

# Stem Cell Therapy in the Treatment of Rheumatic Diseases and Application in the Treatment of Systemic Lupus Erythematosus

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## Abbreviations

ACR	American College of Rheumatology
Allo-HSCT	Allogeneic hematopoietic stem cell therapy
ANCA	Antineutrophil cytoplasmic antibody
ARD	Autoimmune rheumatic diseases
ASC	Adult stem cells
ASSIST	American Scleroderma Stem Cell Versus Immune Suppression Trial
ASTIRA	Autologous Stem Cell Transplantation International Rheumatoid Arthritis
Auto-HSCT	Autologous hematopoietic stem cell therapy
AZA	Azathioprine
BAFF	B-cell-activating factor

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BD	Behcet's disease
BLyS	Soluble B lymphocyte stimulator
CsA	Cyclosporine A
CYC	Cyclophosphamide
DM	Dermatomyositis
DMARD	Disease-modifying antirheumatic drugs
EBMT/EULAR	European Bone Marrow Transplant/European League Against Rheumatism
EMA	European Medicines Agency
ESC	Embryonic stem cells
Flu	Fludarabine
GVHD	Graft-versus-host disease
HCQ	Hydroxychloroquine
HSC	Hematopoietic stem cells
H SCT	HSC transplant
ILD	Interstitial lung disease
iPSC	Induced pluripotent stem cells
IRAKs	IL-1R-associated kinases
ISSCR	International Society for Stem Cell Research
JIA	Juvenile idiopathic arthritis
JSSc	Juvenile systemic sclerosis
LEF	Leflunomide
MMF	Mycophenolate mofetil
MS	Multiple sclerosis
MSC	Mesenchymal stem cells
MSCT	MSC transplant
MTX	Methotrexate
MyD88	Myeloid differentiation factor 88
PM	Polymyositis
PSV	Primary systemic vasculitis
QOL	Quality of life
RA	Rheumatoid arthritis
rbATG	Rabbit antithymocyte globulin
RTX	Rituximab
SCOT	"Scleroderma: Cyclophosphamide or Transplantation" Trial
SCT	Stem cell transplant
SLE	Systemic lupus erythematosus
SLEDAI	SLE disease activity index
SS	Sjögren's syndrome
SSc	Systemic sclerosis
TAP2	Transporter associated with antigen processing 2
TBI	Total body irradiation
TLR	Toll-like receptor
TNF $\alpha$	Tumor necrosis factor alpha
Treg	Regulatory T cells
TRM	Transplant-related mortality

## 1 Biology of Stem Cells and History of Stem Cell Therapy

Stem cell therapy is one of the most fascinating areas in modern medicine. Stem cells are different from other cells in that (a) they are undifferentiated, (b) they can divide for long periods, and (c) they are capable of becoming specialized cell types. These unique characteristics have generated significant excitement in the scientific community to examine the biology underlying their distinct characteristics and more importantly, their application for cell-based therapy.

Three primary categories of stem cells exist: embryonic stem cells (ESC), adult stem cells (ASC), and induced pluripotent stem cells (iPSC) (Table 1). ESC are derived from the blastocysts during embryo development. ESC are pluripotent because they have the potential to self-renew and also to differentiate into any cell type. In the laboratory, ESC lines can remain undifferentiated under specific conditions. Undifferentiated ESC can directly undergo differentiation into specific functional cell types. It is envisioned that differentiated ESC can be used to cure diseases. Examples of clinical applications of ESC include diabetes, heart diseases, traumatic spinal cord injury, muscular dystrophy, and hearing and vision loss. iPSC are adult cells that have been genetically reprogrammed to dedifferentiate into behaving like ESC. Mouse iPSC were first reported in 2006 [1], and soon after, the first human iPSC were successfully generated in 2007 [2].

Research on ASC can be traced back to the 1950s when two kinds of stem cells were discovered in the bone marrow. The first one being hematopoietic stem cells (HSC) and the other being bone marrow stromal cells, which are also known as mesenchymal stem cells (MSC). Since then, ASC have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. HSC can differentiate into all blood cell lineages such as red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, and macrophages [3]. MSC are multipotent and can give rise to a variety of cell types such as bone cells (osteoblasts and osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and stromal cells.

The potential applications of stem cells in clinical medicine are enormous. The unique property that allows stem cells to differentiate into specific cell types offers the possibility of a renewable source of replacement cells and tissues in cell-based therapy. Indeed, over 40 years ago, HSC transfer was initially conducted in the form of bone marrow transplantation with successful allogeneic transplantations performed for an infant with X-linked lymphopenic immune deficiency [4]. Stem cell therapy generated great enthusiasm in the 1980s as a targeted and permanent treatment for many previously incurable autoimmune disorders. In 1986, Jacobs et al. reported that allogeneic HSC transplant in a patient with drug-induced aplastic anemia and severe rheumatoid arthritis not only reversed the hematological abnormality but also simultaneously resulted in a 2-year period of relief from joint pain [5]. HSC therapy also resulted in significant clinical improvements in other autoimmune diseases [6–10]. In 1996, the First International Symposium on HSC Therapy in autoimmune rheumatic diseases (ARD) was convened in Basel, which led to the

**Table 1** Comparison of three categories of stem cells and their clinical applications

	Adult stem cells	Embryonic stem cells	Induced pluripotent stem cells
Source	Various tissues and includes bone marrow, umbilical cord, and blood stem cells	Blastocysts from fertilized eggs	Viral or nonviral reprogramming of somatic cells
Potency	Multipotent	Pluripotent	Pluripotent
Laboratory features	1. Finite – may not live long in culture. Difficult to obtain in large numbers	1. Immortal – endless division in culture without losing function	1. Immortal – endless division in culture without losing function
	2. Less flexible – more difficult to reprogram to another tissue type	2. Plasticity – can be easily manipulated	2. Most difficult among these three to obtain or create
Immunogenic/rejection	Low risk (but with possible second autoimmune disease development)	High risk	Low risk
Ethical issues	No serious ethical issues involved	Destruction of developing life	No serious ethical issues involved
Clinical research/application	HSC therapy	Diabetes, heart diseases, traumatic spinal cord injury, muscular dystrophy, hearing loss, and vision loss	Relative new to science
	Systemic sclerosis		
	Rheumatoid arthritis		
	Systemic lupus		
	Erythematosus		
	Sjogren's syndrome		
	Juvenile idiopathic Arthritis		
	MSC therapy		
	Multiple sclerosis		
	Osteoarthritis		
Sjogren's syndrome			

development of the first consensus guidelines for HSCT in autoimmunity recommending standardized protocols and established the European Bone Marrow Transplant/European League Against Rheumatism (EBMT/EULAR) registry [11]. Since then, over 1,500 HSC transplants for ARD, including systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and juvenile idiopathic arthritis (JIA), have been registered [12]. Despite its promise of potential long-term benefit, acute toxicity such as infection

and bleeding during the aplastic period, complications due to opportunistic infections during the T-cell reconstitution phase, and the possibility of developing a second autoimmune disease should be carefully considered [13, 14].

Multipotent MSC have recently gained significant attention in the treatment of ARD. MSC was initially isolated from guinea pig bone marrow as spindle-shaped cells with progenitor properties that adhered to plastic and formed fibroblast colonies [15]. MSC are not truly pluripotent, and most MSC described to date are actually multipotent progenitors obtained from a wide range of tissues such as bone marrow, umbilical cord, placenta, cord blood, adipose tissue, synovium, and teeth. Human MSC are now phenotypically characterized as CD105<sup>+</sup>, CD73<sup>+</sup> and CD90<sup>+</sup>, CD45<sup>-</sup>, CD34<sup>-</sup>, CD14<sup>-</sup> or CD11b<sup>-</sup>, CD79a<sup>-</sup> or CD19<sup>-</sup>, and negative for HLA class II molecules. Human MSC must also be plastic-adherent cells and have the ability to differentiate into osteoblasts, adipocytes, and chondroblasts [16]. However, these criteria are not unique because CD105, CD73, or CD90 is also expressed on other cell populations, while other cell markers are also expressed in MSC [17]. Moreover, there are various sources of MSC with differentiation potentials that are different from the criteria described above [18]. Essentially, MSC represent a heterogeneous progenitor cell population with immunomodulatory properties, which are able to suppress T- and B-cell proliferation, inhibit the differentiation of monocytes into immature dendritic cells, and affect the functions of NK cells [19, 20]. MSC express low levels of cell surface HLA class I molecules and are negative for HLA class II molecules. Meanwhile, MSC do not express co-stimulatory molecules CD80, CD86, or CD40. Hence, MSC can easily escape immune surveillance [21]. Biologically, the regenerative, immune privileged, immunomodulatory, and tissue-protective properties of MSC suggest that these cells are effective therapeutic reagents in human diseases [20–24].

Preclinical studies have demonstrated the therapeutic efficacy of MSC in various rheumatic autoimmune disorders in animal models including multiple sclerosis (MS) [25–27], osteoarthritis [28–31], rheumatoid arthritis (RA) [32–36], and Sjogren's syndrome (SS) [37, 38]. The hallmark of the clinical application of MSC therapy was phase I study in which 23 patients experienced full remission after treatment of various hematological malignancies in 1995. Moreover, there were no adverse events after intravenous infusion of ex vivo expanded bone marrow-derived MSC [39]. The first published report describing the application of MSC in therapeutic intervention was on breast cancer patients receiving high-dose chemotherapy. This study showed that MSC therapy was safe and had the potential to enhance HSC engraftment [40]. Thereafter, animal studies, in vitro, and clinical studies on MSC have increased rapidly.

## 2 Clinical Studies on SCT for Common Rheumatic Diseases

SCT has been successfully applied in patients with ARD. Here we will review a few clinical trials in SSc, RA, inflammatory myopathies, primary systemic vasculitis (PSV), SS, and pediatric ARDs, such as JIA.

## 2.1 Systemic Scleroderma (SSc)

SSc is a rare chronic systemic autoimmune disease with a prevalence rate of around 5 per 100,000 and an incidence of 1 in 100,000. Based on epidemiological data, approximately 3.4 million individuals are affected globally. Despite advances in early diagnosis and appropriate therapy, the prognosis of SSc patients remains poor, and the disease is associated with a high mortality [41]. The amenable treatment for SSc is immunosuppressive therapy. For example, the standard of regimens for interstitial lung disease (ILD) in SSc is CYC. Nevertheless, two randomized trials and meta-analyses showed no improvement in prognosis of SSc with CYC treatment [42].

In 1994, Ratanatharathorn et al. [43] reported the first successful HSC treatment in SSc patients with untreatable pulmonary hypertension which led to the gradual acceptance of HSC therapy as an optional treatment regimen for severe SSc. Complete or partial remission was observed in small case series and non-randomized clinical trials of HSCT treatment for SSc patients, although there were high rates of transplant-related mortality (TRM) [44]. Data from a single-center retrospective study of SSc patients who received auto-HSCT showed significant skin and lung disease amelioration in 78.3 % of patients at 6 months, and 91 % of patients achieved an overall good response. However, cardiac events result in 6 % TRM [45]. Another subsequent analysis of 57 SSc patients receiving HSCT from the EBMT/EULAR registry showed that sustained improvement in skin score and visceral organ functions was observed in two-thirds of the patients for up to 3 years after HSCT but with a TRM of 8.7 % [46]. TRM was reduced by pretransplant evaluation, early intervention, and the use of amenable conditioning regimen.

More recently, one phase II and two phase III randomized control trials were conducted to evaluate the efficacy, safety, and long-term side effects of auto-HSCT: the American Scleroderma Stem Cell Versus Immune Suppression Trial (ASSIST) [47], Autologous Stem Cell Transplantation International Scleroderma (ASTIS) [48, 49], and the “Scleroderma: Cyclophosphamide or Transplantation” trial (SCOT) [50].

ASSIST is a published open-label, randomized, controlled trial. The result of this phase II clinical trial demonstrated that unmanipulated auto-HSCT steadily ameliorated skin flexibility and pulmonary function defects in patients with SSc. This was found in patients treated with CYC whose disease progressed before being switched to HSCT. After 2 years of follow-up, patients receiving HSC therapy had durable remission in pulmonary function, reduction in interstitial lung lesions visualized on high-resolution CT imaging, and improved quality of life (QOL). More importantly, no TRM was reported [47]. Based on the success of phase II clinical trials [47], a phase III study is in progress to compare the safety and efficacy of the ASSIST trial pretransplant protocols of CYC and G rabbit antithymocyte globulin (rbATG) with the addition of rituximab [50]. In the multicenter phase III ASTIS trial [51], there is an increase in overall and survival benefit in patients administered with CYC

200 mg/kg and rbATG with CD34+ auto-HSCT compared to those with monthly pulse CYC treatment of HSCT that had a 10% TRM. More stringent patient selection and safer conditioning regimens may reduce the TRM of ASTIS [52].

A controlled phase III SCOT trial was conducted to compare intensive immunotherapy and HSCT to monthly pulse CYC [50]. For future intertrial comparison, the SCOT trial shared identical end points and control regimen with the ASTIS trial, but the SCOT trial protocol employed transplant conditioning with total body irradiation (TBI), which differed from both the ASTIS and ASSIST trials that contained ATG as part of their immunoablative protocols [53].

A number of case reports [54, 55] indicated clear, positive therapeutic effects, without immediate toxicity nor severe infection in SSc patients receiving allo-HSCT and MSCT. Further studies using larger samples in randomized controlled trials are required to validate the efficacy and safety of allo-HSCT and MSCT.

## 2.2 Rheumatoid Arthritis (RA)

RA is a chronic, debilitating, systemic ARD affecting 1% of the population [56]. Despite aggressive disease-modifying antirheumatic drugs (DMARD) approaches and efficient biologic agents in RA [56], a considerable proportion of RA patients still suffer from a severe, destructive, refractory disease [52, 57]. Besides biological agents, lymphoablative regimens combined with SCT have been employed as a therapeutic modality for refractory RA. The rationale for this approach is based on the concept of lymphoablation by high-dose chemotherapy, with a subsequent revival of naive T cells derived from reinfused hematopoietic progenitor cells [58].

In 1997, a disabled patient with refractory RA received auto-HSCT and became almost free of joint symptoms in half a year [59]. Since then, phase I/II clinical trials were set up to evaluate the feasibility, safety, and efficacy of auto-HSCT in patients with RA. From the 2001 EBMT/EULAR data, 43 patients from 11 centers underwent auto-HSCT. Among 39 patients evaluated, significant improvement in clinical response was observed in half of the patients, but the disease recurrence rate was around two-thirds within 2 years. One patient died as a consequence of sepsis [60]. In the 2004 data analysis of EBMT/EULAR, 73 refractory RA patients from 15 centers were given auto-HSCT and assessed for treatment response using the American College of Rheumatology (ACR) criteria. Two-thirds achieved an ACR50 improvement response. However, most patients restarted DMARD within 6 months due to persistent or relapsing disease activity. Interestingly, most patients were relatively sensitive to DMARD, which had proven refractory prior to HSCT [61].

In a CYC dose escalation followed by unmanipulated auto-HSCT study, the cohort receiving subablative dosage (100 mg/kg) developed disease recurrence within 3–4 months, while the cohort at the higher dosage (200 mg/kg) had durable remission for 17–19 months [62]. The most common protocol for auto-HSCT

treatment in RA includes CD34 selection and a lymphoablative, rather than myeloablative, conditioning regimen. Data from these heterogeneous studies indicate the feasibility and safety of auto-HSCT in RA. No severe adverse event or TRM was noted [61, 63].

Preclinical data and anecdotal evidence showed that allo-HSCT might be more effective than auto-HSCT [64]. In 1977, four patients with RA underwent allo-HSCT for gold-induced marrow aplasia. Three patients died from transplant-related toxicity. The one surviving patient had complete remission at 2 years follow-up [65]. Three other patients with RA receiving allo-HSCT reached long-term amelioration of their disease [66]. However, the TRM from nonmyeloablative allo-HSCT was 10–20%. The risks of TRM and graft-versus-host disease (GVHD) may discourage physicians from recommending allo-HSCT to RA patients unless all other standard treatments have proven to be noneffective [64].

It is difficult to differentiate the poor prognosis and HSCT-responsive RA patients from refractory ones. Therefore, HSCT for RA patients should only be considered with extra caution. Prospective, randomized controlled long-term follow-up trials are urgently needed to evaluate the risk–benefit ratio. Unfortunately, the EBMT Autologous Stem Cell Transplantation International Rheumatoid Arthritis (ASTIRA) phase III trials were suspended because of failure to recruit sufficient patients [67].

To date, only limited clinical trials of MSCT in RA have been registered [68]. A single-center cohort study demonstrated that 136 patients with intractable RA receiving DMARD plus umbilical cord MSC had a rapid and effective remission. Moreover, repeated treatments achieved better clinical response and more clearly improved the QOL of intractable RA, without serious side effects [69]. It should be noted that the utilization of biologic agents has significantly altered the natural history of RA [70]. Therefore, SCT regimens only have a finite therapeutic potential in a portion of patients with RA, specifically those who fail to respond to currently available therapies [44, 61].

### 2.3 *Sjögren's Syndrome (SS)*

SS is the most common chronic, slowly progressive ARD, which typically affects the exocrine glands leading to xerostomia, keratoconjunctivitis sicca, and systemic features. Prevalence of SS varying from 0.1 to 4.8% has been estimated using different criteria for classification among different study populations, and patients with SS have a 20- to 40-fold increased risk of developing lymphoma [71]. Currently, clinical management of SS remains challenging because of a lack of effective therapeutic agents.

Only a limited number of case reports of HSCT in SS are available. Three SS patients with refractory systemic vasculitis or lymphoma receiving auto-HSCT developed amelioration of the vasculitis and lymphoma but not the SS [72]. Two other patients with severe and refractory SS were able to tolerate high-dose



immunosuppressive drugs and auto-HSCT and had temporary alleviation of disease [73].

Recently, clinical data from 24 refractory SS patients receiving MSCT demonstrated the feasibility, safety, and efficacy of MSCT. In this study, most SS patients reach durable increased salivary flow rate, considerable improvements in disease activity, and organ function after MSCT [38].

## **2.4 Primary Systemic Vasculitis (PSV)**

PSV, as well as its related conditions, Behcet's disease (BD) and relapsing polychondritis, belongs to a heterogeneous group of autoimmune diseases with severe organ damage and an often fatal course [74]. With the development of early diagnosis and optimal standard therapy, the outcome of PSV has been dramatically transformed into a controllable disease. However, one quarter of patients with PSV are resistant [75] to current treatment, and half of them suffer from disease recurrence despite at least 2 years of therapy. There is therefore an obvious unmet need in the treatment of PSV [76].

SCT in PSV is limited. Retrospective analysis of 15 patients with various PSV and related diseases from EBMT showed that 14 of them first received auto-HSCT, while one additional patient received allo-HSCT. Remission rate was beyond 90 %, but one-third had a recurrence of the disease [77]. In a single-center study, four patients with refractory SV with neurological system involvement received nonmyeloablative auto-HSCT. Among them, three patients recovered completely. One patient with BD did not respond to HSCT. No TRM or adverse reactions were noted [72].

The first report of a patient with antineutrophil cytoplasmic antibody (ANCA)-associated renal vasculitis treated beyond conventional therapy with MSCT demonstrated an abrupt and striking recovery from disease, which was clearly confirmed with a second infusion [75]. However, another small clinical study showed that MSCT could not reverse BD's retinal vasculitis process, which might be due to the late and advanced stage of disease [78].

## **2.5 Polymyositis (PM) and Dermatomyositis (DM)**

Inflammatory myopathies are a heterogeneous group of rare conditions including PM and DM characterized by muscle weakness and inflammation [79]. The approximate incidence in the United States is five to ten cases per million. Unfortunately, PM/DM can induce marked disability and mortality unless properly recognized and timely and aggressive therapy is given [80]. In severe refractory cases of PM/DM, auto-HSCT may be a salvage strategy.

In one case report, a severe refractory PM patient with anti-Jo-1 antibody received auto-HSCT after T-cell-depleted myeloablative conditioning with CYC. The patient's strength and respiratory function significantly improved. Chest CT imaging showed remarkable reduction of interstitial shadows [81]. Five other patients with rapidly progressive and refractory ILD due to PM/DM were also successfully treated with auto-HSCT. After treatment, the patients' dyspnea disappeared, and arterial blood gas analysis and pulmonary function testing significantly improved. CT imaging showed a remarkable reduction of interstitial infiltrates [82].

An open-label pilot study of ten patients with intractable PM/DM who underwent allo-MSCT was conducted. Most patients achieved clinical remission along with improved laboratory parameters and tapering of medications. However, none of the patients could completely withdraw therapy after following up for about 1 year. It should also be noted that two patients died following MSCT from disease relapse after infection [83]. To date, the sample size with PVS and PM/DM receiving SCT is still too minute to draw any definitive conclusion.

## 2.6 *SCT in Pediatric ARD*

In children, ARD such as JIA, juvenile systemic sclerosis (JSSc), juvenile SLE, and others are a major cause of morbidity, which is due to both the disease itself and conventional treatment strategies and especially holds true for the subset of patients with severe or refractory disease [84]. Although recent advances in the understanding of the pathogenesis of these diseases have led to significant progress in treat-to-target approach, some ARD patients continue to be refractory to standard treatment. The rate of death in pediatric ARD is about 2–4% [85]. In recent decades, SCT has been successfully employed in severe and refractory pediatric ARD as a novel salvage strategy.

On the other hand, one needs to seriously consider that conditioning regimens at pretransplantation are associated with a high rate of growth retardation, infertility, and late tumors in children with ARD [86]. With advances in SCT techniques, the rate of morbidity and mortality associated with transplantation procedures has been decreasing. Not only are the pretreatment strategies safer and less intense, but antibiotics and antifungal drugs are also more effective. To date, the preferred conditioning regimen used in JIA is a nonmyeloablative regimen of CYC, rbATG, and fludarabine (Flu) [87].

Although it is widely believed that allo-HSCT is a more effective and potentially curative regimen compared to auto-HSCT, there is no statistical difference in long-term survival. Unfortunately, the risk of allo-HSCT-related adverse event is still high, and the risks from GVHD and TRM were generally not acceptable for the pediatric ARD [87]. So far, there are no clinical trials on the use of MSCT in pediatric ARD.

## **2.7 Juvenile Idiopathic Arthritis (JIA)**

JIA is the most common ARD in children [88]. Despite the application of novel treatment regimens, the prognosis of JIA is still poor, especially in children with systemic and polyarticular onset. The mortality of JIA is approximately 0.2% [85]. Since 1997, HSCT has been successfully applied in intractable JIA. The first four patients with severe refractory JIA receiving auto-HSCT all had complete remission and went off drug therapy [89]. Retrospective analysis of a multicenter cohort of 34 patients with JIA after auto-HSCT demonstrated that 53% reached drug-free full remission, 18% had partial recovery, and 21% did not respond to the procedure, with a TRM of 9%. All partial and complete recurrence of disease happened in the first 18 months post-HSCT [90]. In a multicenter, prospective, phase II clinical trial, 22 children with refractory progressive JIA underwent T-cell-depleted auto-HSCT with a regimen of myeloablative and immunoablative including CYC, ATG, and TBI. After a median follow-up of 80 months, eight patients reached durable full remission, seven responded partially, and five experienced a relapse of disease. However, there was a 9% TRM [91].

HSCT has significantly improved QOL for refractory JIA. However, as expected, already damaged joints did not improve nor worsen. If managed before the DMARD treatment and before any severe permanent joint destruction, HSCT is likely to reverse what would otherwise have become a permanent defect. Therefore, it is important to screen carefully those patients who are apt to benefit from HSCT [87].

## **2.8 Juvenile Systemic Sclerosis (JSSc)**

Compared with the adult form, JSSc appears to have a better outcome. However, children with diffuse skin thickening and lung involvement had a 5-year mortality of 10% [92]. Up to this point in time, those with JSSc treated with HSCT have been included in two groups of clinical studies. The data from the EBMT database showed that five JSSc received auto-HSCT, and three of them achieved clinical remission at 23 months follow-up [93], while one had a recurrence of the disease [46]. Another five JSSc patients were included in a clinical study on 26 patients with SSc. After auto-HSCT, three children achieved full remission after more than 5 years of follow-up [93].

## **2.9 Juvenile Dermatomyositis (JDM) and Juvenile Vasculitis (JV)**

Recently, two children with severe progressive refractory DM were administered auto-HSCT. Both had a dramatic improvement in QOL, and sustained recovery was

noted [94]. Notably a 9-year-old girl with severe resistant granulomatosis and polyangiitis became disease-free after allo-HSCT following reduced-intensity conditioning [95].

### **3 Stem Cell Transplantation in the Treatment of Systemic Lupus Erythematosus**

#### ***3.1 The Natural History and Epidemiology of SLE***

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology and clinical heterogeneity. Patients with SLE are presented with diverse clinical symptoms: skin lesions, arthritis, renal disorder, neurologic disorder, and hematologic changes. Major biomarkers include antinuclear antibodies, anti-dsDNA antibody and anti-Sm antibody. Immune-mediated injury in multiple organs leads to high mortality and morbidity [96–104]. Besides the immune imbalance, evidence from familial studies together with high concordance among monozygotic twins suggests the contribution of genetics in SLE [105–108]. To date, there are many single genes, such as coagulation factor II gene (F2), TAP2 (transporter associated with antigen processing 2) gene, VKORC1 gene, and autosomal gene, which are implicated in the pathogenesis of SLE [109–112]. Various environmental agents and toxicants, such as cigarette smoke, alcohol, plastic and electronic products, cosmetic agents, occupationally and non-occupationally related chemicals, ultraviolet light, infections, sex hormones, and certain medications and vaccines, are found to be associated with SLE onset or flares [113–115].

The incidence and prevalence of SLE varies considerably worldwide, ranging from 15 to 100 per 100,000 individuals among different racial groups [116]. SLE appears to be more prevalent in certain ethnic groups, such as the African-Americans, African-Caribbeans, and Asians, but it is also reported that there is a trend toward higher incidence and prevalence of SLE in Europe and Australia compared to the United States [117]. The reported prevalence of SLE in Asian countries varies from 20 to 59 per 100,000 [118, 119].

#### ***3.2 The Deficiency of Traditional Treatment in SLE***

Traditional therapies for the treatment of SLE, notably corticosteroids and immunosuppressive drugs, have led to a significant improvement in survival over the last two to three decades and decreased the progression to end-stage multi-organ failure. The most widely and classically used immunosuppressors include cyclophosphamide (CYC), mycophenolate mofetil (MMF), leflunomide (LEF), methotrexate (MTX), cyclosporine A (CsA), azathioprine (AZA), and hydroxychloroquine (HCQ). Each of these agents, however, can carry high toxicities and many side

effects. They include osteoporosis and dyslipidemia induced by corticosteroids, myelotoxicity and gonadal injury induced by CYC, gastrointestinal discomfort and liver dysfunction by MTX or LEF, and hypertension and nephrotoxicity by CsA. The main concern for the side effects of corticosteroids and immunosuppressive therapies is infection [120]. CYC, particularly in combination with high-dose steroids, is reported to have the strongest effect in suppressing immune responses against microorganisms. The most common infections in patients with SLE treated with these traditional drugs include virus herpes zoster, mycobacterium tuberculosis, cytomegalovirus, Epstein–Barr virus, and fungal infections [120–124]. These infections may worsen the disease and aggravate the economic burden of patients. Furthermore, steroids and immunosuppressive drugs are not universally effective, with partial or no response in many cases.

### ***3.3 The Efficacy and Deficiencies of the New Treatments (Including Small Molecules and Biological Agents)***

Over the past decade, due to a better understanding of SLE immunopathogenesis, many new drugs have been developed to target specific immune cells, co-stimulatory modulation, or cytokines thought to be central to the disease pathogenesis, with the aim of achieving better control of the disease with fewer side effects.

B cells have long been considered central to the pathogenesis of SLE and have been regarded as an important target for biologic drugs. Several B-cell-targeted drugs have been developed. Rituximab (RTX), a monoclonal antibody targeting the B-cell-specific receptor CD20 (anti-CD20), has been reported to be an effective treatment for patients with active SLE who failed to respond to standard therapy. A pooled analysis of the efficacy of RTX from European cohorts diagnosed with biopsy-proven lupus nephropathy showed that administration of RTX resulted in high response rates and significant improvement in 24-h proteinuria, serum albumin, and protein/creatinine ratio [125]. Despite these promising data, two other large randomized controlled studies designed to assess the efficacy of RTX in nonrenal lupus [126] and lupus nephritis [127] did not achieve their respective primary endpoints. In the ACR and EULAR guidelines for the management of patients with refractory lupus nephritis (class III/IV) who have not responded to CYC nor MMF, RTX is still recommended [128]. Belimumab, another B-cell-targeted therapy, is a human immunoglobulin (Ig)-G1 $\lambda$  monoclonal antibody that binds soluble B lymphocyte stimulator (BLyS) and inhibits its biologic activities. The efficacy of belimumab is demonstrated in two large randomized control trials with more than 800 patients in each study [129, 130]. Pooled data showed a beneficial effect in 50.6% of belimumab-treated patients versus 46.2% in the placebo arm. However, the benefits obtained with belimumab are modest and only attained in patients with mild disease who are already receiving standard therapy [130]. Epratuzumab is a monoclonal antibody that targets

CD22, a B-cell-specific surface antigen involved in B-cell signaling. In a phase IIb trial to assess the efficacy and safety of epratuzumab, the overall treatment effect was not statistically significant [131]. Multicenter phase III studies with epratuzumab in patients with SLE are currently ongoing.

Tumor necrosis factor alpha (TNF $\alpha$ ) is an interesting and controversial cytokine in the field of SLE due to its apparent dual role [132]. While TNF $\alpha$  blockade has been successful as a mainstay treatment for RA [133], the assessment of this therapy in SLE patients has not been straightforward. A recent study demonstrated the safety and efficacy of anti-TNF $\alpha$  therapy in SLE [134]. It suggests that any consideration of anti-TNF $\alpha$  for the treatment of SLE patients must be for a short duration only and not recommended for patients with antiphospholipid syndrome [135].

Despite potential benefits of biological inhibitors in the treatment of SLE, concerns exist regarding the occurrence of infections in patients treated with these agents [136, 137]. Both patients and primary physicians need to be aware of the possibility that serious infection may develop. If such a problem is diagnosed, the biologic inhibitor should be discontinued until adequate treatment has been completed [138].

Recently, many small molecule inhibitors have been designed to treat SLE based on multiple targets in Toll-like receptor (TLR) signaling pathways, including TLRs, myeloid differentiation factor 88 (MyD88), and IL-1R-associated kinases (IRAKs). These new chemical drugs, which can be taken orally, include CpG-52364 and IMO-9200 (targeting TLR7/8/9), SM934 (targeting TLR9), E-6446 and AT-791 (targeting TLR7/9 and IL-6), and ST-2825 (interfering with the recruitment of IRAK4 and IRAK1 via MyD88). They penetrate the cell membrane, effectively targeting endosomal TLRs and downstream signaling proteins [139]. Almost all these drugs are in preclinical animal studies or in phase I clinical studies and still require further exploration [140–142]. There are other recombinant small molecule inhibitors like abatacept, which blocks T-cell co-stimulatory ligands (CD80 and CD86) on B cells. Unfortunately, abatacept did not meet primary and secondary endpoints in a phase II clinical trial of SLE patients [143].

### ***3.4 The Mechanisms of SCT in the Treatment of SLE***

The rationale for auto-HSCT is its broad effect on the repopulated immune system, complex regulatory potentials, and long-term beneficial effect via down-regulating immune reactivity. The CD4<sup>+</sup> and CD19<sup>+</sup> cells were significantly reduced [144], and the expression of CD69 declined or normalized. Th2 cell cytokines like IL-4 decreased, while Th1 cell cytokines like interferon  $\gamma$  (IFN- $\gamma$ ) increased after auto-HSCT [145]. The peripheral T-cell receptor repertoire was normalized [146]. Thymic-derived Foxp3<sup>+</sup> regulatory T cells (Treg) regenerated [147], or a newly differentiated population of LAP<sup>high</sup>CD103<sup>high</sup>CD8<sup>TGF- $\beta$</sup>  Treg generated after autologous HSCT [148]. Likewise, responders exhibited

normalization of the previously disturbed B-cell homeostasis with numeric recovery of the naive B-cell compartment [147]. These data reveal that both depletion of the autoreactive immunologic memory and a profound resetting of the adaptive immune system are required to reestablish self-tolerance by auto-HSCT in SLE.

Unlike auto-HSCT, allo-HSCT appears to offer curative potential in that the autoaggressive “old” immune system is replaced by a “new” one [149]. Auto-HSCT aims at restoring tolerance to self but does not affect genetic risk factors for the development of lupus, and therefore relapses are not unexpected, whereas allo-HSCT transfers a completely new immune system to the recipient with a chance for a cure.

MSC have become a major interest in their potential for immune-modulating, anti-inflammatory, and tissue-protective properties. The therapeutic effect of allogeneic MSC was primarily dependent on its systemic immunoregulatory effects on various immune regulatory cells. Allogeneic MSC dose-dependently inhibited T-cell proliferation [150] and inhibited Akt/GSK3 $\beta$  signaling pathway mediated G1/S transition of lupus T cells [151]. The frequency of CD4<sup>+</sup> T cells decreased, and inflammatory cytokines were regulated by allogeneic MSC in both animal models and humans [150, 152, 153]. MSC can regulate T-cell function via two pathways. First, MSC directly inhibit the functions of antigen-specific T cells. Second, MSC inhibit T-cell functions indirectly by stimulating the expansion of Treg [153–156]. In addition to T cells, MSC also suppress B-cell proliferation and plasma cell differentiation [157]. Serum and local levels of B-cell-activating factor (BAFF) and IL-10 significantly declined after MSC transfusion [158], potentially explaining the reduction in specific autoantibody production. Modulation of lymphocyte function may also be mediated by other regulatory factors secreted by MSC, including TGF- $\beta$ , indoleamine 2,3-dioxygenase (IDO), hepatocyte growth factor (HGF), prostaglandin E2 (PEG2), nitric oxide (NO), IL-10, heme oxygenase 1 (HO-1), and HLA-G [159]. MSC may therefore exert some of their clinical effects by interfering with the production or function of such factors.

### ***3.5 History of SCT in the Treatment of SLE***

In 1996, an international collaboration began to explore the concept of immune ablation in patients suffering from severe autoimmune disease and not responding to conventional therapy [11]. It was hoped that following reconstitution of the immune system, a “resetting” of the autoimmune process would occur. In 1997, the first auto-HSCT for SLE was performed by Marmont et al. in Genoa, Italy [160]. Although many protocols were employed, they basically ranged from less aggressive (e.g., 200 mg/kg CYC plus antithymocyte globulin (ATG)) to more intensive (e.g., total body irradiation (TBI) plus CYC/ATG and CD34 selection). However, the initial choice of autologous HSC, with low toxicity, resulted in a high rate of relapse.



Theoretically, allo-HSCT offers the replacement of an autoreactive immune system and provides curative potential for patients with severe and drug-resistant ARD. Some SLE patients also received allo-HSCT previously. MSC were first used in humans for hematopoietic stem cell graft enhancement over 15 years ago [161]. Following many positive animal models of inflammation, organ transplant, autoimmunity, critical ischemia, radiation damage, and tissue scarring, MSC entered clinical trials for inflammatory disorders first in GVHD and then later in MS, Crohn's disease, SLE, and SSc [24].

### ***3.6 The Current Status of SCT in the Treatment of SLE***

In the past two decades, more than 2,000 patients received HSCT, and about 500 patients received MSCT worldwide. For autologous HSCT, phase I/II prospective and retrospective studies have supported autologous HSCT as a potential treatment option for severely affected lupus patients, as profound and prolonged clinical responses were noted [162]. SLE disease activity index (SLEDAI) score, 24-h proteinuria, serum creatinine, serum complements, and autoimmune antibodies, including antinuclear antibody and anti-dsDNA antibody, decreased, and there was a sustained withdrawal of immunosuppressive medication for most patients [145, 162]. The 5-year follow-up data from the CIBMTR database, with 50 patients enrolled, showed that the overall survival was 84%, the probability of disease-free survival was 50%, and treatment-related mortality was 4% [163]. Recently a retrospective survey reviewed the efficacy and safety of autologous HSCT in 28 SLE patients from eight centers reported to the European Group for Blood and Marrow Transplantation (EBMT) registry between 2001 and 2008. The 5-year overall survival was  $81 \pm 8\%$ , and disease-free survival was  $29 \pm 9\%$ , with non-relapse mortality of  $15 \pm 7\%$  [164], suggesting a satisfactory clinical efficacy of autologous HSCT for lupus patients.

In lupus-like animal models, allogeneic HSCT both reversed disease symptoms and prevented disease development. In 2007, Vanikar et al. reported a single-center retrospective study of allo-HSCT in 27 drug-resistant SLE patients along with follow-up for 4.9 years. The average disease-free interval was 7.35 months (range, 2.1–12.7 months), and serum anti-double-strand DNA antibody titers declined [165]. The EBMT data showed two SLE patients who underwent allo-HSCT. However, one patient died of infection at 2.9 months, and the other patient had progression of disease when followed up for 3 years.

As a new stem cell therapy option, in 2007, allogeneic MSCT was first administered in severe and drug-resistant lupus patients. Data from phase I clinical studies showed that disease activity was satisfactorily controlled, and proteinuria and serum autoimmune antibodies declined after allogeneic MSCT [154, 166]. The transfusion of umbilical cord-derived MSC also resulted in clinical benefits in patients with severe lupus, who were otherwise poorly responsive to conventional therapy [153]. A further phase II study, with up to 4 years of follow-up,



demonstrated a good clinical safety profile, with an overall rate of survival of 94 %, and about 50 % patients achieving and remaining clinical remission at 4 years visit, although relapses of disease occurred in 23 % [167]. Based on these studies, there appears to be no difference in clinical efficacy between allogeneic bone marrow and umbilical cord-derived MSCT. MSC infusion induced remission in multi-organ dysfunctions including lupus nephritis [168], diffuse alveolar hemorrhage [169], and refractory cytopenia [170]. Recently a multicenter clinical study showed that 32.5 % patients achieved major clinical response and another 27.5 % patients achieved partial clinical response during 12 months follow-up. Again, a proportion of patients (17.5 %) experienced disease relapse within 6 months of a prior clinical response and required repeated MSCT [171]. However, combining MSCT and HSCT may achieve higher efficacy for SLE patients. Autologous MSCT was also applied in two lupus patients but received no clinical efficacy [172]. Recently, combined transplantation of autologous HSCT and allogeneic MSCT was used in a Chinese female lupus patient and achieved disease remission for 36 months [173], suggesting a novel and effective therapy option for refractory SLE.

## **4 Lessons Learned from Stem Cell Transplantation in Systemic Lupus Erythematosus**

In the past two decades, SCT has represented an important breakthrough for patients suffering from severe and refractory SLE. Because it is an invasive procedure, SCT inevitability comes with risks, including treatment-related morbidity and mortality. However, with careful patient selection and adoption of conditioning regimens, TRM can be reduced. Indeed, lessons learned now from utilizing SCT in SLE will contribute to better outcomes in future clinical studies (Tables 2 and 3).

### ***4.1 The Potential Benefits and Limitations of SCT in SLE***

Currently there are more than ten clinical trials listed on [clinicaltrials.gov](http://clinicaltrials.gov) designed to evaluate SCT as a cure for SLE (Table 2). Stem cells under consideration include MSC and HSC from bone marrow and umbilical cord. The basic premise for HSCT is to reconstruct the immune system by replacing abnormal lymphocytes in patients with SLE, whereas the goal behind using MSC is to modulate the patient's existing microenvironment in the immune system, for example, by suppressing autoreactivity or upregulating the number of Treg [174]. In addition to MSC and HSC, iPSC provide an alternative source for stem cells. iPSC enable us to model normal and diseased cellular growth as well as the development of SLE. Along with extensive assessment of patient-specific disease pathogenesis, this approach may provide a personalized therapeutic choice for SLE patients in the future.

**Table 2** Clinical trials of SCT in SLE

Study title	Purpose	Stem cells used	Status	Sponsor/reference
Pilot study of total body irradiation in combination with cyclophosphamide, antithymocyte globulin, and autologous CD34-selected peripheral blood stem cell transplantation in children with refractory autoimmune disorders	To determine the safety and long-term complications of total body irradiation in combination with cyclophosphamide, antithymocyte globulin, and autologous CD34-selected peripheral blood stem cell transplantation in children with refractory autoimmune disorders	Autologous (or syngeneic) CD34-selected peripheral blood stem cell	Started November 2000, completed in July 2010	Fred Hutchinson Cancer Research Center NCT00010335
Immune ablation and hematopoietic stem cell support in patients with SLE: a phase II study	To examine the immunosuppressive therapy to the point of complete immune ablation and HSC recovery	Autologous HSC	Started September 2002, completed in November 2007	Richard Burt, MD Northwestern University NCT00271934
Lymphocyte depletion and stem cell transplantation to treat severe SLE	To study a new approach to treating patients with severe SLE, which involves collecting stem cells from the patient, completely shutting down the patient's immune system (rituximab, fludarabine, and cyclophosphamide), and then giving back the patient's stem cells	G-CSF (growth colony stimulating factor) was used to boost production of autologous HSC	Started January 2004, completed in October 2013	National Cancer Institute (NCI) NCT00076752
Allogeneic blood stem cell transplantation for patients with life-threatening SLE	To examine the outcomes after replacing the abnormal immune cells of patients with SLE that cause the disease with normal immune cells that are generated from the transplant blood stem cells from the healthy donor	HSC	Started June 2004, no recent verification on the recruitment status	National Heart, Lung, and Blood Institute City of Hope National Medical Center NCT00325741

<p>Cyclophosphamide and rATG/rituximab in patients with SLE</p>	<p>To examine whether treatment using chemotherapy followed by stem cell infusion will result in improvement of lupus disease. After intense chemotherapy destroys the cells in the immune system that may be causing this disease; stem cell infusion will start to produce a normal immune system that will no longer attack body</p>	<p>HSC</p>	<p>Started August 2005, recruiting</p>	<p>Richard Burt, MD Northwestern University NCT00278538</p>
<p>Mesenchymal stem cells transplantation for refractory SLE</p>	<p>To explore the outcomes after eliminating abnormal cells in immune system and restoring the body with a new population of progenitor cells in patients with SLE</p>	<p>Allogeneic MSC</p>	<p>Started March 2007, no recent verification on the recruitment status</p>	<p>Nanjing Medical University National Natural Science Foundation of China NCT00698191</p>
<p>Mesenchymal stem cell transplantation reverses multi-organ dysfunction in systemic lupus erythematosus mice and humans</p>	<p>To evaluate the efficacy and safety of using allogeneic MSC in patients with treatment-refractory SLE during a 12-18 months follow-up period</p>	<p>Allogeneic MSC</p>	<p>Completed in 2008</p>	<p>California Institute for Regenerative Medicine (RN1-00572) NIDCR/NIH R01DE017449 and R21 DE017632 National Natural Science Foundation of China (30772014)  Chinese Education Ministry (20050315001), Jiangsu Province 135 Talent Foundation (RC2007002) [154]</p>
<p>Umbilical cord-derived MSC transplantation for active and refractory SLE</p>	<p>To explore safety and efficacy of allogeneic umbilical cord-derived MSC to treat patients with active and refractory SLE who have been resistant to multiple standard treatments</p>	<p>Human umbilical cord-derived MSC</p>	<p>Started January 2012, no recent verification on the recruitment status</p>	<p>The affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School NCT01741857 [171]</p>

**Table 3** Lessons learned from current SCT in SLE

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SCT has become a viable treatment for SLE in the past two decades that employs the use of HSC, MSC, and iPSC

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Limitations of SCT exist including disease relapse, side effects due to conditioning therapy, treatment-related mortalities, and GVHD

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Those who choose to undergo SCT should seek out legitimate studies and institutions with proper counseling and follow-up by their medical providers

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To ensure the development of novel approaches, standardized treatment protocols, and safety criteria for SCT, international research centers should be established through the support of government or private agencies

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Despite the positive outlook for SCT, limitations do exist. The biggest challenge for auto-HSCT is the high rate of disease relapse as well as serious side effects arising from conditioning therapy [175]. Jayne et al. reported that although 66% patients achieved clinical remission by 6 months, 32% of patients subsequently relapsed, and transplant-related mortality (TRM) was 12% at 1 year [176]. The US single-arm data showed a 4% (2/50) TRM [163]. The 7-year retrospective data from EBMT showed that the relapse incidence (RI) was  $56 \pm 11\%$ , and non-relapse mortality was  $15 \pm 7\%$  [164]. The mechanism for disease flare after auto-HSCT is not clearly understood. Niu et al. showed that the function of HSC is altered by both genetic and inflammatory factors in lupus mice [177]. Moreover, bone marrow CD34<sup>+</sup> cells expressed a higher percentage of surface markers for CD95, CD123, and CD166 compared to healthy controls [178], thereby implying that abnormal autologous HSC in lupus patients may lead to higher rates of relapse after HSCT. Although allo-HSCT can completely restore the immune system, its clinical application has unfortunately demonstrated a high rate of treatment-related mortality and a high risk for GVHD, which limits its widespread use.

SLE patients with a hypersensitive state or a severe allergic history are not suitable for SCT. Caution should be exercised with SCT, where intensive immunotherapy may increase the risk of life-threatening cardiac complications, bleeding events, and severe infections. Therefore, the following exclusion criteria for SCT in SLE should be carefully considered:

1. Organ dysfunction: Patients with advanced organ failure (heart, lung, and kidney) or active gastrointestinal bleeding should be excluded from SCT.
2. Uncontrolled infection: Any patient with an uncontrolled acute or chronic infection, including HIV, human T-lymphotropic virus type 1 and 2, hepatitis B, and hepatitis C, should be excluded.
3. Pregnancy: Pregnancy should always be excluded within 7 days of administering immunosuppressant or SCT.

These guidelines and recommendations will promote careful patient selection and clinical outcome, which are crucial for the most appropriate clinical niche of SCT in SLE.

In MSC therapy, most clinical protocols have depended on *in vitro* culturing of MSC to expand the cell population from the donor to get the required number of

cells for therapeutic applications. This *ex vivo* manipulation process has to be carefully monitored to maintain the desired therapeutic property *in vitro* (e.g., immunomodulation). Based on reported phase I/II clinical studies, the safety and efficacy data acquired from allogeneic MSCT in severe and drug-resistant SLE patients are encouraging and thus provide a foundation for double-blinded, randomized placebo-controlled trials. However, numerous questions still need to be addressed. First, what is the most appropriate MSC source for use in clinical applications? Second, what should the dose of infused MSC be? Third, is a preconditioning regimen necessary before MSCT? Fourth, what is the optimal time to administer MSCT? When lupus has progressed or at disease onset? Furthermore, Should it be applied to only drug-resistant cases? More double-blinded and controlled clinical studies are needed to confirm proper treatment protocols.

#### ***4.2 Medical Personnel Influence: Communicating with Patients and Public Education***

All the aforementioned SCT appear to offer curative potential, but as mentioned previously, limitations and possible risks to the patients' lives exist. This therapeutic strategy is in its early stages of clinical studies, and much more data and experience need to be acquired. Patients with SLE refractory to conventional therapy may opt to participate in clinical trials in hopes of a cure to their chronic symptoms. However, they should be diligent in seeking out legitimate studies undertaken by reputable academic institutions. Their medical providers should also assist in this process as well as advise their patients on the goals and end points of those studies. The rapid increase in centers carrying out SCT throughout various countries will require supervisory and ethics committees to monitor the production of stems cells, protocol safety, and adverse events. To ensure patients are not vulnerable to possible unproven therapies, these guidelines have to be strictly reinforced because any deviations could lead to inconclusive results. Relevant clinical experiences, both success and failures, should be communicated openly in professional conferences. Groups such as the International Society for Stem Cell Research (ISSCR) and European Medicines Agency (EMA) provide guidelines regarding these matters.

Confusing medical terms, physical or mental stresses, and financial obligations may overwhelm patients who eventually do undergo SCT therapy. Specific guidelines and instructions should be made available to the physicians, patients, and caregivers to help all parties understand what to expect throughout the SCT journey. Qualified healthcare professionals and counselors should be trained and be available to prepare the patients and assist them with questions on SCT throughout and post-SCT follow-up. Various ill side effects and discomfort may occur from the time the patient first receives a chemotherapeutic regimen, which is performed to prepare the body for SCT (also known as "conditioning"), to the actual SCT. At any of these phases, good communication between the medical team and the patient will ensure effective, high-quality care.

### ***4.3 Active Participation and Support from the Society and Government for SLE***

With its incidence nearly tripled in the last 40 years of the twentieth century and its estimated incidence rates at 1–25 per 100,000 in North America, South America, Europe, and Asia [117, 179], active support from the society and government agencies will expedite understanding of the etiology and pathogenesis of SLE, leading to the development of therapeutic interventions and improving quality of life for patients. To establish an international SCT center for SLE or ARD will not only provide a platform for researchers and clinicians to collaborate and exchange data and experience but also standardize and regulate SCT protocols in order to ensure patient safety. For example, the current quality of stem cells with regard to the source (donor's age or disease severity), heterogeneity, potency, and cell phenotype (cell surface markers) used for either animal studies or clinical trials is varied among labs. Further coordinated international studies from both the scientific and clinical community will help to develop novel approaches and standardize treatment protocols and safety criteria for the use of SCT in patients with SLE and other rheumatologic diseases.

## **5 Summary**

The evidence base for the benefit of stem cell therapies for SLE has increased progressively over the last 5 years, with an initial interest in high-dose immunosuppression supported by HSCT followed by growing work in MSCT. There is therapeutic benefit from both HSCT and MSCT approaches, although the safety and tolerability profiles vary considerably. Current uncontrolled studies show improvement in SLE patients that had only been followed for short lengths of time. Larger randomized, controlled trials with long-term follow-up are warranted in order to establish safety criteria for the use of SCT. These multicenter studies should be designed to minimize discrepancies resulting from the use of different protocols and to compare clinical safety and efficacy between steroids combined with MSC or HSC treatment and steroids combined with traditional immunosuppressive drug therapy, such as CYC or MMF. To be sure, further elucidation of the molecular mechanisms between stem cells and the host immune system will also be necessary to understand the pathogenesis of SLE and perhaps other novel therapeutic applications.

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