are more prone to SAD and should be closely monitored for SAD [114]. On the other hands, Loh. et al. reported that a very small percentage of patients with SLE who received PB $CD34^+$ stem cells and used ATG developed SAD. They state that sex, type of ATG used, and CD34+stem cells have little effect on the development of SAD [88]. This controversy shows the information on the factors contributing to the SAD development is incomplete and more studies are required to address the issue.

4.3.6.4. Management of HSCT complications. Considering the lack of direct information on the management of HSCT complications in SLE patients, indirect data extracted from the similar situations such as autoimmune diseases, may be useful for managing HSCT complications in SLE (Table 3) [75,106,115,116].

4.4. Allogeneic HSCT

The number of allogeneic HSCT is low. This is due to limitations of allogeneic HSCT, including preparative regimen toxicity, donor availability, poor engraftment, and late transplant problems such as graft-versus-host-disease (GVHD) [107].

In a woman with SLE and sickle cell anemia, allogeneic BMT was carried out with the reduced intensity conditioning (RIC), and post-transplantation cyclophosphamide (PTCy). RIC and PTCy used to decrease the risk of GVHD and increase safety, and efficacy of the transplantation. In this patient, engraftment was still functional after 5.5-years of BMT. Moreover, SLEDAI score was improved and urine protein to creatinine ratio, was normalized at 15 months after transplantation. Moreover, remitted therapy was limited [117]. In another study, highly enriched haplo mismatched allogeneic HSCs used for the treatment of female NZB/W F1 mice. The results showed transplantation prevents the incidence of the disease symptoms and increase overall survival rate. Moreover, autoantibody production, proteinuria and accumulation of B cells in thymus reduced indicating complete or partial replacement of the immune system [118]. Allogeneic HSCT could compensate the reduction of C1q in SLE patients with C1q deficiency [119]. Overall, these results suggest allogeneic HSCT could be effective in treatment of SLE patients; however, given the few number of studies on allogeneic HSCT, future studies are necessary to evaluate safety, efficacy, complications, and limitations of HSCT in animal models of SLE and SLE patients.

Table 3
Management of HSCT complications.

	Disease	Management(s)
1	Autoimmune hemolytic anemia	➢Corticosteroids ➢IVIG, ➢Cyclosporine ➢,Mycophenolate, ➢Splenectomy ➢Rituximab
2	Autoimmune thyroid disease	•Hyperthyroidism: ➢ Thyroid suppression (eg, methimazole, propylthiouracil, radioiodine) ➢ surgery • Hypothyroidism: ➢ Thyroid replacement (eg, levothyroxine)
3	Autoimmune thrombocytopenia	➢Corticosteroids ➢IVIG ➢Rituximab ➢Vincristine ➢Alemtuzumab ➢Thrombopoietin receptor agonists (eg. romiplostim, eltrombobag)
4	Immune-mediated neuropathies	➢Corticosteriods ➢IVIG ➢Rituximab for refractory cases
5	Myasthenia gravis	➢Pyridostigmine ➢Immunosuppression with prednisone, cyclosporine, azathioprine, mycophenolate mofetil ➢Acetylcholinesterase inhibitors ➢Thymectomy

4.5. Conclusion

Taken together, these results suggest both MSCT, and HSCT could improve the disease activity, and severity in the animal models and human patients of SLE disease. Both treatments resulted in an improvement in the clinical manifestation of the diseases, and skewed immunological parameters in favor of the disease improvement. Overall, both therapeutic methods seems to be safe; as few complications have been reported. Engineered MSCs/HSCs expressing various factors such as anti-inflammatory cytokines or combination therapy utilizing MSCs/HSCs and the other factor may be more effective in the modulation of immune responses and improvement of the disease. Despite the clear efficacy of MSCT/HSCT in treatment of SLE shown in many studies, some issues, including choice of the tissue that stem cells should be derived, autologous versus allogenic or xenogenic origin of stem cells, type of stem cell such as MSC or HSC, predictive factors of transplantation outcome remain greatly unknown and should be addressed in the next studies to increase therapeutic efficacy of MSCT/HSCT and minimize the complications of the transplantation.

CRediT authorship contribution statement

Maryam Zare Moghaddam: Moghaddam, Writing – original draft, Conceptualization. **Mohammad Javad Mousavi:** Writing – review & editing, Conceptualization. **Somayeh Ghotloo:** Writing – review & editing, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Abbreviation list

AD-MSCT Adipose tissue-derived mesenchymal stem cell transplantation
AIHA Autoimmune hemolytic anemia
ANA Antinuclear antibody
Anti-dsDNA Anti-double stranded DNA
APS Anti-phospholipid syndrome
ASCT Autologous stem cell transplantation

ATG	Anti-thymocyte globulin
BM	Bone marrow
BMT	Bone marrow transplantation
BUN	Blood urea nitrogen
CD	Cluster of differentiation
CMV	cytomegalovirus
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DC	Dendritic cells
ERK	Extracellular signal-regulated kinase
FLT3L:	FMS-like tyrosine kinase 3 ligand
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
GVHD	Graft-versus-host disease
HMGB-1	High-mobility group box 1
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplantation
IDO	Indolamine 2, 3 oxygenase
IFN-γ:	Interferon gamma
IL-6	Interleukin 6
ITGAL:	Integrin alpha L chain
ITP	Immune thrombocytopenia
MCP-1	Monocyte chemotactic protein-1
MEK	Mitogen-activated protein kinase kinas
MHC	Major histocompatibility complex
MSC	Mesenchymal stem cell
MSCT	MSC transplantation
NK	Natural killer
PB	Peripheral blood
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PGE2	Prostaglandin E2
PTCy	Post-transplantation cyclophosphamide
RA	Rheumatoid arthritis
RBCs	Red blood cells
RIC	Reduced intensity conditioning
RNAs	Ribonucleic acids
SAD	Secondary autoimmune diseases
SCT	Stem cell therapy
SF-36	36-Item short form survey
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SSc	Systemic sclerosis
TBI	Total body irradiation
TGF-β:	Transforming growth factor Beta
Th	T helper
TNF-α:	Tumor necrosis factor alpha
UC	Umbilical cord

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