

Safety of Mesenchymal Stem Cells Therapy in Patients with Inflammatory Bowel Diseases – 5 Year Follow-Up

Knyazev Oleg Vladimirovich^{1*}, Parfenov Asfold Ivanovich², Konoplyannikov Anatoliy Georgievich³, Kagramanova Anna Valeryevna^{4*}, Churikova Alevtina Alekseevna⁴, Ruchkina Irina Nikolaevna¹, Lishinskaya Albina Aleksandrovna¹, Boldireva Oksana Nikolaevna¹ and Fadeeva Nina Aleksandrovna¹

¹Central Research Institute of Gastroenterology, Department of Treatment Inflammatory Bowel Diseases, Russia

²Central Research Institute of Gastroenterology, Department of Intestinal Pathology, Russia

³Central Research Institute of Gastroenterology, Department of Experimental Radiotherapy, Russia

⁴Candidate of Science, Scientist Researcher, Russia

Abstract

Aim: To compare safety profile of therapy in patients with ulcerative colitis (UC) and Crohn disease (CD), receiving anti-inflammatory therapy, using bone marrow-derived mesenchymal stromal cells (MSC) and standard therapy with 5-aminosalicylic acid (5-ASA), glucocorticosteroids (GCS) and immunosuppressive agents (IS).

Materials and methods: Adverse events were analyzed in 103 patients with inflammatory bowel disease (IBD) after administration MSCs (56 patients UC and 47 patients CD). The findings were compared with data obtained in 208 patients with UC and CD, receiving standard anti-inflammatory therapy. All analyzed patients were similar in demographic characteristics, the duration of disease, the extent of disease, course of disease, phenotype and degree of disease.

The analyzed groups did not include patients, treated with anti-TNF therapy. The safety of therapy was evaluated by presence of complications, developed during follow-up period.

Results: We conducted analysis of side effects in 103 IBD patients, treated with mesenchymal stem cells, comparing with 208 UC and CD patients, treated with standard anti-inflammatory therapy and finally we did not reveal any differences in developing acute post-transfusional toxicity, infectious complications, exacerbation of chronic inflammatory diseases, serious infectious complications, malignancy and death in UC and CD patients, besides transitive febrile.

Conclusion: Results of our study show that innovative method of cell therapy is safe in clinical practice.

Keywords: Safety of cell therapy; Mesenchymal stromal cells; Crohn disease; Ulcerative colitis; Inflammatory bowel diseases

Aim of Study

To compare safety profile of therapy in patients with ulcerative colitis (UC) and Crohn disease (CD), received combined anti-inflammatory therapy including MSC and standard therapy, including 5-ASA, Glucocorticosteroids (GCS) and immune-suppressive therapy.

Introduction

Mesenchymal stromal cells (mesenchymal stem cells; MSC) are a heterogeneous group of cells, that can be isolated from many tissues (bone marrow, adipose tissue, dental pulpe). First described in 1960-years of XX century [1], MSC have recently received attention in a number of different clinical fields for their potential therapeutic effects.

Although often described as «adult stem cells», MSC's have limited cellular differentiation ability. Instead, pre-clinical evidence suggests that MSCs exert their beneficial effects largely through immunomodulatory and paracrine mechanisms. MSCs home to sites of inflammation and secrete bioactive molecules, and thus may be especially effective in different pro-inflammatory diseases [2].

There is a growing body of literature demonstrating the efficacy of MSC therapy in a variety of pre-clinical models, including acute lung injury [3,4], septic shock [5], acute myocardial infarction [6]. Several small clinical trials have investigated efficacy and safety of MSCs in diseases including chronic heart failure, acute myocardial infarction, hematological malignancies, Crohn disease [7] and graft-versus-host disease.

However, safety concerns represent a significant barrier to the successful translation of MSCs into an acceptable clinical therapeutic. Potential risk is associated with its proliferative capacity, susceptibility to infectious complications given their immune-suppressive effects, embolism of the cells, zoonoses associated with cell culture reagents, and acute or chronic immunogenicity of the cells themselves [8].

Therefore, we conducted a systematic review of randomized and non-randomized controlled trials as well as uncontrolled clinical trials in foreign literature that examined the safety and efficacy of intravascularly delivered MSCs, and revealed their most frequent adverse events [9]. Adverse events were grouped according to the immediacy of the event -acute infusional toxicity, fever, the occurrence of

***Corresponding authors:** Knyazev Oleg Vladimirovich, Central Research Institute of Gastroenterology, Doctor of science, Head of Department of Treatment Inflammatory Bowel Diseases, Russia, E-mail: oleg7@bk.ru

Kagramanova Anna Valeryevna, Central Research Institute of Gastroenterology, Candidate of Science, Scientist Researcher, Russia, Tel: +79260804444; E-mail: kagramanova@me.com

Received May 05, 2015; **Accepted** August 13, 2015; **Published** August 20, 2015

Citation: Knyazev OV, Parfenov AI, Konoplyannikov AG, Kagramanova AV, Churikova Alevtina Alekseevna, et al. (2015) Safety of Mesenchymal Stem Cells Therapy in Patients with Inflammatory Bowel Diseases – 5 Year Follow-Up. J Biotechnol Biomater 5: 192. doi:10.4172/2155-952X.1000192

Copyright: © 2015 Vladimirovich KO, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

organ system complications (neurological, pulmonary, cardiovascular, gastrointestinal and renal, and hematologic systems), infection, and the occurrence of longer term adverse effects (death, malignancy).

Included studies were conducted in 14 different countries from Asia, the Middle East, Europe, and North America. There were eight RCTs (n=369 patients) [10-17], 10 non-RCTs (n=466 patients) [18-27] and 18 uncontrolled clinical trials (n=252 patients) [28-45]. Six of 36 studies were multi-center [12,13,20,23,32,33]. One non-controlled study had a mixed adult-pediatric population [39], all other studies included only adult participants. The follow-up period was reported in all studies and the duration ranged from 0.5 to 60 months.

There were following diseases analyzed: eight randomized controlled studies included patient populations with cardiovascular diseases-acute myocardial infarction [11,12], chronic heart failure [10,16], with neurological disease either ischemic stroke [13], spinal cord injury [17], following stem cell transplantation for hematological malignancies [15]. The 10 non-RCTs included patient populations with old myocardial infarctions [25], stem-cell transplant post renal transplant [27], stem cell transplant for hematological malignancy [18,19,23], graft-versus-host disease [20,26], or healthy volunteers [24].

Sixteen studies used autologous MSC [10,11,13,14,16,17,22,24,25,27,29,31,32,37,43,45], eight used allogenic MSC [12,18,20,34,35,39,40,41]. Nine of the 36 studies cryopreserved MSCs prior to administration [12,18,20,21,23,29,31,32,44], and one study used both fresh and cryopreserved MSC [33], while the remainder of studies used only fresh MSCs. A meta-analysis revealed no significant differences in the occurrence of acute infusional toxicity, infectious complications, recurrence of chronic inflammatory diseases, serious infectious complications, malignancy and death between patients treated with MSC and control group. Significant association was demonstrated between MSC injection and transient fever.

Further we demonstrate our data for safety profile of allogenic mesenchymal stromal bone marrow cells in patients with inflammatory bowel diseases over a 5-year follow-up period.

Materials and Methods

Systemic transplantation of allogenic bone marrow MSC was performed in 74 UC and 64 CD patients ranging from 2008 to 2014 years.

First analysed group included 56 UC patients, follow-up period comprised in median 62 ± 4 months. This group consists of 29 (51.78%) man and 27 (48.22%) women (Table 1). Mean age was 35.4 ± 1.42 years. The second control group included 84 UC patients, receiving standard anti-inflammatory therapy with 5-ASA and GCS. This group consists of 46 (54.8%) man and 38 (45.2%) women. Mean age – 34.98 ± 1.23 years.

Third group included 47 CD patients; mean follow-up period was 64 ± 4 months. Nineteen (40.4%) man and twenty-eight (59.26%) women were included in the third group. Mean age was 30.4 ± 1.2 years. Fourth control group consisted of 124 CD patients, receiving standard anti-inflammatory therapy including 5-ASA, GCS and IS. In this group were

56 (45.2%) man and 68 (54.8%) women. Mean age was- 36.8 ± 1.5 years.

We did not include patients, receiving anti-TNF therapy, in analysed groups.

Technique of receiving and cultivation MSC in an appropriate for systemic transplantation amount (150-200 millions of cells) was published [46]. This method is validated by Federal Supervisory Agency for Health Care and Social Development Ministry of Healthcare and Social Development of the Russian Federation (License 2006/206). Bone marrow cells were isolated by means of flushing the sternum or iliac crest of healthy donor under local anesthesia and aseptic conditions. All donors signed informed consent for using bone marrow samples for scientific purposes. MSC culture was injected intravenous drip-feed in dosage 1,5-2 mln by 1 kg body weight. For systemic transplantation 130-160 mln allogenic MSC, cultivated, were suspended in 200 ml sterile isotonic solution, consisting of heparin in concentration 50 U/ml. MSC culture was injected during 40-60 minutes by means of intravenous drip-feed infusion. Mathematical modeling of MSC treatment was performed to assess maximal efficacy and minimal side effects of MSCs. We analyzed several trials, in which regimen of MSC administration, frequency and the rationale for the cell dose were examined [13,14,44,45]. All patients signed inform consent for participating in study before MSC injection. Thus, procedure of MSC cultivation was performed according GMP.

Safety of therapy was assessed by presence of complications, occurred during follow-up period, for example acute infusional toxicity, fever; complications (neurological, pulmonary, cardiovascular (arrhythmias, etc.), urinary, gastrointestinal tract and blood system), infection complications, exacerbation of chronic inflammatory diseases, serious infectious complications (pneumonia, sepsis, abscess), malignancy, death. All persons, monitoring the complications were blinded with the treatment.

Results and Discussion

In the first group 3/56 UC patients (5,4%) have acute infusional toxicity-looks like hives immediately or after MSC injection, in the second group allergic reaction like papular urticaria was noticed in 1/84 (1,2%) patient, treated with sulfasalazin. Allergic reaction like hives in first group patients had no statistically significance in compare with second group of patients ($\chi^2=0,35$; $p=0,87$). In 16/56 (28,6%) patients of first group were noted increasing of temperature around 37,2-37,4°C during 12 hours after MSC injection or fever around 38,0°C, in 1/84 (1,2%) patients of second group was reported increasing temperature above 37,7°C, caused by intravenous injection of prednisolon. Fever and temperature increasing after MSC injection were statistically significant compared to control group – relative risk (RR) was 24,0 (95% CI 3.27 - 175.89); $\chi^2=21,12$; $p=0,000043$. In the first UC group non-serious infectious complications and exacerbation of chronic inflammatory diseases were revealed in 7/56 (12,5%) patients, in second group - in 14/84 (16,7%) patients. There was no significant difference in risk of infectious complications and exacerbation of chronic inflammatory diseases between two groups of UC patient, receiving standard anti-inflammatory therapy and MSC (RR-0,75; 95% CI 1.5-23.58; $\chi^2=0,16$; $p=0,66$). In the first group serious infectious complications (pneumonia, pleurisy, activation of latent tuberculosis) were detected in 1/56 patients (1,8%), in the second – in 5/84 (5,9%). There was no difference in this complications between two groups (RR-0,3; 95%CI 0.04-2.5; $\chi^2=0,59$; $p=0,44$). Colorectal cancer was documented only in 1/56 (1,8%) patient in the first group. Diagnosis of colon cancer was established in 10 days after MSC injection (Table 2).

	Male-to-female ratio (%)	Mean Age, years
1 group (n=56)	29:27 (51:48)	35,4 ± 1,42
2 group (n=84)	46:38 (54:45)	34,98 ± 1,23
3 group (n=47)	19:28 (40:59)	30,4 ± 1,2
4 group (n=124)	56:68 (45:54)	36,8 ± 1,5

Table 1: Demographic characteristics of patients with CD and UC.

Side effects in all analyzed clinical trials	Frequency in 1 group UC patients	Frequency in 2 group UC patients	95% CI	p
Acute infusion reaction	3/56	1/84	0.48-42.18	0,87
Fever	16/56	1/84	3.27-175.89	0.0000043
Serious infectious complications	1/56	5/84	0.04-2.5	0.44
Non-serious infectious complications	7/56	14/84	1.5-23.58	0,66
Malignancy	1/56	4/84	0.05-4.96	0,97
Lethal cases	1/56	1/56	0.1-23.49	0,66

Table 2: Summary analysis of side effects in UC patients, receiving MSC and in control group.

Side effects in all analysed clinical trials	Frequency in 3 group CD patients	Frequency in 4 group CD patients	95% CI	p
Acute infusion reaction	2/47	0	-	0.07
Fever	22/47	0	8.1-422.0	<0.001
Serious infectious complications	1/47	3/124	0.09-1.85	0.7
Non-serious infectious complications	12/47	48/124	1.5-23.58	0,66
Malignancy	0	2/124	-	0.93
Lethal cases	0	1	-	0,61

Table 3: Summary analysis of side effects occurred after MSC injection and in control group of patients with CD.

During five-year follow-up period malignancy was found in 4/84 (4,8%) in the second group (RR-0,5, 95%CI 0.05-4.96; χ^2 -0,01; $p=0.97$). In the first and in the second groups during five-year follow-up one lethal case from each group was documented and it was 1,8% и 1,2%, respectively (RR-1,5; 95%CI 0.1-23.49; χ^2 -0,19; $p=0.66$).

In the third group of CD patients acute infusional toxicity like hives and Quincke's edema were detected in 2/47 patients (4,25%) immediately after MSC injection, in the fourth group there were no complications during anti-inflammatory therapy, but these manifestations have no statistically significance between groups (χ^2 -2,3, $p=0.07$). Increase in body temperature up to 37,2-37,4°C during 12 hours after MSC injection or fever up to 38,0°C was noticed in 22 patients of third group (46,8%), in the fourth group of patients there was no fever, associated with intravenous interventions (medication injection) or per os administration was found in 0/124 (0%). Fever and mild increase of temperature after MSC injection were statistically significant compare to control group – RR – 58,5 (95% CI 8.1: 422.0), χ^2 -58,5, $p<0.001$. Non-serious infectious complications and exacerbation of chronic inflammatory diseases during therapy observed in 12 patients of 47 in the third group, that accounts 25,5%, in the fourth group-in 48 (38,7%) patients of 124, that had no significant difference: RR – 0,67 (95% CI 0.39 - 1.15), χ^2 -1,86, $p=0.17$ (Table 3).

There were no differences between third and fourth groups in risk of serious infectious complications (pneumonia, peurisy, activation of latent tuberculosis) during standard anti-inflammatory CD therapy and therapy with MSC. In the third group one patient developed pneumonia 1/47 (2,1%), in the fourth group two cases of pneumonia and one case of latent tuberculosis activation were detected – 3/124 (2,4%) (RR-0,88, 95%CI 0.09-1.85; χ^2 -0,21; $p=0.7$).

In the third group of CD patients no cases of colorectal cancer were found. In the third group during five-year follow-up period no lethal outcomes were documented, in the fourth group one lethal case (0,8%), unlinked to underlying disease was found (χ^2 -0,26; $p=0.61$). In the fourth group malignant transformation was noted in 2 patients (1,6%) from 124 (χ^2 -0,01; $p=0.93$).

In patients with UC and CD, receiving MSC treatment, no cardiovascular, pulmonary, neurological, renal, and hematologic systems complications were detected.

Conclusion

Our study includes comparative analysis of adverse events, associated with MSC treatment and standard anti-inflammatory therapy in UC and CD patients. We analyzed advanced outcomes in 103 IBD patients, receiving MSC therapy and compared this data with 208 UC and CD patients, who had the same demographic characteristics, disease duration, extent of disease, course of disease, phenotype of disease, type of severity. Thus we did not observe any significant differences in MSC safety, aside from transient fever.

This analysis did not reveal any differences in acute post-transfusional toxicity, infectious complications, exacerbation of chronic inflammatory diseases, serious infectious complications, malignancy and lethal cases in UC and CD patients, treated with standard anti-inflammatory therapy.

We have detected significant association between MSC injection and fever. However, fever was transient and not associated with long term sequelae. The mechanisms for fever are not clear but could be related to acute inflammatory reactions by a subset of patients to particular preparations of MSCs, not unlike similar reactions occasionally observed with red blood cell and fresh frozen plasma administration [47].

Although malignant transformation is a theoretical risk, our own experience and literature analysis, presented in this review found no association between MSCs and tumour formation. Concerns related to tumourigenicity of MSCs were raised by preclinical studies demonstrating increased tumour burden in vivo [48]. Although recent position papers have suggested low probability of malignant transformation and tumour formation with MSCs [8]. Malignancy occurred only in studies involving participants with ongoing or previous malignancies; no de novo malignancies were observed.

Although MSC immunomodulatory effects may be beneficial in pro-inflammatory diseases, these same effects may leave a patient susceptible to infection [49]. The question arises-whether immunosuppressive therapy could increase risk of infections? This review did not demonstrate any evidence of increased susceptibility to infections with MSC administration.

In our review, infections were common in already immunosuppressed patients (e.g., following hematopoietic stem cell transplant), however the infection rates were similar to those in control group of patients [47].

Currently obtained data show that despite of strong immunosuppressive effect due to autoimmune aggression, MSC did not hinder the activity of immunocompetent cells, directed against infectious agents [50,51].

Absence of post-transfusal reaction may be explained by low MSC immunogenicity, due to absence HLA class II and low level of expression HLA I class at their surface. The use of fetal bovine serum for culturing MSCs could be one of the reasons for above mentioned post-transfusal toxicity, and another potential concern with MSC therapy application is the use of dimethyl sulfoxide as cryopreservative, which has toxic side effects and could cause hypersensitivity reactions. Thus, greater vigilance may be needed in future studies for reporting cellular viability and monitoring for potential dimethyl sulfoxide related adverse events. Results from our study should provide some assurance to investigators and health regulators that, with the present evidence, this innovative therapy appears safe.

References

1. Friedenstein AJ, Piatetzky-Shapiro II, Petrakova KV (1966) Osteogenesis in transplants of bone marrow cells. *J Embryol Exp Morphol* 16: 381-390.
2. François S, Bensidhoum M, Mouiseddine M, Mazurier C, Allenet B, et al. (2006) Local irradiation not only induces homing of human mesenchymal stem cells at exposed sites but promotes their widespread engraftment to multiple organs: A study of their quantitative distribution after irradiation damage. *Stem Cells* 24: 1020-1029.
3. Matthay MA, Goolaerts A, Howard JP, Lee JW (2010) Mesenchymal stem cells for acute lung injury: preclinical evidence. *Crit Care Med* 38: S569-573.
4. Mei SH, McCarter SD, Deng Y, Parker CH, Liles WC, et al. (2007) Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1. *PLoS Med* 4: e269.
5. Mei SH, Haitsma JJ, Dos Santos CC, Deng Y, Lai PF, et al. (2010) Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis. *Am J Respir Crit Care Med* 182: 1047-1057.
6. Boyle AJ, McNiece IK, Hare JM (2010) Mesenchymal stem cell therapy for cardiac repair. *Methods Mol Biol* 660: 65-84.
7. Knyazev OV, Parfenov AI, Sherbakov PL, Homeriki SG, Ruchkina IN, et al. (2013) Efficacy and safety of mesenchymal stem cells in patients with refractory Crohn disease. *Cell transplantation and tissue engineering*. 8: 76-84.
8. Prockop DJ, Brenner M, Fibbe WE, Horwitz E, Le Blanc K, et al. (2010) Defining the risks of mesenchymal stromal cell therapy. *Cytotherapy* 12: 576-578.
9. Manoj M Lalu, Lauralyn McIntyre, Christina Pugliese, Dean Fergusson, Brent W Winston, et al. (2012) Safety of Cell Therapy with Mesenchymal Stromal Cells (Safe Cell): A Systematic Review and Meta-Analysis of Clinical Trials. *PLoS One* 7: e47559.
10. Chen S, Liu Z, Tian N, Zhang J, Ye F, et al. (2006) Intracoronary transplantation of autologous bone marrow mesenchymal stem cells for ischemic cardiomyopathy due to isolated chronic occluded left anterior descending artery. *J Invasive Cardiol* 18: 552-556.
11. Chen SL, Fang WW, Qian J, Ye F, Liu YH, et al. (2004) Improvement of cardiac function after transplantation of autologous bone marrow mesenchymal stem cells in patients with acute myocardial infarction. *Chin Med J (Engl)* 117: 1443-1448.
12. Hare JM, Traverse JH, Henry TD, Dib N, Strumpf RK, et al. (2009) A randomized double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. *J Am Coll Cardiol* 54: 2277-2286.
13. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, et al. (2010) A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. *Stem Cells* 28: 1099-1106.
14. Lee PH, Kim JW, Bang OY, Ahn YH, Joo IS, et al. (2008) Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy. *Clin Pharmacol Ther* 83: 723-730.
15. Ning H, Yang F, Jiang M, Hu L, Feng K, et al. (2008) The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study. *Leukemia* 22: 593-599.
16. Wang JA, Xie XJ, He H, Sun Y, Jiang J, et al. (2006) A prospective, randomized, controlled trial of autologous mesenchymal stem cells transplantation for dilated cardiomyopathy. *Zhonghua Xin Xue Guan Bing Za Zhi* 34: 107-110.
17. Xie ZW, Cui GX, Li YZ, Li BW, Zhu SW, et al. (2007) Curative effect of autologous mesenchymal stem cell transplantation on spinal cord injury. *Journal of Clinical Rehabilitative Tissue Engineering Research* 11: 1277-1279.
18. Baron F, Lechanteur C, Willems E, Bruck F, Baudoux E, et al. (2010) Cotransplantation of mesenchymal stem cells might prevent death from graft-versus-host disease (GVHD) without abrogating graft-versus-tumor effects after HLA-mismatched allogeneic transplantation following nonmyeloablative conditioning. *Biol Blood Marrow Transplant* 16: 838-847.
19. Gonzalo-Daganzo R, Regidor C, Martín-Donaire T, Rico MA, Bautista G, et al. (2009) Results of a pilot study on the use of third-party donor mesenchymal stromal cells in cord blood transplantation in adults. *Cytotherapy* 11: 278-288.
20. Kebriaei P, Isola L, Bahceci E, Holland K, Rowley S, et al. (2009) Adult human mesenchymal stem cells added to corticosteroid therapy for the treatment of acute graft-versus-host disease. *Biol Blood Marrow Transplant* 15: 804-811.
21. Koç ON, Day J, Nieder M, Gerson SL, Lazarus HM, et al. (2002) Allogeneic mesenchymal stem cell infusion for treatment of metachromatic leukodystrophy (MLD) and Hurler syndrome (MPS-IH). *Bone Marrow Transplant* 30: 215-222.
22. Lazarus HM, Haynesworth SE, Gerson SL, Rosenthal NS, Caplan AI (1995) Ex vivo expansion and subsequent infusion of human bone marrow-derived stromal progenitor cells (mesenchymal progenitor cells): implications for therapeutic use. *Bone Marrow Transplant* 16: 557-564.
23. Lazarus HM, Koc ON, Devine SM, Curtin P, Maziarz RT, et al. (2005) Co-transplantation of HLA-identical sibling culture-expanded mesenchymal stem cells and hematopoietic stem cells in hematologic malignancy patients. *Biol Blood Marrow Transplant* 11: 389-398.
24. Liu L, Sun Z, Chen B, Han Q, Liao L, et al. (2006) Ex vivo expansion and in vivo infusion of bone marrow-derived Flk-1+CD31-CD34- mesenchymal stem cells: Feasibility and safety from monkey to human. *Stem Cells Dev* 15: 349-357.
25. Mohyeddin-Bonab M, Mohamad-Hassani MR, Alimoghaddam K, Sanatkar M, Gasemi M, et al. (2007) Autologous in vitro expanded mesenchymal stem cell therapy for human old myocardial infarction. *Arch Iran Med* 10: 467-473.
26. Ringdén O, Uzunel M, Rasmusson I, Remberger M, Sundberg B, et al. (2006) Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. *Transplantation* 81: 1390-1397.
27. Vanikar AV, Trivedi HL, Feroze A, Kanodia KV, Dave SD, et al. (2011) Effect of co-transplantation of mesenchymal stem cells and hematopoietic stem cells as compared to hematopoietic stem cell transplantation alone in renal transplantation to achieve donor hypo-responsiveness. *Int Urol Nephrol* 43: 225-232.
28. Arima N, Nakamura F, Fukunaga A, Hirata H, Machida H, et al. (2010) Single intra-arterial injection of mesenchymal stromal cells for treatment of steroid-refractory acute graft-versus-host disease: A pilot study. *Cytotherapy* 12: 265-268.
29. Duijvestein M, Vos AC, Roelofs H, Wildenberg ME, Wendrich BB, et al. (2010) Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: Results of a phase I study. *Gut* 59: 1662-1669.
30. Fang B, Song Y, Liao L, Zhang Y, Zhao RC (2007) Favorable response to human adipose tissue-derived mesenchymal stem cells in steroid-refractory acute graft-versus-host disease. *Transplant Proc* 39: 3358-3362.
31. Honmou O, Houkin K, Matsunaga T, Niitsu Y, Ishiai S, et al. (2011) Intravenous administration of auto serum-expanded autologous mesenchymal stem cells in stroke. *Brain* 134: 1790-1807.
32. Karussis, Karageorgiou C, Vaknin-Dembinsky A, Gowda-Kurkalli B, Gomori JM, et al. (2010) Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. *Arch Neurol* 67: 1187-1194.
33. Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, et al. (2008) Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: A phase II study. *Lancet* 371: 1579-1586.

34. Liang J, Zhang H, Hua B, Wang H, Lu L, et al. (2010) Allogeneic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: A pilot clinical study. *Ann Rheum Dis* 69: 1423-1429.
35. Liang J, Zhang H, Wang D, Feng X, Wang H, et al. (2012) Allogeneic mesenchymal stem cell transplantation in seven patients with refractory inflammatory bowel disease. *Gut* 61: 468-469.
36. Meuleman N, Tondreau T, Ahmad I, Kwan J, Crokaert F, et al. (2009) Infusion of mesenchymal stromal cells can aid hematopoietic recovery following allogeneic hematopoietic stem cell myeloablative transplant: a pilot study. *Stem Cells Dev* 18: 1247-1252.
37. Mohamadnejad M, Alimoghaddam K, Mohyeddin-Bonab M, Bagheri M, Bashtar M, et al. (2007) Phase 1 trial of autologous bone marrow mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis. *Arch Iran Med* 10: 459-466.
38. Ringdén O, Uzunel M, Sundberg B, Lönnies L, Nava S, et al. (2007) Tissue repair using allogeneic mesenchymal stem cells for hemorrhagic cystitis, pneumomediastinum and perforated colon. *Leukemia* 21: 2271-2276.
39. Sun L, Akiyama K, Zhang H, Yamaza T, Hou Y, et al. (2009) Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans. *Stem Cells* 27: 1421-1432.
40. Sun L, Wang D, Liang J, Zhang H, Feng X, et al. (2010) Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. *Arthritis Rheum* 62: 2467-2475.
41. Wang D, Zhang H, Cao M, Tang Y, Liang J, et al. (2011) Efficacy of allogeneic mesenchymal stem cell transplantation in patients with drug-resistant polymyositis and dermatomyositis. *Ann Rheum Dis* 70: 1285-1288.
42. Weng JY, Du X, Geng SX, Peng YW, Wang Z, et al. (2010) Mesenchymal stem cell as salvage treatment for refractory chronic GVHD. *Bone Marrow Transplant* 45: 1732-1740.
43. Yang Z, Zhang F, Ma W, Chen B, Zhou F, et al. (2010) A novel approach to transplanting bone marrow stem cells to repair human myocardial infarction: Delivery via a noninfarct-related artery. *Cardiovasc Ther* 28: 380-385.
44. Zhang X, Li JY, Cao K, Lu H, Hong M, et al. (2010) Cotransplantation of HLA-identical mesenchymal stem cells and hematopoietic stem cells in Chinese patients with hematologic diseases. *Int J Lab Hematol* 32: 256-264.
45. Zhang ZX, Guan LX, Zhang K, Zhang Q, Dai LJ (2008) A combined procedure to deliver autologous mesenchymal stromal cells to patients with traumatic brain injury. *Cytotherapy* 10: 134-139.
46. Zib AF, Konoplyannikov AG, Kolesnikova AI, Pavlov VV (2004) Application of cell cultures in medicine from mesenchymal stem cells of human bone marrow. *News of Russian Academy of science* 59: 71-76.
47. Hendrickson JE, Hillyer CD (2009) Noninfectious serious hazards of transfusion. *Anesth Analg* 108: 759-769.
48. Djouad F, Plence P, Bony C, Tropel P, Apparailly F, et al. (2003) Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. *Blood* 102: 3837-3844.
49. Uccelli A, Moretta L, Pistoia V (2008) Mesenchymal stem cells in health and disease. *Nat Rev Immunol* 8: 726-736.
50. Karlsson H, Samarasinghe S, Ball LM, Sundberg B, Lankester AC, et al. (2008) Mesenchymal stem cells exert differential effects on alloantigen and virus-specific T-cell responses. *Blood* 112: 532-541.
51. Majumdar MK, Keane-Moore M, Buyaner D, Hardy WB, Moorman MA, et al. (2003) Characterization and functionality of cell surface molecules on human mesenchymal stem cells. *J Biomed Sci* 10: 228-241.