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Immunological and clinical effects of stem cell therapy in systemic lupus erythematosus: a review of clinical trials and animal studies

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Abstract

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with diverse clinical manifestation arising from an abnormal immune response to self-antigens. The exact etiology of SLE is unknown, but genetic and environmental factors are likely to be important in the etiology and pathogenesis. Conventional therapy for patients with SLE include corticosteroids, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs (NSAIDs). Complications associated with conventional therapy in patients with SLE as well as resistance and tolerance to conventional therapy have led to a shift to new methods of therapy. Major characteristics of stem cells such as the ability to undergo long-term self-renewal and their capacity for pluridifferentiation has introduced them as therapeutic candidates. Clinical trials using stem cells for the treatment of SLE have increased progressively over the last ten years, and the efficacy and therapeutic effects of this therapy method have been evaluated in several studies. This article aimed to review the immunological and clinical effects of stem cells from different sources such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs) in the treatment of patients with SLE published in ISI Web of Science and PubMed databases from 2000 to 2020. The relevant data regarding animal models of SLE is also reviewed.

HSCs and MCSs are the most common source of stem cells employed for the treatment of SLE. Stem cell therapy might influence immune response in patients with SLE leading to decrease in autoantibodies and ameliorate disease activity and renal injury.

Regardless of controversies in the results of studies that may be due to patient selection criteria, source of stem cells and dose of intervention, it seems that stem cell therapy in SLE has immunomodulatory effects which exhibit clinical remission and improve quality of life.

Key words: Systemic lupus erythematosus, Hematopoietic stem cells, Induced pluripotent stem cells, Mesenchymal stem cells.

Context

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which results from intolerance to nuclear self-antigens; it mainly affects younger women (1, 2). Genetic and environmental factors are involved in the pathogenesis of SLE. Human leukocyte antigen (HLA) genes such as HLA-DRB1, DQA1, and DQB1 and null alleles of complement components such as C1q, C2, and C4 show a high correlation with SLE. Abnormalities in epigenetic modifications such as DNA methylation and histone acetylation have also been reported in SLE (3-5). Factors such as smoking, silica, pesticides, hormones, and infection with the Epstein–Barr virus (EBV) are considered as environmental risk factors for SLE (6, 7). Interactions between autoreactive Th and B cells lead to the production of pathogenic anti-nuclear autoantibodies (ANA) (mostly anti-dsDNA autoantibodies) and eventually cause damage to multiple organ systems (8). SLE patients have higher serum levels of IL-1, IL-10, IL-12, and interferon gamma (IFN-γ). Additionally, the number of IL-17 producing cells and the level of IL-17 are increased in the peripheral blood of these patients (3). Regulatory T cells/Th17 cells ratio alters shifting towards Th17 cells in patients with SLE resulting in a loss of self-tolerance and the development of autoimmunity (9-11).

Conventional therapies for SLE approved by the US Food and Drug Administration (FDA) in the past 25 years include corticosteroids, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs (NSAIDs) (12, 13). Long-term corticosteroid therapy is associated with osteoporosis, and adrenal, hepatic, and gastrointestinal disfunction (14). Hydroxychloroquine is associated with retinal toxicity, and the main side effect of aspirin is gastrointestinal bleeding (15). Some patients with severe or refractory SLE show resistance or tolerance to conventional therapies. In recent decades, stem cell therapy has been considered as a new therapeutic strategy for SLE (16, 17).

Evidence Acquisition

This article aimed to review the immunological and clinical effects of stem cells from different sources such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs) in the treatment of patients with SLE published in ISI Web of Science and PubMed databases from 2000 to 2020. The relevant data regarding animal models of SLE is also reviewed.

Results

Haematopoietic stem cells (HSCs)

Some evidence suggests that the function of HSCs is impaired in patients with SLE. Bone marrow aspirates from patients with SLE have shown increased apoptosis of HSCs which may explain the defective hematopoiesis in these patients (18, 19). Traynor et al. (2002) showed that infusion of 1.4×106 autologous CD34+ cells/kg into 15 patients with the persistent and severe form of SLE reduced the systemic lupus erythematosus disease activity index (SLEDAI) and anti-dsDNA autoantibodies at a median follow up of 36 months (range, 12-66 months). They also evaluated the effects of autologous CD34+ cells (median dose of 2.4×106 CD34+ cells/kg) infused into 4 patients with persistent SLE. Th2 cell cytokines such as IL-4 were decreased, while Th1 cell cytokines such as IFN-γ were increased at a median follow up of 12 months (range, 9-22 months) (20). Su et al. (2013) performed a long-term follow-up study on autologous HSC therapy in 5 patients with severe or pediatric SLE. They reported that autologous HSC therapy with peripheral blood CD34+ cells resulted in decreased CD4+ and CD19+ cells at a median follow up of 66 months (range, 40-83). In another study, Alexander et al. (2009) reported that infusion of autologous peripheral blood CD34+ cells with a median dose of 2.6×106 cells/kg (range, 2×106-6.1×106 cells/kg) into 7 SLE patients reduced SLEDAI and regenerated T-regs during a median follow up of 60 months (range, 24-96 months). Some studies have shown the high rate of disease flares after autologous HSC therapy, and the exact mechanism of disease flares is not clearly understood (21). The possible reason for disease flares in SLE patients after autologous HSC therapy may be associated with the abnormality of these cells in such patients (22). In allogenic HSC therapy, the dysregulated old immune system is replaced with a new one,

and genetic risk factors are ruled out (23). In their study, Vanikar et al. (2007) infused allogenic peripheral and bone marrow-derived HSCs (mean CD34+ count: 6×106 cells/kg) into the peripheral circulation, thymus, portal vein, and bone marrow of 27 SLE patients. The patients showed a decline in anti-dsDNA autoantibody levels at a mean follow up of 4.9 years (range, 4.2-5.4 years). Cao et al. (2017) demonstrated that infusion of 2.8-27×106 autologous CD34+ cells/kg into 22 patients with SLE caused decreases in anti-dsDNA autoantibodies, ANA, and 24-h proteinuria at 100 days after infusion.Leng et al. (2017) investigated the effects of autologous peripheral blood CD34+ cells transplantation (2×106 cells/kg) on proteinuria in 23 patients with lupus nephritis (LN). They found remarkable decrease in proteinuria during 120 months of follow up.

A review of these trials suggests that HSCs might influence immune response in patients with SLE leading to decrease in autoantibodies and ameliorate disease activity and renal injury. Immune cells such as T cell subsets as one of the major factors that are associated with the pathogenesis and progression of SLE is also affected by HSCs.

Induced pluripotent stem cells (iPSCs)

Renal failure, a major factor of mortality and morbidity, affects more than 50% of SLE patients (24). Renal tubular cells-derived iPSCs from SLE patients exhibit similar properties to embryonic stem cells such as morphology, expression of pluripotency, and genetic markers. Further studies are necessary to establish an efficient protocol to differentiate iPSCs into functional renal tissues and then employ them in autologous kidney replacement therapy (25). In recent years, iPSC technology has facilitated the study of gene expression patterns and other characteristic of stem cells in SLE patients compared to healthy individuals that can be considered as a starting point for therapeutic use of these cells in future (26-28).

Mesenchymal stem cells (MSCs)

Bone marrow MSCs from SLE patients showed the down-regulated expression of IL-7 and IL-6 mRNA (29) and did not express cellular adhesion molecule CD106 and hematopoietic marker CD45 (30). Additionally, these cells had positive effects on the mitogen-activated protein kinase (MAPK) signaling pathway (31). Other studies have shown that bone marrow MSCs were defective in inhibiting the proliferation of T and B cells and exhibited a potential for impairment in the immune system (32, 33). Liang et al. (2010) performed one intravenous infusion of allogenic BM-MSCs (1×106 cells/kg) into 15 patients with persistently active SLE. Anti-dsDNA auto antibodies, SLEDAI, and 24-h proteinuria decreased at the mean follow up of 17.2±9.5 months. Sun et al. (2009) showed that intravenous infusion of allogenic BM-MSCs (≥1×106 cells/kg) into 4 SLE patients improved kidney function and SLEDAI in 12-18 months follow up. In another study, Sun et al. (2010) evaluated the effects of intravenous allogenic UC-MSCs (1×106 cells/kg) infusion into 16 patients with active SLE. This infusion resulted in increased peripheral blood T-regs and improvement in the levels of serum ANA, anti-dsDNA antibodies, complement C3 and serum albumin, and also in renal function at a median follow up of 8.25 months (range, 3-28 months). Wang et al. (2013) demonstrated that intravenous infusion of allogenic BM-MSCs and UC-MSCs (1×106 cells/kg) into 87 patients with persistently active and drug-resistant SLE induced clinical remission and improvement in organ dysfunction at a mean follow up of 27 months. Gu et al. (2013) indicated that intravenous infusion of allogenic BM-MSCs or UC-MSCs (1×106 cells/kg) into 81 patients with refractory and active lupus nephritis resulted in improved glomerular filtration rate (GFR) and renal remission within the 12-month follow-up period. In another clinical trial, deng et al. (2017) showed that there was no remarkable difference in serum albumin and complement levels, renal function and SLEDAI in patients with LN following allogenic UC-MSCs (2×108 cells) infusion compared to control group during 12 months follow up. Diffuse alveolar hemorrhage (DAH) is an infrequent complication of SLE. MSCs therapy might have a therapeutic

role for SLE-associated DAH. Shi et al. (2012) showed that intravenous infusion of allogenic UC-MSCs (1×106 cells/kg) into 4 SLE patients with DAH improved hemoglobin and platelet levels and oxygen saturation within the six-month follow up period. In their study, Li et al. (2013) investigated the effects of MSCs on regulatory T cells and Th17 cells. They indicated that infusion of allogenic BM/UC MSCs (1×106 cells/kg) into 35 SLE patients with refractory cytopenia resulted in an increase in regulatory T cells and a decrease in the percentage of Th17 cells in parallel with an improvement in the hematological index.

Given that SLE is considered as a MSC-mediated disease, allogenic MSC transplantation (MSCT) could be expected to have better therapeutic effects than autologous MSC therapy in patients with SLE, so there are no reports regarding MSCT with autologous MSCs in SLE. These studies indicate that MSCs similar to HSCs could influence on immune system factors such as T cell subsets and ameliorate disease activity and renal injury in patients with SLE.

Stem cell therapy in animal models of SLE

Among animal models, spontaneous mouse models of SLE (NZB/W F1, MRL/lpr and B6/lpr mice) are most commonly used in the field of stem cell research (34, 35). Gu et al. (2010) showed that multi-infusion of 1×106 human UC-MSC into 8 female MRL/lpr mice (at the 18th, 19th, and 20th weeks of age) alleviated lupus nephritis and decreased the level of 24-h proteinuria and anti-dsDNA autoantibodies. Tang et al. (2019) investigated the therapeutic effects of human dental pulp stem cells (HDPSCs) and periodontal ligament stem cells (HPDLSCs) in 40 B6/lpr mice. They found that both HDPSCs and HPDLSCs could efficiently downregulate 24-h proteinuria, anti-dsDNA antibodies and glomerular IgG/IgM in B6/lpr mice. Chang et al. (2011) performed intravenous infusion of 1×106 human UC-MSC into 15 female NZB/W F1 mice. This intervention resulted in decreased levels of anti-dsDNA autoantibodies and alleviated renal injury and nephritis. In a study by Choi et al. (2012), 5×107 human adipose tissue-derived MSC was infused at an interval of two weeks into 26 female NZB/W F1 mice (age varied from 6 to 60 weeks). This infusion improved serologic and histologic abnormalities and increased the proportion of CD4+ FOXP3+ cells in the spleen. Liu et al. (2014) studied the effects of MSCs on four female MLR/lpr mice. Intravenous infusion of BALB/c MSCs along with BALB/c BM-HSCs at the ratio of 5:1(HSCs: MSCs) (1×106: 0.2×106) improved the therapeutic effects of HSCs by decreasing the transfusion-associated graft-versus-host reaction and ameliorating renal functions when compared with mice transplanted with HSCs alone. Zhou et al. (2008) found that intravenous injection of human BM-MSCs into female MLR/lpr mice, decreased serum levels of anti-dsDNA antibodies, proteinuria, and autoimmune progression. Schena et al. (2008) performed stem cell therapy on female NZB × NZW F1 mice with intravenous injections of 1.25×106 allogenic BM-MSCs of C57BL/6J mice at 27, 28, and 29 weeks of age. This therapy had no effects on proteinuria or anti-dsDNA autoantibodies levels.In another study, Tani et al. (2017) reported no significant improvement in the nephritis score in 60 female NZW F1 mice following 36 weeks after allogenic BM-MSCs (1×106 cells/kg) perfusion. Liu et al. (2019) designed a study to evaluate therapeutic effects of human placenta-derived MSCs in 30 female LN-prone MRL/lpr mice. Six weeks after infusion of 1×106 cells/kg, gene expression levels of nuclear factor kappa B (NF-κB) and tumor necrosis factor-α (TNF-α) decreased, leading to improvement in renal injury.

Stem cell therapy in mouse models of SLE indicates that both MSCs and HSCs isolated from mice or human tissues might be a good agent for the treatment of lupus in mice. It seems factors such as dose and source of stem cells and also combination cell therapy with stem cells from different sources could affect the outcome of studies in this field.

Conclusion

SLE, a chronic inflammatory autoimmune diseases arising from an abnormal immune response, is the leading causes of death and disability in the world (1, 2). Complications

associated with conventional therapy in patients with SLE as well as resistance and tolerance to conventional therapy led to a shift to new methods of therapy (16, 17). Stem cells as a novel therapy have made significant progress in recent decades. Conventional therapy and stem cell therapy work in different ways. Stem cell therapy takes several months to develop, whereas conventional therapy has a shorter onset of action. Therefore, longitudinal follow up is needed for better conclusions regarding the efficacy and adverse effects of stem cell therapy. The efficacy, dosage, and toxic effects of conventional therapy were determined years ago, but the methods of stem cell therapy need to be optimized as standard protocol. In this paper, we reviewed human and animal studies and evaluated the efficacy of this novel therapeutic approach for the treatment of SLE. Regardless of controversies in the results of studies, it seems that stem cell therapy in SLE has immunomodulatory effects which exhibit clinical remission and improve quality of life. Additionally, the injection of stem cells might be a good choice for an alternative therapy with no or low-level side effects in patients suffering from SLE. However, more studies employing optimal and standard methods, a larger sample size, and longitudinal follow up are needed for better conclusions. The interactions of other factors such as stage of disease, methods of patient selection, source of stem cells, route of administration, combination with conventional therapy, and age and nutritional status of patients should be considered in making a better decision to employ stem cell therapy as an effective and safe method of treatment for SLE.

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