Research Highlight

A big step forward in the treatment of refractory systemic lupus erythematosus: allogeneic mesenchymal stem cell transplantation

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Systemic lupus erythematosus (SLE) is a severe, potentially life-threatening disease. Although treatments with glucocorticoids and immunosuppressants following the Guidelines of American College of Rheumatology (ACR) or KDIGO (Kidney Disease: Improving Global Outcomes) have brought relief to SLE patients, some patients fail for refractory to conventional immunosuppressive treatment or other reasons.

Over the past 20 years, stem cell transplantation (SCT) has emerged as a therapy for refractory autoimmune rheumatologic diseases, which may arrest the autoimmune disease process and lead to sustained remissions. Since the first consensus statement in 1997^[1], approximately 200 cases of autologous bone marrow or hematopoietic SCT have been reported worldwide for patients with severe SLE refractory to conventional immunosuppressive treatment, and the results showed that hematopoietic SCT can achieve sustained clinical remissions (ranging from 50% to 70% disease-free survival at 5 years) associated with immunological changes that were not seen with other forms of treatments^[2].

The efficacy of SCT in SLE has been attributed to resetting an aberrant

immune system either through direct immune replacement with hematopoietic stem cells or through immunomodulation with mesenchymal stem cells (MSCs), shifting the immune system from a highly pro-inflammatory disease environment to a less inflammatory one^[3]. Unlike hematopoietic stem cells, MSCs are multipotent cells capable of differentiating into a variety of mesenchymal lineages including cartilage, bone, muscle, tendon, ligament and adipose tissue, and lack significant immunogenicity for no MHC-II and costimulatory molecule expression. MSCs reside in bone marrow, skeletal muscle, adipose tissue, connective tissue, umbilical cord blood, and placental products^[4]. The mesenchymal stem cell for transplantation are easily harvested compared with the hematopoietic stem cells which needs a conditioning regimen before transplant. In recent years, mesenchymal stem cell transplantation (MSCT), as a newly therapeutic regimen, has entered clinical trials for inflammatory disorders, first in graft-versus-host disease, and then in MS, Crohn disease (including fistula closure), SLE and systemic sclerosis^[5]. In addition, clinical trials for treating ischemia in myocardium, kidney and limbs have also been conducted. Noticeably, MSCT has produced promising results in treatment of autoimmune diseases. The data available thus far, however, came from small-scale and short-term clinical trials, the feasibility and safety of MSCT

remain to be determined.

Recently, Sun's research team of Njing University Medical School and his collaborators in Hong Kong and USA have reported a long-term follow up data for allogeneic MSCT in refractory SLE patients^[6]. In this research, 87 patients with persistently active SLE who were refractory to standard treatments or had life-threatening visceral involvement were enrolled. All patients were intravenously infused with allogeneic bone marrow or umbilical cord derived MSCs (1×10^6 cells/kg of body weight). During the 4 years follow up and with a mean follow up period of 27 months, the overall rate of survival was 94% (82/87). Complete clinical remission rate was 28% at 1 year (23/83), 31% at 2 years (12/39), 42% at 3 years (5/12) and 50% at 4 years (3/6). Rates of relapse were 12% (10/83) at 1 year, 18% (7/39) at 2 years, 17% (2/12) at 3 years and 17% (1/6) at 4 years. The overall rate of relapse was 23% (20/87). Disease activity declined as revealed by significant changes in SLEDAI score, levels of serum autoantibodies, albumin and complements. A total of 5 patients (6%) died after MSCT from non-treatment-related events in 4 years follow up, and no treatment-related adverse event was observed. Compared to two studies of autologous stem cell transplantation (ASCT) for SLE with a similar mean follow up time (29 months and 26 months respectively), the overall survival rate

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was higher in the current study (94% compared to 84% and 62% in ASCT, respectively), no transplantation-related mortality (0 in MSCT compared to 4% and 12% in ASCT, respectively), and rate of complete clinical remission was similar^[7, 8]. These results suggest that allogeneic MSCT is more effective and safe treatment for severe refractory SLE patients, even if this study has not been a randomized controlled trial.

To further validate the role of MSCT ameliorating lupus nephritis, the authors investigated the effects of allogeneic MSCT (bone marrow-derived mesenchymal stem cells) and the underlying mechanisms in MRL/lpr mice, an SLE animal model. The results showed that treatment with MSCT for 8 weeks could significantly prolong the survival of MRL/lpr mice, reduce the sizes of spleen and the level of 24-h proteinuria, alleviate the glomerulonephritis and pathological autoantibody deposition in kidney, decrease the percent of marginal zone B cells, Transitional 1/2 B cells, activated B cells and plasma cells, decrease serum levels of BAFF, IL-10 and anti-dsDNA autoantibodies, increase the levels of serum TGF- β . Moreover, MSCs also could suppress the level of B-cell activating factor (BAFF) which secreted by dendritic cells *in vitro*. These

results confirmed that allogeneic MSCT could ameliorate the clinical symptoms in lupus mice, and the mechanism of suppressing the excessive activation of B cells via inhibiting BAFF production was also concordance with MSCs' immunomodulation property^[9]. Other researches also indicated that MSCs exerted complex paracrine and endocrine actions including the secretion of growth factors and cytokines, modulation of immune response, antiapoptotic and anti-inflammatory effects, and so on.

While allogeneic MSCT has already achieved sustained clinical remissions and serologic improvements in SLE patients and in lupus animal models, especially for lupus nephritis, there are major gaps in our knowledge, such as duration of engraftment, impact on normal tissues and organs, and phenotypic changes occurring in MSCs exposed to inflammatory/ischemic target tissue, and so on. To examine the safety, efficacy and the action mechanisms of MSCT for severe SLE, larger, randomized, double-blind clinical trials, including mechanistic studies, are required.

report written on behalf of the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). *Br J Rheumatol* 1997; 36: 390–2.

- 2 Illei GG, Cervera R, Burt RK, Doria A, Hiepe F, Jayne D, *et al.* Current state and future directions of autologous hematopoietic stem cell transplantation in systemic lupus erythematosus. *Ann Rheum Dis* 2011; 70: 2071–4.
- 3 Chang JW, Hung SP, Wu HH, Wu WM, Yang AH, Tsai HL, *et al.* Therapeutic effects of umbilical cord blood-derived mesenchymal stem cell transplantation in experimental lupus nephritis. *Cell Transplant* 2011; 20: 245–57.
- 4 Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, *et al.* Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. *Cytotherapy* 2005; 7: 393–5.
- 5 Tyndall A. Successes and failures of stem cell transplantation in autoimmune diseases. *Hematology Am Soc Hematol Educ Program* 2011; 2011: 280–4.
- 6 Wang D, Zhang H, Liang J, Li X, Feng X, Wang H, *et al.* Allogeneic mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus: 4 years experience. *Cell Transplant* 2012. DOI: 10.3727/096368912X658719.
- 7 Burt RK, Traynor A, Statkute L, Barr WG, Rosa R, Schroeder J, *et al.* Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *JAMA* 2006; 295: 527–35.
- 8 Jayne D, Passweg J, Marmont A, Farge D, Zhao X, Arnold R, *et al.* Autologous stem cell transplantation for systemic lupus erythematosus. *Lupus* 2004; 13: 168–76.
- 9 Ma X, Che N, Gu Z, Huang J, Wang D, Liang J, *et al.* Allogeneic mesenchymal stem cell transplantation ameliorates nephritis in lupus mice via inhibition of B-cell activation. *Cell Transplant* 2012. DOI: 10.3727/096368912X658692.

1 Tyndall A, Gratwohl A. Blood and marrow stem cell transplants in autoimmune disease. A consensus