

Clinical Study

Double Allogenic Mesenchymal Stem Cells Transplantations Could Not Enhance Therapeutic Effect Compared with Single Transplantation in Systemic Lupus Erythematosus

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The clinical trial of allogenic mesenchymal stem cells (MSCs) transplantation for refractory SLE patients has shown significant safety and efficacy profiles. However, the optimum frequency of the MSCs transplantation (MSCT) is unknown. This study was undertaken to observe whether double transplantations of MSCs is superior to single transplantation. Fifty-eight refractory SLE patients were enrolled in this study, in which 30 were randomly given single MSCT, and the other 28 were given double MSCT. Patients were followed up for rates of survival, disease remission, and relapse, as well as transplantation-related adverse events. SLE disease activity index (SLEDAI) and serologic features were evaluated. Our results showed that no remarkable differences between single and double allogenic MSCT were found in terms of disease remission and relapse, amelioration of disease activity, and serum indexes in an SLE clinical trial with more than one year followup. This study demonstrated that single MSCs transplantation at the dose of one million MSCs per kilogram of body weight was sufficient to induce disease remission for refractory SLE patients.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multiorgan involvement and loss of tolerance against self-antigens followed by antibody production. Current treatments of severe SLE flares consist of toxic immunosuppressive drugs, most commonly cyclophosphamide (CYC), mycophenolate mofetil, and leflunomide [1]. However, the therapeutic options in cases of SLE refractory to standard treatments are indeed limited, and the disease remains potentially fatal in some patients [2].

Mesenchymal stem cells (MSCs) have potent immunosuppressive capacity, which is demonstrated by the inhibition of T lymphocytes proliferation and proinflammatory

cytokines production *in vivo* and *in vitro*. MSCs, furthermore, suppress antibody production of B cells and the generation and function of antigen presenting cells [3, 4]. The immunomodulation of MSCs is for a large extent mediated by soluble factors and induced under inflammatory conditions [5]. Previous studies showed that MSCs/osteoblast lineage played a critical role in maintaining the hematopoietic stem cell (HSC) niche [6, 7]. Recently, it has been demonstrated that MSCs themselves constitute an essential HSC niche component, and they are spatially associated with HSC niche *in vivo* bone marrow [8].

As the first example of efficacy, clinical trials for prevention and treatment of graft-versus-host disease (GVHD) after HSC transplantation show that MSCs can

modulate allogenic immune responses and effectively treat human disease. Now these multipotential cells have been applied in various physical and immune injuries including liver cirrhosis, multiple sclerosis, and Crohn's disease [9–11]. Our previous studies also showed that allogenic bone marrow or umbilical-cord-derived MSCs transplantation is safe and effective in treating drug-resistant SLE patients [12–14]. In these pilot clinical studies, all patients received once intravenously MSCs infusion. Additionally, we found that some patients were also well responsive to another dose of MSCs after disease relapse. On the other hand, animal studies indicated that multiple MSCs transplantations could enhance clinical efficacy in lupus mice [15]. However, it is unknown whether multiple MSCs infusions are superior to single transplantation in patients, and the optimal dosage and frequency for MSCs therapy is still obscure. So in this study, we compare the efficacy between single and double transplantations of allogenic MSCs in SLE patients. The conclusion of this study can provide further potentiality of allogenic MSCs transplantation in clinical application for SLE.

2. Materials and Methods

2.1. Patients. From March 2007 through February 2010, 58 patients with SLE refractory to standard therapies were enrolled in allogenic MSCs transplantation (MSCT) trial at the Affiliated Drum Tower Hospital of Nanjing University Medical School after signing informed consent. The study was approved by the Ethics Committee at The Drum Tower Hospital of Nanjing University Medical School and registered at ClinicalTrials.gov (Identifier: NCT00698191). All enrolled patients had at least 4 of 11 American College of Rheumatology criteria for SLE [16]. The inclusion and exclusion criteria have been shown as previously [12]. The trial was conducted in compliance with current Good Clinical Practice standards and in accordance with the principles set forth under the Declaration of Helsinki (1989).

2.2. MSCs Purification and Identification. Bone-marrow-derived MSCs (BMMSCs) were obtained from healthy family donors after signing informed consents. Bone marrow mononuclear cells were separated by density gradient centrifugation as previously described [13, 14]. Those without appropriate bone marrow donors were infused with umbilical-cord-derived MSCs (UCMSCs). UCMSCs were prepared by the Stem Cell Center of Jiangsu Province. Fresh umbilical cords were obtained from informed and healthy mothers in local maternity hospitals after normal deliveries. The purification procedure was described as previously [12].

Criteria for release of MSCs for clinical use included presence of visible clumps, spindle-shape morphology, and absence of contamination by pathogens (as documented by aerobic and anaerobic cultures before release), as well as by virus for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, human immunodeficiency virus antibodies I and II, cytomegalovirus IgM, and syphilis

antibody (as determined by enzyme-linked immunosorbent assay [ELISA] before release), cell viability greater than 92% (as determined by trypan blue testing), and immune phenotyping proving expression of CD73, CD105, CD90, CD29 (>90%), and absence of CD45, CD34, CD14, CD79, and HLA-DR (<2%).

2.3. MSCs Transplantation Procedures. Randomization was conducted between once and double MSCT groups. The enrolled 58 refractory SLE patients were randomly assigned into once or double MSCT groups. Of all the patients, 30 were randomly given a single MSCs transplantation, and the other 28 patients received double allogenic MSCs transplantations, with an interval for 1 week. Before MSCT, all patients were administered CYC (10 mg per kilogram per day) intravenously on days 4, 3, and 2 to inhibit active lymphocytes. Patients received allogenic MSCs intravenously at the density of one million cells per kilogram of body weight in each transplantation.

2.4. Follow-Up and Outcome Characteristics. After MSCT, all patients returned for scheduled followup at 1, 3, 6, and 12 months and then yearly thereafter. Medical history, physical examination, and serologic testing were performed. Complete remission was defined as SLEDAI score < 3 and steroid requirement \leq 10 mg/day of prednisone or its equivalent, combined with British Isles Lupus Assessment (BILAG) D scores or better in all organs but not hematological system [17, 18]. Complete remission for hematological system was defined as white blood cell count > 4,000/ μ L, hemoglobin > 11 g/dL, platelet count > 100 \times 10⁹/L, and steroid maintenance \leq 10 mg/day of prednisone or its equivalent. Disease relapse was defined as an increase in SLEDAI score \geq 3 from the previous visit, or experience 1 new domain with a BILAG A score or 2 new domains with a BILAG B score after a previous response [17, 18]. Transplantation-related mortality included all deaths associated with transplantation of MSCs, except those related to recurrence of underlying disease. The investigators assessed and recorded adverse events and their severity throughout the study.

After UC-MSCT, the dose of prednisone and immunosuppressive drugs was tapered when clinical efficacy was achieved for each patient. The withdrawal of prednisone and immunosuppressant was permitted if patient's condition continued to improve. No other immunosuppressant was used unless disease relapsed. If the patient underwent disease relapse, he or she will withdraw from the study and will be given higher dose of prednisone or other immunosuppressants according to disease conditions. The patient's clinical data after relapse and change of clinical regimens will not be included for analysis.

2.5. Statistical Analysis. Descriptive statistics was used to summarize patient characteristics. Differences in patient demographics prior transplantation were analyzed by unpaired *t*-test, Chi-Square test, or Fisher's exact test. All tests were 2 sides. Rates of overall survival, disease complete remission, relapse, and adverse event at different visit times

at two groups were analyzed by a Kaplan-Meier survival curve and were statistically tested with the log-rank test. We calculated the hazard ratio (HR) and their 95% CIs using the univariate Cox proportional hazards model. Serial data were compared within and between groups by repeated measures ANOVA. All *P* value of less than 0.05 was considered as a significant difference.

3. Results

3.1. Patient Demographics and Disease Manifestations before MSCCT. Fifty-eight patients with refractory SLE enrolled in this trial, and all patients underwent allogenic MSCCT and were followed up for more than 12 months. The mean followup was 27 months (range from 12 to 48 months) in single transplantation group and 26 months (range from 12 to 40 months) in double transplantation group. Patients' demographics pretransplantation have been shown in Table 1. The two cohorts were balanced in gender, race, MSCs source, clinical manifestations, and disease activity prior transplantation. Medium disease duration was shorter in single than in double transplantation group (mean \pm SD 60.2 \pm 50.0 months versus 92.1 \pm 64.3 months, *P* = 0.039).

3.2. Overall Survival, Disease-Free Survival, and Relapse. With medium followup of over 24 months in both cohorts, one death was observed in double transplantation group. The survival rate was 100% for single and 96.4% for double transplantation group, respectively (log-rank = 1.071, *P* = 0.301). Rate of complete remission was 53.3% (16/30) in single transplantation group and 28.6% (8/27) in multiple transplantation group during 4-year followup by Kaplan-Meier survival curves (log-rank = 3.374, *P* = 0.066, Figure 1(a)). In a multivariable Cox regression model for complete remission, there was no difference between single and double transplantation group (HR 0.38, 95%CI 0.14–1.02; *P* = 0.060). Disease duration (HR 1.00, 95%CI 0.99–1.01, *P* = 0.290) and MSC source (HR 0.69, 95%CI 0.28–1.69, *P* = 0.420) were also not associated with complete remission. Rate of disease relapse was not statistically different in single transplantation group (8/30, 26.7%) compared to that of double transplantation group (6/27, 22.2%, log-rank = 0.075, *P* = 0.784, Figure 1(b)). The average time to relapse was 21 months (mean value, from 6 to 45 months) and 12 months (mean value, from 3 to 24 months) in single and double transplantation group, respectively. Cox regression showed that no difference in disease relapse was found between the two groups (HR 1.16, 95%CI 0.39–3.49, *P* = 0.790).

We calculated the overall percentage of disease relapse that occurred in two groups (8/30, 26.7% in single MSCCT group; 6/27, 22.2% in double MSCCT group). Additionally, the exact rate of disease relapse was calculated by Kaplan-Meier survival curve (Figure 1(b)), and the variable was correlated with time point when relapse occurred. In the present data, for those who had disease relapse, most relapse events occurred after 24 months followup. For example, in once MSCCT group, 7 patients completed 30 months followup

TABLE 1: Patient demographics pretransplantation.

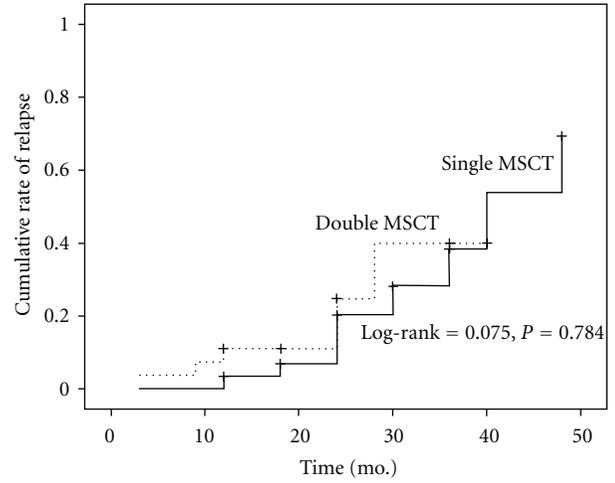
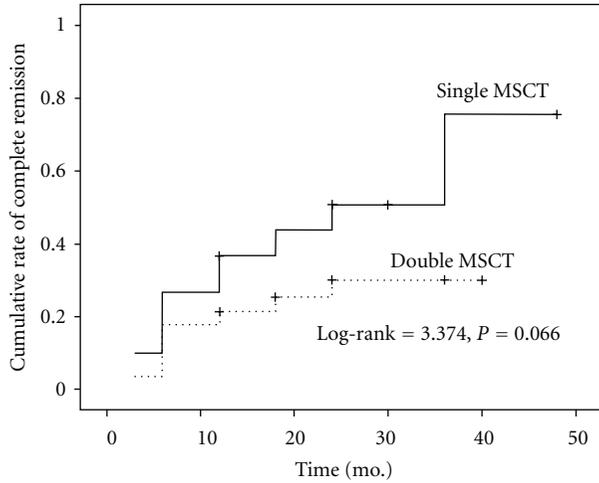
Variable	No. of patients	
	Single MSCCT (<i>n</i> = 30)	Double MSCCT (<i>n</i> = 28)
Age in years	30 (12–47)	33 (16–54)
Gender, <i>n</i> (F/M)	25/5	26/2
Race, <i>n</i> (Asian/others)	30/0	28/0
Disease duration (m)	62 (7–232)	92 (12–264)
MSCs source, <i>n</i>		
Bone marrow (BM)	12	9
Umbilical cord (UC)	18	19
Medium followup for survivors (m)	27 (12–48)	26 (12–40)

MSCCT, mesenchymal stem cells transplantation.

and had achieved a previous clinical response, in which 4 had relapse at 40, 36, 48, and 30 months, respectively (Figure 1(b), Supplementary Material available online at doi:10.1155/2012/273291).

3.3. Disease Activity and Serum Indexes. Disease activity shown by SLEDAI scores decreased significantly in both groups after allogenic MSCs transplantation by repeated measures ANOVA (*F* = 59.36, *P* < 0.001, Figure 2(a)). There was no correlation between SLEDAI decline and MSCs transplantation frequency (*F* = 3.31, *P* = 0.074). Serum albumin also significantly improved after MSCCT at each group (*F* = 50.89, *P* = 0.000), and there was no difference between the two groups (*F* = 0.018, *P* = 0.896, Figure 2(b)). Serum complement 3 (C3) and anti-double-strand DNA (dsDNA) antibody similarly improved in both groups by the same analyzed methods (Figures 2(c) and 2(d)).

3.4. Amelioration of Renal Function and Hematologic Indexes by Allogenic MSCCT. Twenty-six patients (26/30, 86.7%) in single MSCCT group and 24 patients (24/27, 88.9%) in double MSCCT group underwent renal involvement at baseline, shown by the presence of proteinuria, or hematuria, or renal dysfunction. The 24 hour proteinuria significantly declined after allogenic MSCCT within each group by repeated measures ANOVA (*F* = 19.29, *P* = 0.001). However, once MSCCT group demonstrated much lower levels of proteinuria compared to double MSCCT group at the first 12-month visits (*F* = 5.31, *P* = 0.026, Figure 3(a)). For those who had renal dysfunction at baseline, serum creatinine significantly ameliorated after MSCCT within each group (*F* = 6.30, *P* = 0.003), and there was no difference between the two groups (*F* = 0.401, *P* = 0.534, Figure 3(b)). Twelve patients (12/30, 40.0%) in single MSCCT group and 13 patients (13/28, 46.4%) in double MSCCT group suffered hematologic involvement at baseline; platelet counts and hemoglobin levels significant improved after allogenic MSCCT in each group (*F* = 10.001, *P* = 0.000 for platelet counts, *F* = 9.237, *P* = 0.000 for hemoglobin levels); no difference was found between the two groups (*F* = 0.098, *P* = 0.760 for platelet counts, *F* = 0.015, *P* = 0.905 for hemoglobin levels, Figures 3(c) and 3(d)).



No. single	30	30	27	12	4	2
No. double	28	27	17	5	2	0

(a)

No. single	30	30	27	12	4	2
No. double	28	27	17	5	2	0

(b)

FIGURE 1: Rate of complete remission (a) and disease relapse (b) for patients with single and double MSCs transplantations, by Kaplan-Meier survival curve analysis.

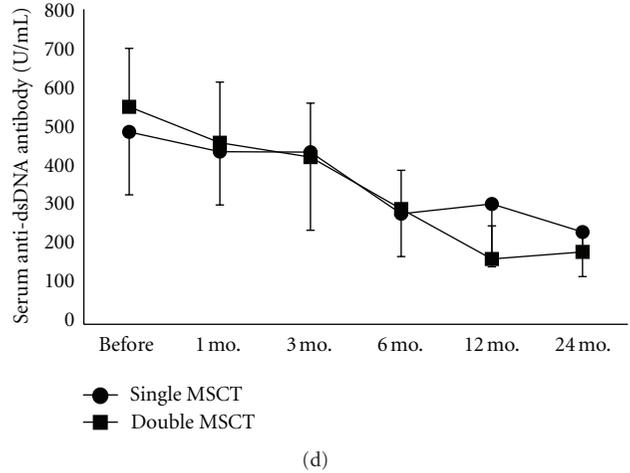
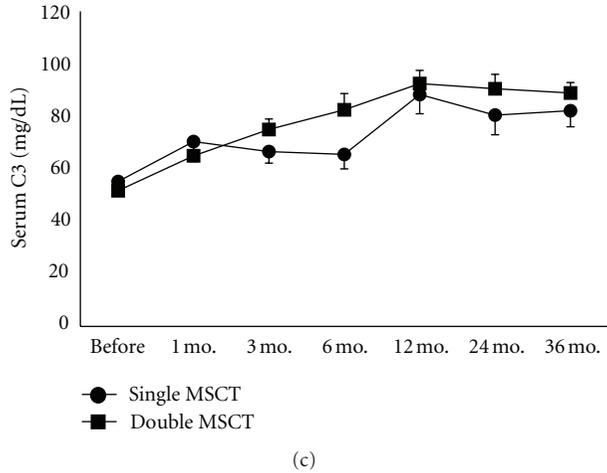
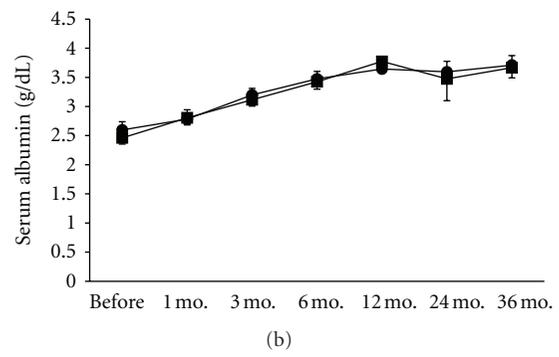
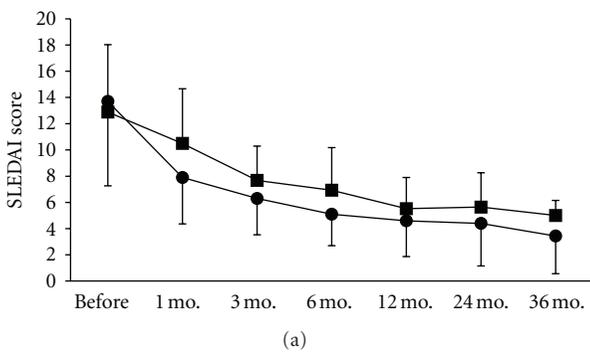


FIGURE 2: Comparisons of SLEDAI score (a), serum albumin (b), Complement 3 (C3, (c)), and anti-double-strand DNA antibody (dsDNA, (d)) for patients with single and double MSCs transplantations, by repeated measures ANOVA. Values are the mean \pm SEM.

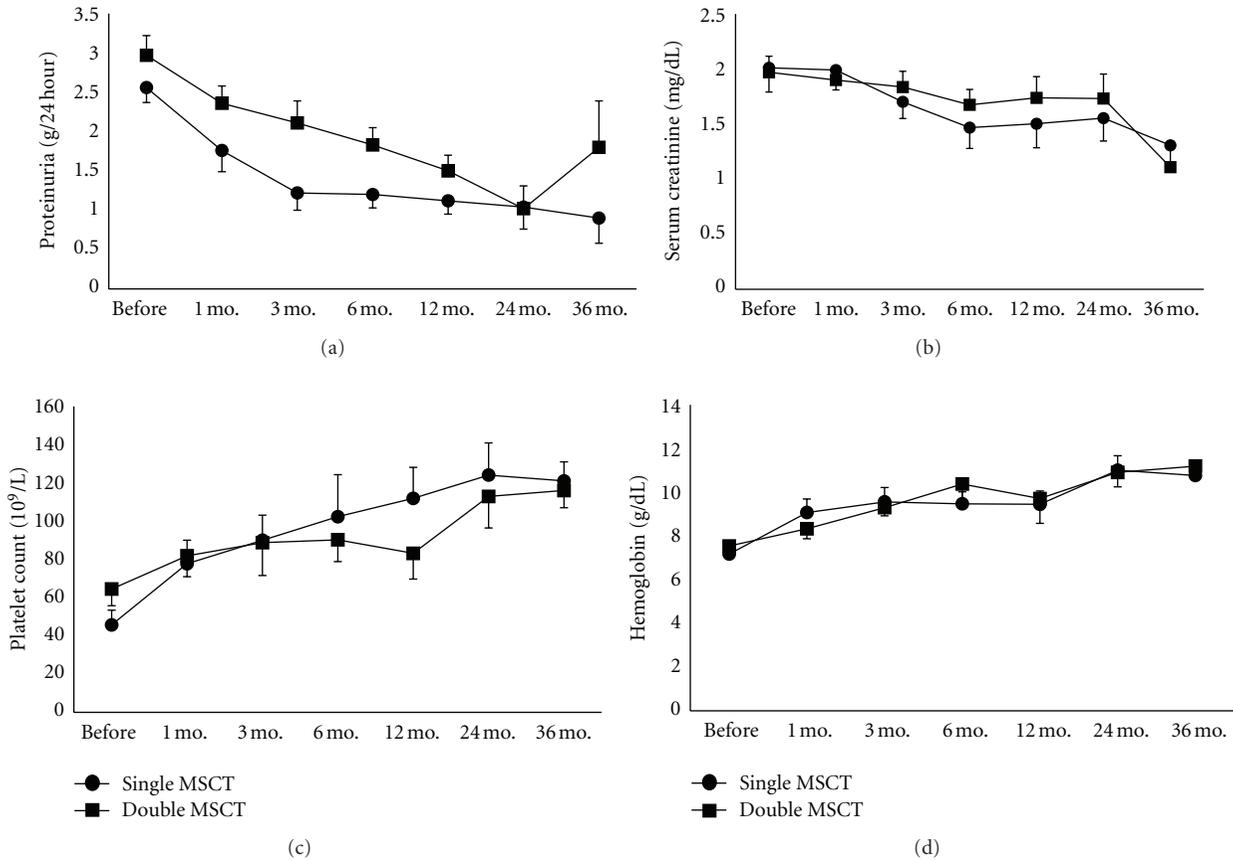


FIGURE 3: Comparisons of proteinuria (a), serum creatinine (b), platelet count (c), and hemoglobin level (d) between patients given single or double MSCs transplantations, by repeated measures of ANOVA. Values are the mean \pm SEM.

3.5. Adverse Events. One patient in double transplantation group underwent uncontrolled disease recurrence 6 months after MSCT due to upper respiratory tract infection. She was not responsive to conventional treatments and finally died of acute heart failure. During 4 years followup, 7 patients in single transplantation group (23.3%) and 9 patients in double transplantation group (32.1%) suffered infection events, and no statistical difference was found between the two groups. Of 7 patients in single transplantation group, 3 had upper respiratory tract infection, 3 had intestinal infection, and one had oral fungi infection. Of 9 patients in double transplantation group, 4 had upper respiratory tract infection, 2 had intestinal infection, one had herpes zoster infection, one had pneumonia, and one had pulmonary tuberculosis. All the adverse events were not considered transplantation related.

3.6. Maintenance Therapy. Two patients in both single (2/30; 6.7%) and double transplantation groups (2/28; 7.1%) had discontinued immunosuppressive drugs in the last followup. Dose of prednisone was tapered to 5–10 mg/day for 24 patients (24/30, 80.0%) in single MSCT group and 22 patients (22/28, 78.6%) in double MSCT group, respectively. Maintenance therapy regimen was defined as the dose of prednisone was not more than 10 mg/day, combined with the dose of immunosuppressive drug was not more than

0.4–0.6 gm/3 months of CYC, 10 mg/day of leflunomide, or 0.5 gm/day of mycophenolate mofetil. Eleven and 7 patients in single (11/30; 36.7%) and double (7/28; 25.0%) transplantation groups achieved above-mentioned maintenance therapy in the last followup. Time to reach maintenance therapy was not different between single (11.8 months, 3–24 months) and double (10.0 months, 4–15 months) transplantation groups.

4. Discussion

Systemic infusions of mesenchymal stem cells have been widely used in clinical applications. However, the appropriate dose of cells for each patient is still unknown. The dose of MSCs in current studies relied to a large extent on clinical experience and lack of rigorous standards. In a phase II clinical trial for MSCs transplantation in GVHD and followed up for 5 years [19], the therapeutic dose of MSCs ranged from 0.8 million to 9.0 million per kilogram for responders and from 0.6 million to 1.9 million per kilogram for nonresponders. However, no significant correlation has been made between the dose of MSCs received and clinical outcomes. Furthermore, single, double, and repeated doses of MSCs have been administered, but with no obvious pattern to the observed outcomes. A small clinical study showed that repeated intermittent MSCs infusions, ranged

from 4 to 8 times, with a 3- to 14-day interval, 10 to 20 million MSCs each time, could successfully improve signs and symptoms, as well as Th1/Th2 rebalance for 4 patients with sclerodermatous chronic GVHD [20]. Recently, Lim et al. [21] applied different dose of third-party-derived-bone marrow MSCs for two patients with GVHD (ranged from 0.5 to 2 million cells per kilogram each infusion), and the outcomes showed that a dose of one million per kilogram was as effective as that of 2 million per kilogram of recipient. Nevertheless, these case studies were insufficient to provide evidence for clinicians and larger-scale clinical trials are needed to determine the optimal cells dose for a better clinical application.

This study for the first time represents a large single-institution series of refractory SLE patients receiving single or double MSCs transplantations. We found a considerable improvement in disease remission for patients transplanted single and double allogenic MSCs. In previous studies, we have proposed that single allogenic MSCs transplantation ameliorated disease phenotype in SLE mice and humans [13]. Additionally, multiple infusions of allogenic UC MSCs, at 18, 19, and 20 weeks, seemed to significantly ameliorate lupus nephritis in MRL/lpr mice, compared to single transplantation [15], our animal and clinical data suggest that there may exist disparity between lupus mice and humans.

Although the routes of administration are different between diseases, such as intraportal injection for liver cirrhosis [22] and intrathecal injection for multiple sclerosis or amyotrophic lateral sclerosis [23], intravenous infusion is intensively recommended and applied for most type of diseases [24, 25]. In the present study, we focused on comparing the difference between single and multiple transplantations of allogenic MSCs intravenously, with each dose of one million cells per kilogram of body weight. The dose of infused MSCs for each transplantation was based on the previous successful treatment with the same dose in refractory SLE patients and lupus models [12–14]. Additionally, the current consensus report of the International MSCT Study Group has preferred a dose of 1-2 million MSCs per kilogram for a single intravenous infusion [26]. Based on our previous studies and current reports [15, 27], we chose one-week interval between two times of MSCs transplantation for patients. The current data revealed an optimal dose of infused allogenic MSCs for SLE patients. However, whether this is the case in other disorders still needs further investigations.

Most enrolled patients were unresponsive to CYC treatment before MSCT (for at least 6 months), the low dose of CYC given 4 days before MSCs infusion to each patient was used to inhibit active lymphocytes responses but not to treat disease. So we do not think the same pretreatment regimens before MSCT in both groups would influence the clinical response between once and double MSCT. Furthermore, the dose of CYC in the present study is much lower than that used in hematopoietic stem cells transplantation (total 30 mg/kg versus 200 mg/kg), and our previous animal studies had demonstrated that the addition of CYC before MSCT could not enhance clinical efficacy in MRL/lpr lupus mice [28]. Moreover, allogenic MSCT could act more effective

than CYC in treating MRL/lpr lupus mice [13]. Recently, we have compared the clinical efficacy between patients given and not given CYC for pretreatment at baseline, and the results showed no difference between the two groups (unpublished data). So patients' clinical response was not resulted from CYC pretreatment.

The role of transplanted MSCs *in vivo* is mainly dependent on their multiple differentiation and tissue repairing, as well as extensive immune modulation [7, 29]. Although most of *in vitro* experiments showed that the immunoregulatory effect of MSCs on T cells or B cells is in a dose-dependent manner [30, 31], the reason that repeated transplantations of allogenic MSCs *in vivo* failed to enhance therapeutic efficacy in SLE patients is unclear. It is undoubted that the dose of MSCs in patients is not the more the better, and the appropriate dose of MSCs is most important for clinical treatment. There is no necessity of double transplantations for SLE patients for each therapy. More studies are needed to investigate the role of multiple infused MSCs *in vivo*.

5. Conclusion

This study provides evidence that single transplantation at the dose of one million MSCs per kilogram of body weight is sufficient to induce disease remission in the treatment for refractory SLE patients, and double MSCT had no enhanced effect.

Authors' Contribution

D. Wang and K. Akiyama contributed equally to this work.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

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References

- [1] F. A. Houssiau and E. M. Ginzler, "Current treatment of lupus nephritis," *Lupus*, vol. 17, no. 5, pp. 426–430, 2008.
- [2] M. Y. Karim, C. N. Pisoni, and M. A. Khamashta, "Update on immunotherapy for systemic lupus erythematosus - What's hot and what's not!," *Rheumatology*, vol. 48, no. 4, pp. 332–341, 2009.

- [3] A. J. Nauta and W. E. Fibbe, "Immunomodulatory properties of mesenchymal stromal cells," *Blood*, vol. 110, no. 10, pp. 3499–3506, 2007.
- [4] N. G. Singer and A. I. Caplan, "Mesenchymal stem cells: mechanisms of inflammation," *Annual Review of Pathology: Mechanisms of Disease*, vol. 6, pp. 457–478, 2011.
- [5] M. J. Hoogduijn, F. Popp, R. Verbeek et al., "The immunomodulatory properties of mesenchymal stem cells and their use for immunotherapy," *International Immunopharmacology*, vol. 10, no. 12, pp. 1496–1500, 2010.
- [6] L. M. Calvi, G. B. Adams, K. W. Weibrecht et al., "Osteoblastic cells regulate the haematopoietic stem cell niche," *Nature*, vol. 425, no. 6960, pp. 841–846, 2003.
- [7] A. Uccelli, L. Moretta, and V. Pistoia, "Mesenchymal stem cells in health and disease," *Nature Reviews Immunology*, vol. 8, no. 9, pp. 726–736, 2008.
- [8] S. Méndez-Ferrer, T. V. Michurina, F. Ferraro et al., "Mesenchymal and haematopoietic stem cells form a unique bone marrow niche," *Nature*, vol. 466, no. 7308, pp. 829–834, 2010.
- [9] L. Peng, D. Y. Xie, B. L. Lin et al., "Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: short-term and long-term outcomes," *Hepatology*, vol. 54, no. 3, pp. 820–828, 2011.
- [10] S. Guiducci, F. Porta, R. Saccardi et al., "Autologous mesenchymal stem cells foster revascularization of ischemic limbs in systemic sclerosis: a case report," *Annals of Internal Medicine*, vol. 153, no. 10, pp. 650–654, 2010.
- [11] J. Liang, H. Zhang, D. Wang et al., "Allogeneic mesenchymal stem cell transplantation in seven patients with refractory inflammatory bowel disease," *Gut*, vol. 61, no. 3, pp. 468–469, 2012.
- [12] L. Sun, D. Wang, J. Liang et al., "Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 62, no. 8, pp. 2467–2475, 2010.
- [13] L. Sun, K. Akiyama, H. Zhang et al., "Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans," *Stem Cells*, vol. 27, no. 6, pp. 1421–1432, 2009.
- [14] J. Liang, H. Zhang, and B. Hua, "Allogeneic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study," *Annals of the Rheumatic Diseases*, vol. 69, no. 8, pp. 1423–1429, 2010.
- [15] Z. Gu, K. Akiyama, X. Ma et al., "Transplantation of umbilical cord mesenchymal stem cells alleviates lupus nephritis in MRL/lpr mice," *Lupus*, vol. 19, no. 13, pp. 1502–1514, 2010.
- [16] E. L. Smith and R. H. Shmerling, "The American College of Rheumatology criteria for the classification of systemic lupus erythematosus: strengths, weaknesses, and opportunities for improvement," *Lupus*, vol. 8, no. 8, pp. 586–595, 1999.
- [17] D. Jayne, J. Passweg, A. Marmont et al., "Autologous stem cell transplantation for systemic lupus erythematosus," *Lupus*, vol. 13, no. 3, pp. 168–176, 2004.
- [18] J. T. Merrill, C. M. Neuwelt, D. J. Wallace et al., "Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial," *Arthritis and Rheumatism*, vol. 62, no. 1, pp. 222–233, 2010.
- [19] K. Le Blanc, F. Frassoni, L. Ball et al., "Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study," *The Lancet*, vol. 371, no. 9624, pp. 1579–1586, 2008.
- [20] H. Zhou, M. Guo, C. Bian et al., "Efficacy of bone marrow-derived mesenchymal stem cells in the treatment of sclerodermatous chronic graft-versus-host disease: clinical report," *Biology of Blood and Marrow Transplantation*, vol. 16, no. 3, pp. 403–412, 2010.
- [21] J. H. Lim, M. H. Lee, H. G. Yi, C. S. Kim, J. H. Kim, and S. U. Song, "Mesenchymal stromal cells for steroid-refractory acute graft-versus-host disease: a report of two cases," *International Journal of Hematology*, vol. 92, no. 1, pp. 204–207, 2010.
- [22] M. Mohamadnejad, K. Alimoghaddam, M. Mohyeddin-Bonab et al., "Phase I trial of autologous bone marrow mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis," *Archives of Iranian Medicine*, vol. 10, no. 4, pp. 459–466, 2007.
- [23] P. Kharaziha, P. M. Hellström, B. Noorinayer et al., "Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I-II clinical trial," *European Journal of Gastroenterology and Hepatology*, vol. 21, no. 10, pp. 1199–1205, 2009.
- [24] G. Martino, R. J. M. Franklin, A. B. Van Evercooren, and D. A. Kerr, "Stem cell transplantation in multiple sclerosis: current status and future prospects," *Nature Reviews Neurology*, vol. 6, no. 5, pp. 247–255, 2010.
- [25] K. English, A. French, and K. J. Wood, "Mesenchymal stromal cells: facilitators of successful transplantation?" *Cell Stem Cell*, vol. 7, no. 4, pp. 431–442, 2010.
- [26] M. S. Freedman, A. Bar-Or, H. L. Atkins et al., "The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the international MSCT study group," *Multiple Sclerosis*, vol. 16, no. 4, pp. 503–510, 2010.
- [27] J. S. Lee, J. M. Hong, G. J. Moon et al., "A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke," *Stem Cells*, vol. 28, no. 6, pp. 1099–1106, 2010.
- [28] K. Zhou, H. Zhang, O. Jin et al., "Transplantation of human bone marrow mesenchymal stem cell ameliorates the autoimmune pathogenesis in MRL/lpr mice," *Cellular and Molecular Immunology*, vol. 5, no. 6, pp. 417–424, 2008.
- [29] A. Uccelli and D. J. Prockop, "Why should mesenchymal stem cells (MSCs) cure autoimmune diseases?" *Current Opinion in Immunology*, vol. 22, no. 6, pp. 768–774, 2010.
- [30] J. A. Kim, S. Hong, B. Lee et al., "The inhibition of T-cells proliferation by mouse mesenchymal stem cells through the induction of p16INK4A-cyclin D1/cdk4 and p21waf1, p27kip1-cyclin E/cdk2 pathways," *Cellular Immunology*, vol. 245, no. 1, pp. 16–23, 2007.
- [31] A. Corcione, F. Benvenuto, E. Ferretti et al., "Human mesenchymal stem cells modulate B-cell functions," *Blood*, vol. 107, no. 1, pp. 367–372, 2006.



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