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Systemic Lupus Erythematosus & Stem Cell Therapy

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ABSTRACT

Systemic lupus erythematosus is an autoimmune disease characterized by a diverse range of clinical presentation and severe complications involving multiple organ systems. The global prevalence of this disorder ranges from 13 to 7713.5 per 100 000 individuals, with non-Caucasian women at the highest risk of developing the disease. SLE is a social as well as public health problem as this condition ranks among one of the top twenty leading causes of death in females from the age of five to sixty-four years of age and current treatments using multidisciplinary approaches can only work to control symptoms and further progression of disease while no true cure exists. Recent studies involving stem cell therapy in other autoimmune disorders with similar pathogenesis to systemic lupus erythematosus have encouraged clinic trials focused on investigating whether stem cells may be effective in treating this autoimmune disease. Mesenchymal stem cells are multipotent and capable of differentiating into many different cell types and are therefore seen as a promising strategy to treat even severe cases of systemic lupus erythematosus and lupus nephritis. These stem cells have a immunomodulatory effect and are known to affect the proliferative activity of immune cells such as T lymphocytes, B lymphocytes, natural killer cells and macrophages, which are all involved in the pathogenesis of SLE. Clinical trials in progress have indicated promise regarding stem cell therapy as a safe and tolerable treatment, however, further trials must be conducted in order to assess the efficacy of stem cell therapy in the long-term amelioration of disease.

Keywords

Systemic Lupus Erythematosus, Stem Cells.

Abbreviations

SLE: Systemic Lupus Erythematosus, ACR: American College of Rheumatology, ANA: antinuclear antibody, LE: lupus erythematosus, EULAR: European Alliance of Associations for Rheumatology, SS: Sjögren syndrome, Th17: T-helper 17, IL18RAP: IL-18 receptor accessory protein, NK: natural killer cells, APCs: Antigen presenting cells, Breg: B regulatory cells, Treg: T regulatory cells, BM-MSC: Bone marrow-derived stem cells.

Introduction

Epidemiology of Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the presence of autoantibodies that exhibits a broad range of clinical manifestations and can involve one or more organs or organ systems [1,2]. The chronic disease course and morbidity associated with SLE contributes to long-term and life-threatening organ system damage. SLE has a substantial impact on individual and public health, ranking among one of the top twenty leading causes of death in females from the age of five to sixty-four years of age [3,4]. The overall complexity of SLE diagnosis has made epidemiological studies difficult to conduct.

The epidemiology of SLE varies substantially between different sexes, age groups, ethnicities and is unevenly distributed across geographical regions with higher amounts of cases occurring in high-income countries. Individuals of Asian, Black, Hispanic, and Indigenous ethnicity/race experience increased prevalence and severity of disease [5]. Overall, the global incidence of SLE reported ranged from 1.5 to 11 per 100,000 person-years, and the global prevalence ranged from 13 to 7713.5 per 100 000 individuals [6]. Most studies consistently report that women were more likely

to be affected by SLE than men in all international regions, and a higher incidence and prevalence of SLE were reported in countries/regions with a higher income level. These patterns associated with income level could potentially be attributed to better healthcare systems and easier access to healthcare specialists that may better an individual's chances at receiving a proper diagnosis [7]. Overall, estimates of SLE incidence and prevalence vary due to some countries' lack of SLE epidemiology studies and further studies should be conducted as diagnostic testing improves to gain a more holistic understanding of the prevalence of this disease. Since the potential for SLE to develop severe complications is common, attendant direct costs are high as well as indirect costs associated with loss of economic productivity due to illness [7]. These issues lead to a need for improved diagnostic techniques as well as effective therapeutic approaches.

Diagnosis

To treat individuals more effectively with SLE, early detection is imperative. A biomarker is a measurable indicator of a normal biological process, pathogenic process, or a response to drug interaction [8]. Immunological biomarkers are found in blood, urine or tissue and can be used to measure disease progression and offer insight into diagnosis and management of several diseases including SLE [8]. Because SLE causes damage to more than one organ and is characterized by a heterogeneous clinical manifestation, many biomarkers may need to be taken into consideration to assess the state of the disease holistically [8].

The classification criteria for SLE were established by the American College of Rheumatology (ACR) and focuses on laboratory biomarkers, including proteinuria, urinary casts, hemolytic anemia with reticulocytosis, white blood cells, lymphocytes, platelets, the presence of Smith (Sm) antibody, antinuclear antibody (ANA), DNA antibody, total complement activity, complement (2, 3, and 4), and lupus erythematosus (LE) cells [8,9]. In 2019, a new classification criteria for SLE were developed by the European Alliance of Associations for Rheumatology (EULAR) and ACR [9]. Positive ANA is an obligatory entry criterion for SLE by the EULAR/ACR-2019 SLE classification, and three immunologic biomarkers (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) and seven clinical indices (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) are additional criteria to be diagnosed with SLE [10]. Since diagnosis is dependent on many factors, the speed and efficiency of diagnosis is limited, and more advanced understanding of biomarkers is needed to effectively treat this disease.

Pathophysiology

There are a number of different aspects that contribute to the pathogenesis of SLE. As with most autoimmune disorders, a complex interaction between genetic, hormonal, epigenetic and immunoregulatory factors all play a role in the development of SLE, though a full understanding of how these factors is all intertwined is unclear. The female predominance associated with SLE suggests a X-linked genetic factor or hormonal factor that plays a role in the development of lupus [11].

XIST is a long non-coding RNA essential for X chromosome activation in early stages of development. Yu *et al.* recently investigated the role of XIST in the regulation of X-linked immune genes, such as TLR7, in adult B cells [12-14]. By looking at single-cell transcriptome data of females affected by SLE, it

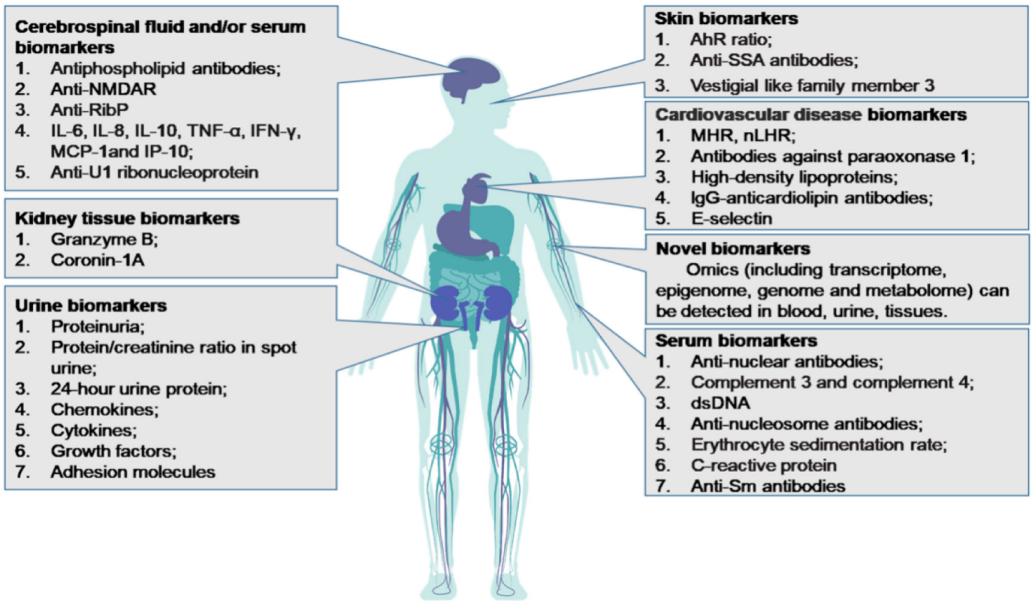

Figure 1: Common biomarkers for SLE and their measurement sites in patients with SLE. AhR ratio: the ratio of aryl hydrocarbon receptor in Th17 cells to Treg; anti-NMDAR: antibodies against N-methyl-D-aspartate receptor; anti-RibP: antibodies against ribosomal proteins; anti-SSA: antibodies against Sjogren's syndrome A; dsDNA: double-stranded DNA; IgG: immunoglobulin G; IFN: interferon; IL: interleukin; IP-10: IFN-γ-inducible protein 10; MCP-1: monocyte chemotactic protein-1; MHR: monocyte-to-high-density lipoprotein cholesterol ratio; nLHR: low-density granulocytes-to-high-density lipoprotein cholesterol ratio; PON1: antibodies against paraoxonase1; Sm: Smith; TNF: tumor necrosis factor [8].

was able to be determined that XIST and XIST dependent genes were dysregulated in these individuals and that their unique B cell populations play a role in the development of autoimmunity [12-14].

Cytokine pathways are also believed to play a role in SLE pathogenesis. In 2a recent publication by Peng et al., tear samples were examined from patients with Sjögren syndrome (SS) and SLE with established dry eye syndrome. Researchers considered T-helper 17 (Th17) cell-related cytokines, including interleukin (IL)-1b, IL-2, IL-4, interferon (IFN)-y, IL-6, IL-8, IL-17F, tumor necrosis factor (TNF)-α, IL-21, IL-22, and IL-23 [15,16]. When compared to healthy individuals, the study revealed abnormal regulation of the Th17 expression pathway in SLE and SS individuals; this suggests a pathogenic role in dry eye syndrome and that the T helper 17 pathway is implicated in multiple aspects of SLE pathogenesis, making this pathway a potential target for future treatments [15,16].

Additionally, in an investigation of the role of IL-18 and IL-18 receptor accessory proteins as neutrophils-driving cytokines, neutrophils from SLE patients were found to have elevated expression of IL18RAP [17]. This finding suggests that IL-18 likely contributes to SLE pathogenesis by neutrophil dysfunction via the upregulation of IL18RAP expression and has further systemic effects [17,18].

Clinical Manifestations and Severe Complications

SLE often affects multiple organs and organ systems throughout the body. Lupus nephritis (LN) is described by roughly 50% of patients with SLE and can progress into end-stage renal disease in more than 10% of cases [11]. When LN is diagnosed, it is continually monitored using renal pathology results and routine clinical laboratory data. It has been found that in LN, disease progression often includes presentation with acute renal dysfunction, arterial hypertension and corticosteroids dose independently predict an increase in damage over time. SLE can be associated with a 1.8-fold increased mortality rate for all-cause mortality and increased rates of hospitalized infections, the most common of which being sepsis [11].

History of Treatment

As SLE varies greatly in its presentation in each affected individual, this disease is treated based on clinical symptoms with a goal of managing these symptoms, limiting flares, and maintaining the lowest set point of active disease to prevent or slow organ damage and increase quality of life. Anti-inflammatory drugs are used to treat pain and fever associated with flares while antimalarials have been found to be effective in treating joint pain, fatigue, and inflammation of the lungs [19]. Corticosteroids are administered in several ways including injections and intravenous infusion to help lower overall inflammation rates in the body [19]. Immunosuppressants may be prescribed to limit the hyperactivity of the immune system; however, this treatment is not without risk [20]. Adverse side effects including risk for severe infections increase the longer immunosuppressant treatment is continued. Additionally, B-lymphocyte stimulator protein inhibitors are a type of biological medication that can help return aberrant B-cells to normal levels in hopes of controlling symptoms associated with SLE [20,21]. Additional medication may be needed to treat other side effects of lupus such as osteoporosis or heart disease and high blood pressure. Pregnant patients with SLE experience higher risk of spontaneous abortions, stillbirths, preeclampsia, and fetal growth restriction [22]. Therefore, preconception counseling and plans of treatment are necessary. Overall, while a combination of many types of treatment are typically combined to treat SLE, there is currently no cure for SLE. More recent understanding of the complexity of autoimmune diseases such as SLE has led to the development of a more detailed model of disease that can be investigated for future avenues of treatment, including the potential use of stem cells as therapy for more targeted treatments.

Discussion

Introduction to Stem Cells & Stem Cell Therapy

Severe forms of SLE are known to affect multiple organs or organ systems including the heart, brain, and lungs in addition to the kidneys; these severe cases of disease have a poor prognosis in the majority of SLE patients, with a predicted 10-year mortality rate of 10-15% [23]. Stem cell-based therapies have recently been a subject of interest for many researchers due to their ability to repair tissues and their anti-inflammatory properties that have been successful in treating a variety of other autoimmune disorders. More specifically, mesenchymal stem cells (MSCs) have been attracting attention in the development of a future treatment for lupus due to anti-inflammatory and immunomodulatory properties that could target the symptoms of SLE [23,24].

MSCs differentiate into a variety of specialized cell types and can be harvested and isolated from a variety of tissue types as well as bone marrow, peripheral blood, umbilical cord, placenta, and adipose tissue [25]. MSCs are suitable for treatment of autoimmune diseases because of their influence on modulate innate and adaptive immune responses including their effect on T lymphocytes, B lymphocytes, natural killer (NK) cells, antigen-presenting cells (APCs) and macrophages [25,26]. Transplanted MSCs can act on a multitude of tissues or organs through cell-to-cell contact or through secret cytokines and extracellular vesicles, offering hope for treating the systemic effects of SLE [26,27].

MSCs and B cells

In patients with SLE, B cells are abnormally activated. This over activation leads to large quantities of autoantibodies such as anti-dsDNA and ANA and secretions of pro-inflammatory cytokines like IL-10 and TGF-β [27]. MSCs have the potential to inhibit the hyperactivity of patients with SLE through the involvement of the PD-1/PD ligand pathway [27,28]. Regulatory B cells (Bregs) exert immunosuppressive functions through the production of IL-10 and TGF-β in SLE; MSCs on the other hand can induce Bregs expansion and inhibit excessive inflammatory responses through their stimulation of IL-10-producing Breg induction [2,28].

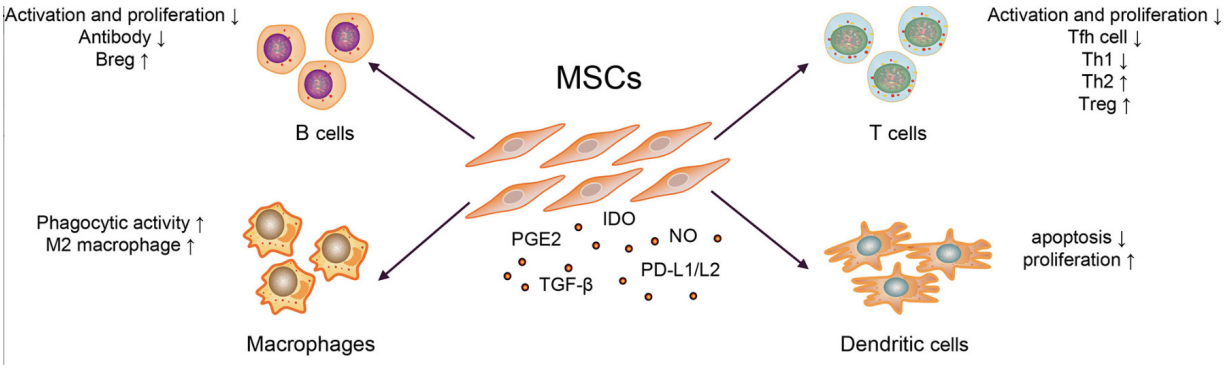

Figure 2: Mechanisms of MSC Therapy in SLE [27].

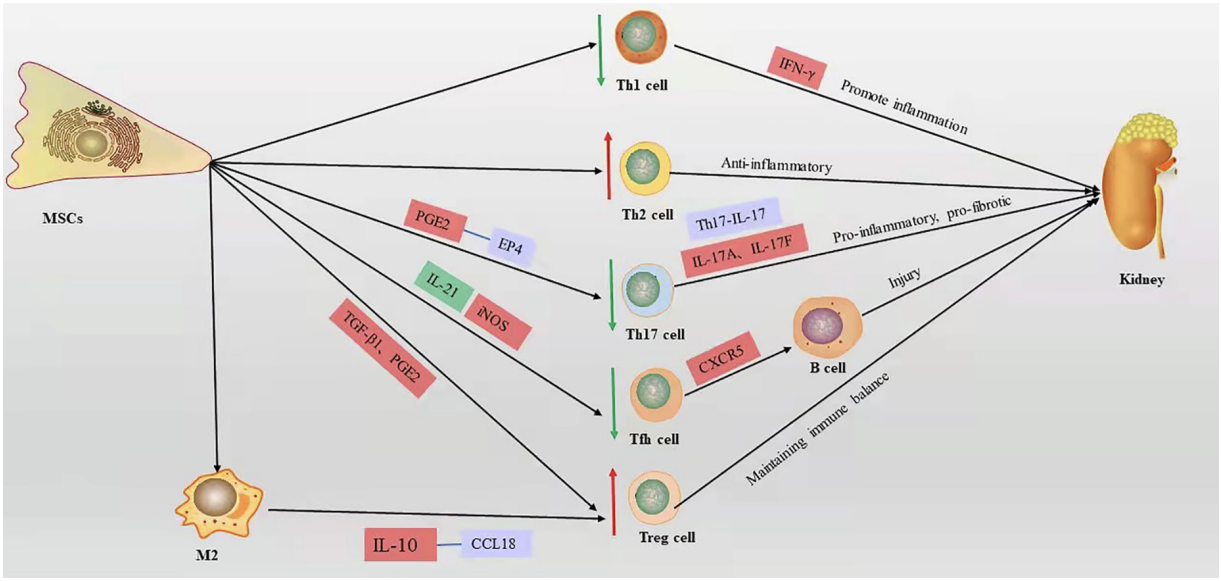

Figure 3: T cell action in SLE and the immunomodulatory effect of MSCs on T cells in LN [31].

MSCs and T cells

Abnormal activation of T cells and imbalance of Th1 and Th2 along with other cell subsets are involved in the pathogenesis of SLE. MSCs inhibit T cell proliferation and cytokine production through direct contact with T cells in a CCL2-dependent manner [27,29]. Patients with SLE have higher levels of IL-6, IL-12, IL-17, IFN-γ and IL-10 and lower levels of IL-4 compared with healthy controls as well as an increased ratio of Th1 + Th17 to Th2 cells [27]. Recent studies have shown that MSCs could inhibit T cell activation in a dose-dependent manner by inhibiting the differentiation of CD4+ T cells into Th1, Th17, and Tfh cells, promoting Treg proliferation and secretion of IL-10, reducing the ratio of Th1/Th2; and restoring the proportion of Treg/Tfh cells [27,29,30]. Transplantation of MSCs therefore offers the ability to normalize the ratio of Th1 to Th2 cells and increase the number of Treg cells to regulate the immune environment in SLE, reducing inflammation and creating a stable environment in T cells that once functioned abnormally.

MSCs and Natural Killer Cells

NK cells are granular lymphocytes that serve as a link between the innate and adaptive immune systems and are known to play a role in the pathogenesis of autoimmune diseases [23]. NKs also produce a variety of cytokines and chemokines, such as TNF-α, CCL3, and CCL4, which amplify and recruit inflammatory responses through various mechanisms [23,32]. Several studies have shown that the proportion of NKs and the total number of NKs in the blood of SLE patients are significantly lower when compared to individuals without autoimmune disease [23,32,33]. MSCs derived from human blood marrow inhibit IL-12-induced proliferation of NKs through such derived immunomodulatory factors such as IDO and PGE2; MSCs can also inhibit cytotoxic activity and their cytokine IFN-γ production [23,33,34]. This inhibitory effect is related to downregulation of the activating NK receptors NKp30, NKp44 and NKG2D [23,34]. Overall, MSCs possess the ability to inhibit the proliferation and toxic activity of NKs; however, timing and mucosal environment are imperative to consider before transplantation due to the ability of NKs to potentially lyse MSCs and affect their immuno-modulatory function [23,34,35].

MSCs and Macrophages

In patients with SLE, macrophages are prevalent in high quantities in the kidneys, where renal macrophage infiltration has been attributed with a poor prognosis. Macrophage depletion has been

shown to improve the clinical condition of LN, highlighting the need for a treatment targeting the reduction of these macrophages [31]. Recent studies have introduced new ideas about macrophage subsets, including the proinflammatory M1 type and the alternative activated anti-inflammatory M2 type [31,36]. The balance between M1 and M2 macrophages plays a crucial role in pathogenesis of nephritis, as dysregulated M2 macrophages play a pro-inflammatory part in LN [31,36,37]. Recent studies have investigated various types of MSCs and their impact on macrophages in lupus nephritis; Human placental MSCs shift macrophage differentiation from M1 into M2 macrophages, helping to suppress the inflammation caused by M1-types and restore damaged tissue [38]. Murine MSCs induce macrophage M2 polarization through secreted TGF-β and induce anti-inflammatory effects [39-41], while human umbilical cord MSCs increase CD206 expression in lupus-prone mice and SLE patients to promote M2 type macrophages and their phagocytosis, subsequently improving inflammatory response and renal injury [31,37]. Thus, MSCs improve SLE by restoring the M2-type polarization of macrophages and promoting the balance in the different types of macrophages.

Studies in Animal Models

In an *in vivo* study conducted in 2022, the effect of stem cell-derived exosome-educated macrophages was examined in a mouse model [42]. Exosomes were isolated from bone marrow-derived mesenchymal stem cells (BM-MSCs) via ultrafiltration and size-exclusion chromatography and used to treat macrophages from the kidney of MRL/*lpr* mice [42,43]. Following treatment, an upregulation of CD206, B7H4, CD138, Arg-1, CCL20 and anti-inflammatory cytokine was observed [42,43]. This finding suggests the polarization of macrophages to an anti-inflammatory phenotype and the promotion of Treg cells [42]. Overall, this study provides evidence that exosomes from BM-MSCs increase the production of IL-17+ Treg cells and the polarization of macrophages in an induced lupus nephritis model, which corrects part of the pathogenic pathways associated with SLE [42].

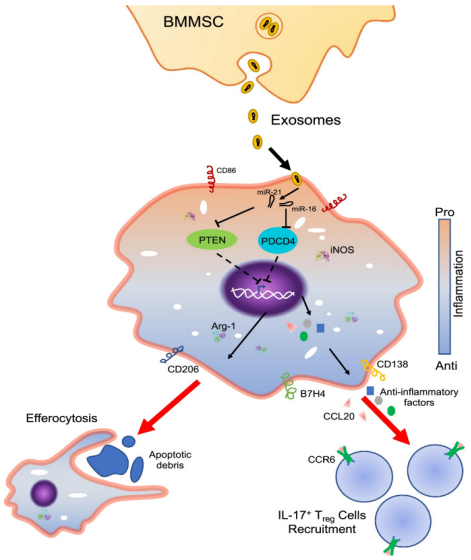

Figure 4: BM-MSCs effect on macrophages in MRL/*lpr* mice model [42].

A study focused on restoring the balance in Th17/Treg cells in a Pristane-induced lupus mouse model using mesenchymal stem cells was conducted in 2023 [44]. SLE was induced in mice by intraperitoneal immunization with Pristanse and confirmed via the presence and measurements of biomarkers [44,45]. BM-MSCs were isolated from healthy BALB/c mice and cultured in vitro [44,45]. Systemic MSCs transplantation was performed, and various biomarkers were measured and compared across various initiation treatment time points [44]. Parameters including specific cytokines (IL-17, IL-4, IFN-γ, TGF-β), percentage of Th cell subsets (Treg/Th17, Th1/Th2), and amelioration of lupus nephritis determined by enzyme-linked immunosorbent assay were investigated [44]. It was found that MSCs were able to reduce overall clinicopathological manifestations of SLE and that MSCs transplantation delayed disease progression in a stage-dependent manner [44]. When transplantation of MSCs occurred in the early stages of disease, the development of autoimmune symptoms presentation was not completely prevented, however, partial therapeutic effects were observed [44]. In late stages of disease, MSCs significantly reduced the development of autoimmune manifestations through induction of an endogenous increase in TGF-β and restoration of cytokine imbalance in SLE [44]. MSCs were found to delay the onset of renal dysfunction, proving them to be favorable as treatment for halting disease progression [44]. The study highlights that differences in response pattern of MSCs on Th cell subsets is dependent on stage of disease and suggests that levels of inflammatory cytokines play a significant role in the pathogenesis of SLE [44,46]. In the future, studies focused on MSCs need to not only look at the effects of transplantation in patients with SLE, but also consider the time, dose, and disease progression at time of transplantation to determine the most effective therapeutic treatment to prevent renal deterioration. The immunomodulatory effects of MSCs are highly dependent on the stage of lupus disease and offer promise of treatment in future clinical studies.

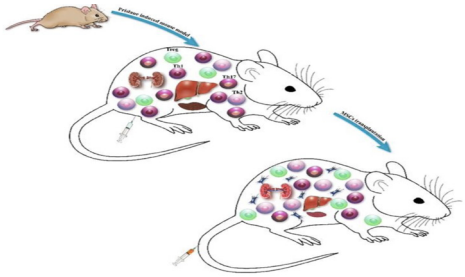

Figure 5: MSC transplantation in Pristane-induced lupus mouse model [44].

Clinical Trials

Success in the stability of *in vivo* BM-MSCs in mouse models led to a clinical trial focused on the safety and tolerability of bone-marrow derived stem cell transplants of humans in 2022 [47]. While MSCs have been a subject of interest in treating SLE in animal models for a while, clinical trials to evaluate the safety of these treatments in humans are needed to move forward with

future treatment of refractory lupus nephritis, which are currently lacking. The promising nonclinical results of BM-MSCs in mouse studies fueled a nonrandomized, open-label, single-arm phase I clinical trial in order to evaluate the tolerability and efficacy of a single administration of haploidentical allogeneic BM-MSCs in seven LN patients [47]. A three-by-three design was used with a starting dose of 2.0×10^6 cells/kg and escalated to 3.0×10^6 cells/kg if no negative side effects were observed [47]. Patients were assessed 28 days after infusion to determine the maximum tolerable dose. In this trial, seven patients with lupus nephritis were enrolled. Participants received BM-MSCs through intravenous infusion and there was no dose-limiting toxicity at the initial dose (2.0×10^6 cells/kg) or escalated dose (3.0×10^6 cells/kg). NCI-CTC grade I events were reported as adverse events including a toothache, arthralgia, and diarrhea [47,48]. Overall, the maximum tolerated dose was determined to be 3.0×10^6 cells/kg in patients with lupus nephritis and future phases of this trials will be needed to determine the efficacy of this treatment on pathogenesis and clinical presentation of SLE [47-50].

In 2022, a clinical trial was performed with the aim of analyzing the effects of MSC transplantation on treatment-resistant lupus nephritis [49]. Nine patients were selected for this phase I trial based on the fact that they had presented a biopsy indicative of LN [49]. The participants received a systemic infusion of 2×10^6 allogeneic adipose-derived (AD) MSCs/kg and were followed for 12 months post-intervention [49]. Urine protein levels decreased during the first month of observation and slightly increased but remained lower than original baseline levels up to three months after infusion [49]. Additionally, complete renal response (proteinuria < 0.5 g/24 h) and partial response (proteinuria > 0.5 g/24 h, but > 50% decrease in proteinuria) were observed in 33.3% and 44.4% of the patients, within the three-month mark with rates also decreasing beyond three months. The median score of Systemic Lupus Erythematosus Disease Activity Index decreased significantly from 16 at the baseline to 6 at sixth months post-treatment, however, this value increased at the one year mark [49]. Overall, allogeneic AD-MSC transplantation was found to be safe and showed efficacy in protein reduction in urine, which suggests improved kidney function in LN. While this treatment was seen to be effective, the most promising results were one month after infusion, with disease activity beginning to return around six months after treatment. This trend suggests that multiple infusions in different doses may be needed to keep this disease in remission in future clinical trials [49] and is supportive of other similar clinical trials investigating the effect of allogeneic MSCs on SLE and LN as summarized in Figure 6 [49].

Refs.	Study design & Subjects	Length of follow-up	Cell source	Cumulative cell dose	Treatment regimen	Clinical outcomes after MSCT				Maximum effect	
						Pr.uria	Disease activity	GFR	Clinical response at the end of study	Based on pr.uria	Based on disease activity
Sun et al. [33]	Open-label single-arm CT; 4 refractory LN patients	12 mo.	BM	$\geq 1\times10^6$ MSCs/kg body weight	Single dose	↓↑	↓↑	NA	CR: 100%	6 mo.	6 mo.
Sun et al. [31]	Open-label single-arm CT; 16 refractory SLE patients	24 mo.	UC	1×10^6 MSCs/kg body weight	Single dose	↓	↓	↑	NA	24 mo.	24 mo.
Liang et al. [30]	Open-label single-arm CT; 15 drug-resistant SLE patients	> 12 mo.	BM	1×10^6 MSCs/kg body weight	Single dose	↓	↓	↑	NA	12 mo.	12 mo.
Wang et al. [39]	Open-label single-arm CT; 87 active and refractory SLE patients	1–4 years	BM and/or UC	1×10^6 MSCs/kg body weight	Single dose	↓	↓	↓	CR: 92%	36 mo.	48 mo.
Gu et al. [18]	Open-label single-arm CT; 81 active and refractory LN	12 mo.	BM and/or UC	1×10^6 MSCs/kg body weight	Single dose	↓	↓	↑	CR: 23.4% PR: 20.8%	12 mo.	12 mo.
Wang et al. [19]	Open-label single-arm CT; 40 active and refractory SLE patients	12 mo.	UC	1×10^6 MSCs/kg body weight	Two doses with 7-day interval	↓↑	↓↑	↓↑	CR: 32.5% PR: 27.5%	9 mo.	6 mo.
Yang t al. [40]	Open-label double-arm CT; 37 active SLE patients	12 mo.	UC	3×10^7= ~0.5×10^6/kg for a 70-kg average person	Single dose	↓	↓	NA	NA	NA	NA
Deng et al. [28]	Double-blind RCT; 18 active LN patients; MSC therapy (12 Pt) vs. Placebo (6 Pt))	6 mo.	UC	2×10^8 = ~3×10^6/kg for a 70-kg average person	Two doses of 1×10^8 cells with 7-day interval	↓↑	↓	↓↑	CR: 75% in MSCT & 83% in placebo	3 mo.	6 mo.
Barbado et al. [29]	Open-label single-arm CT; 3 compassionate refractory LN patients	9 mo.	BM	1.5×10^6 MSCs/kg body weight	Single dose	↓↑	↓	↓↑	CR: 66.6% PR: 33.3%	1 mo.	9 mo.
Yuan et al. [41]	Open-label single-arm CT; 11 active and refractory SLE patients	6 mo.	UC	1×10^6 MSCs/kg body weight	Single dose	↓	↓	→	CR: 18.1% PR: 63.6%	NA	NA
Present study	Open-label single-arm CT; 9 refractory LN patients	12 mo.	AD	2×10^6 MSCs/kg body weight	Single dose	↓↑	↓↑	↓↑	CR: 11.1% PR: 11.1%	1 mo.	6 mo.

CT: Clinical Trial, RCT: Randomized Clinical Trial, UC: Umbilical Cord, BM: Bone Marrow, AD: Adipose-derived, MSCT: Mesenchymal stromal cell therapy, "NA": Not applicable, "↓": Decreased, "→": Without change, "↑": Increased, ↑↓: Temporary improvements, Pr.uria: proteinuria, mo.: month.

Figure 6: Recent trial findings investigating the effect of allogeneic MSCs for treatment of SLE [49].

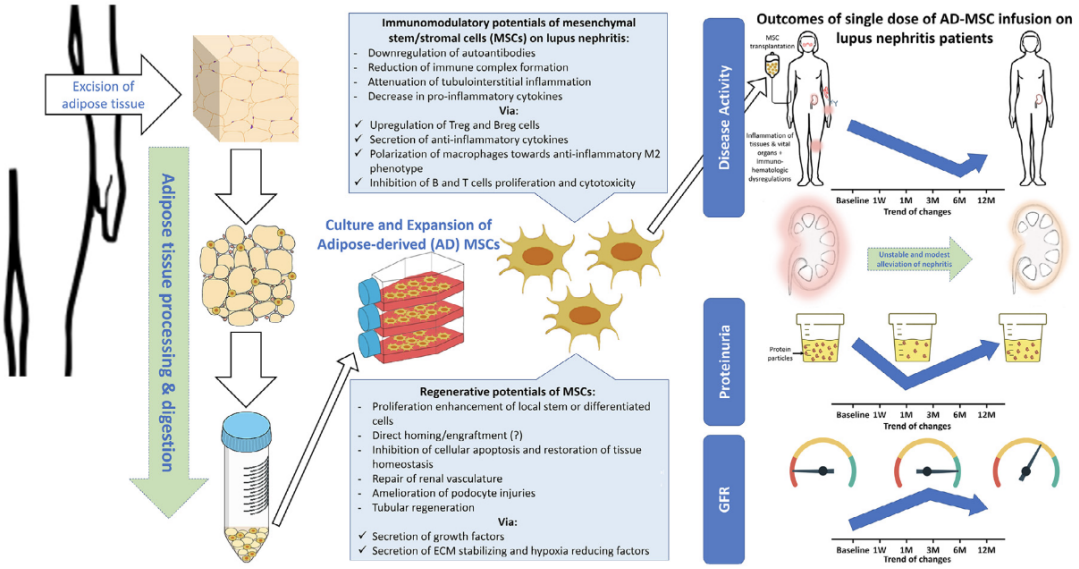

Figure 7: Summary of study findings regarding the efficacy of MSC treatment on lupus nephritis [49].

Conclusions and Future Considerations

The increasing prevalence and public health impact of systemic lupus erythematosus is a persistent problem in society today due to lack of effective means of treatment in correcting the imbalance across various organ systems associated with this autoimmune disease. Individuals with SLE are at a higher risk of developing severe and fatal complications such as renal failure. The complexity of systemic lupus erythematosus is not fully understood; however, these mesenchymal stem cells have been shown to have an immunomodulatory effect and influence the functionality of immune cells such as T lymphocytes, B lymphocytes, natural killer cells and macrophages. Researchers have found that infusions of mesenchymal stem cells derived from various sources such as adipose tissue and bone marrow can improve symptoms and normalize various biomarkers associated with the pathogenesis of lupus nephritis in both mouse and human models. While stem cell therapy with mesenchymal stem cells has been proven to be a safe and nontoxic treatment in limited doses, most clinical trials associated with the investigation of stem cells as therapy are still in phase I of clinical trial. Drug efficacy has been determined to be short-lived and it is unknown whether repeated doses of MSCs infusion can lead to complete disease remission or not. Additional research trials are needed to further test the prognosis of stem cells as a form of long-term treatment in systemic lupus erythematosus and investigate which factors, such as stage of disease, are important to understand when developing a therapeutic approach.

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