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Evaluation of Immune response to Intravenously Administered Human Cord Blood Stem Cells in the Treatment of Symptoms Related to Chronic Inflammation

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Abstract

Objective: Numerous investigations suggest that Mesenchymal Stem Cells (MSCs) in general represent a valuable tool for therapy of symptoms related to chronic inflammatory diseases. Blue Horizon Stem Cell Therapy Program is a leading provider of adult and children's stem cell therapies. Uniquely we have safely and efficiently treated over 600 patients with documenting each procedure.

Methods: The purpose of our study is primarily to monitor the immune response in order to validate the safety of intravenous infusion of human umbilical cord blood derived MSCs (UC-MSCs), and secondly, to evaluate effects on biomarkers associated with chronic inflammation. Twenty patients were treated for conditions associated with chronic inflammation and for the purpose of anti-aging. They have been given one intravenous infusion of UC-MSCs.

Results: Our study of blood test markers of 20 patients with chronic inflammation before and within three months after MSCs treatment demonstrates that there are no significant changes and MSCs treatment was safe for the patients. Analysis of different indicators of chronic inflammation and aging included in initial, 24-hours, two weeks and three months protocols showed that stem cell treatment was safe for the patients; there were no adverse reactions. Moreover, data from follow-up protocols demonstrate significant improvement in energy level, hair, nail growth and skin conditions.

Conclusion: Intravenously administered UC-MSCs were safe and effective in the improvement of symptoms related to chronic inflammation. Further close monitoring and inclusion of more patients are necessary to fully characterize the advantages of UC-MSCs application in treatment of symptoms related to chronic inflammation.

Keywords: Chronic inflammatory diseases; Umbilical cord blood; Mesenchymal stem cells; Intravenous infusion

Introduction

Prolonged inflammation, known as chronic inflammation, is characterized by continued active inflammation response and tissue destruction. Variety of factors can cause chronic inflammation, including bacterial, viral, and parasitic infections, chemical irritants, and indigestible particles. Immune cells including macrophages, neutrophils and eosinophils are involved directly or by production of inflammatory cytokine production in pathology of chronic inflammation [1].

Regulated inflammatory responses are essential to maintain homeostasis. Inflammatory responses that fail to regulate themselves can become chronic and contribute to progression of disease [2]. Improved understanding of the sterile inflammatory process is one of the most important areas of biomedical investigation [3]. The pharmaceutical industry is searching for better-tolerated anti-inflammatory drugs. Numerous investigations suggest that Mesenchymal Stem Cells (MSCs) represent a valuable tool for therapy in chronic inflammatory diseases. MSCs, multipotent adult stem cells, feature the potential to regenerate tissue damage and inhibit inflammation. MSCs can be safely transplanted in autologous and allogeneic ways as they are non-immunogenic, representing a therapeutic option for chronic inflammatory diseases. There are more than 200 registered clinical trial sites for evaluating MSC therapy, and 22 are on autoimmune diseases [4].

Stem cell therapy is a potential method for treatment of some disorders [5]. Sources for stem cells vary, each of which have uses for certain diseases [6-8]. MSCs are one source for stem cells that are multipotent, non-hematopoietic and have the capability for self-renewal and differentiation. MSCs can be isolated from different human tissues, including marrow, synovium, periosteum, muscle, liver, dermis, spleen, thymus, umbilical cord blood /placental blood (UCB), cord matrix, amniotic fluid, placenta, fetal liver, and adipose tissue [6-12]. Umbilical cord MSCs (UC-MSCs) for stem cell therapy have advantages over bone marrow MSCs (BM-MSCs) because they are easily available, collection from the donor is not invasive or painful, and there are no ethical considerations [13]. UC-MSCs are more primitive than BM-MSCs and have the capability to differentiate into different cells [14-17].

MSCs derived from a number of both allogeneic and autologous sources have been rapidly gaining momentum. There is a number of current clinical trials listed on clinicaltrials.gov and a handful of FDA approvals for their use in various countries outside of the US.

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Blue Horizon Stem Cell (BHSC) program is associated with the Stem Cell Centre, Hongqiao Brain Hospital and Wuhan University School of Basic Medical Science, Wuhan, China. BHSC has safely and efficiently treated over 600 patients with documenting each procedure. In the study conducted by Jiang et al human bone marrow-derived mesenchymal stem cells transplantation has demonstrated its effectiveness for the treatment of spinal cord injury [18].

The purpose of this study is primarily to monitor the immune response in order to validate the safety of intravenous infusion of UC-MSCs, and secondly, to evaluate effects on biomarkers associated with chronic inflammation. The study was approved by Institutional Review Board of the Institute of Regenerative Cellular Medicine (US Department of Health and Human Services, IRB # 00009500. Protocol #: BH-IN-7101b, IRB Approval Number: IRCM 2014-040).

Materials and Methods

20 patients were treated for conditions associated with chronic inflammation and for the purpose of anti-aging. Chronic inflammatory diseases included osteoarthritis, post traumatic arthritis, inflammatory back pain, left shoulder bursitis and herniated disc. They have been given one intravenous infusion of UC-MSCs (**Table 1**).

Protocol

Preparation of UC-MSCs: Umbilical cord bloods were collected from primiparous pregnant women receiving Caesarean section in accordance with the sterile procedure guidelines in each hospital. UC blood samples were processed within 4 hours.

Isolation of MSCs from umbilical cord bloods: Cord blood sample was diluted with phosphate buffer saline (PBS) (1:1). 15 mL of Ficoll-Hypaque pipetted into a 50 mL conical centrifuge tube. 30 mL of the mixture of PBS and sample slowly layered over the Ficoll-Hypaque and centrifuged 30 min at 450 g. Using Pasteur pipette, the interface layer containing the mononuclear cells was transferred to a centrifuge tube. Cells were washed with PBS and recovered by centrifugation for 10 min at 200 g and room temperature. The cell pellet was re-suspended in PBS and the washing procedure was repeated. The cells were counted and 1.0 $\times 10^8$/4 cells were re-suspended in 1.25 ml/5 mL of cryopreservation solution correcspondingly (10% DMSO).

Sterility assurance: The pregnant donor women passed medical examinations before they donate UC. They tested for communicable diseases such as HBV, HCV, HIV and Syphilis. After collection, each cord blood sample was tested for communicable diseases such as HBV, HCV, HIV and Syphilis. The isolated cells were cultured to test for bacteria and fungus, endotoxins, and to insure viability.

Transportation and cryopreservation protocols: Cells were analysed by FACS sorter. An automated temperature control device was placed in the transport package with the cells. For the purpose of this pilot study, all cells were hand delivered.

Thawing: Each frozen tube of UC-MSCs was thawed by placing in 37°C water bath for one minute with water level not exceeding 80% of the body of the cryotube. The tube was quickly pulsed down and content was transferred to a sterile syringe for the subsequent infusion steps. The cell count and viability of thawed cells was evaluated with the trypan blue exclusion test.

Infusion: 1.25 ml of 1.0 $\times 10^8$/5 stem cells were suspended in 100 ml of saline and usually infused in the patient no more than one hour. Human Albumin (final 1%) was added to the saline for stabilization.

Outcome measures: safety evaluation and effects on chronic inflammation

Blood test included general health blood test panel and inflammatory markers (CRP, IL-6, IL-8, TNF-alpha and Fibrinogen). Blood tests were carried out before stem cell treatment and within three months after stem cell treatment. At 0, 3, 6 month intervals the patient have been interviewed and asked to fill out a SF-36 questionnaire. During the interview patients were asked about adverse reactions connected to stem cell treatment, including pain, chills, fever, hives, chest pain, drop in blood pressure, shortness of breath, nausea, flushing, and headache. Additional secondary outcome measures included sleep, energy level, libido, mood, skin, hair and nail growth. All questioners were approved by Institutional Review Board of the Institute of Regenerative Cellular Medicine.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study. This article does not contain any studies with animal subjects.

Statistical analysis

Methods of descriptive statistics (significance is equal to 95%) and probability theory were used. Analysis of results with the methods of descriptive statistics was realized with the application of statistical software package SigmaStat 3.5.

Results

Isolation and characterization of MSCs

MSCs were isolated from umbilical cord bloods from healthy births. Each cord blood sample was tested for communicable diseases such as HBV, HCV, HIV and Syphilis. The isolated cells were cultured to test for bacteria and fungus, endotoxins, and to insure viability (Table 1).

Infusion and safety evaluation

1.25 ml of 1.0 $\times 10^8$/5 ml stem cells stem cells were suspended in 100 ml of saline and usually infused in the patient no more than one hour. To determine the overall safety of the use of intravenous infusion of UC-MSCs, subjects were followed up by the clinic within 24 hours, closely monitored for the first two weeks, and then followed up by analysis of specific biomarkers associated with inflammation, as well as a general blood panel for safety and any additional effects/secondary outcome measures.

Blood work results analysis

On the base of comparative analysis of initial and 3 months follow up blood work results of 20 patients, undergoing stem cell treatment, we can make the following conclusions:

1. Blood work results (up to 90 tests) of 20 patients mostly did not reveal deteriorations of blood work markers.
2. Blood tests (general blood panel and specific biomarkers associated with inflammation), carried out before stem cell treatment and within three months after stem cell treatment, allow, with high degree of probability, to conclude that introduction of stem cells doesn't influence blood markers in patients. Hence, assuming that the infusion of stem cells with 50% probability can lead to changes of blood markers (50% is

the maximum entropy), almost with 100% of probability it is possible to conclude that this treatment doesn't lead to essential changes in blood markers and the stem cell treatment was safe for the patients.

3. Ten patients have significant improvement of some blood work markers (Table 2).

N	MNC* Count	Viability
1	$1.42x10^7$	**85%**
2	$1.55x10^7$	**82%**
3	$1.58x10^7$	**82%**
4	$1.86x10^7$	**85%**
5	$1.28x10^7$	**83%**
6	$1.68x10^7$	**81%**
7	$1.77x10^7$	**85%**
8	$1.28x10^7$	**82%**
9	5.5×10^8	**85%**
10	5.4×10^8	**85%**
11	4.2×10^8	**84%**
12	4.0×10^8	**84%**
13	4.0×10^8	**84%**
14	4.8×10^8	**85%**
15	4.2×10^8	**84%**
16	4.0×10^8	**85%**
17	4.6×10^8	**85%**
18	4.1×10^8	**85%**
19	4.2×10^8	**90%**
20	3.7×10^8	**85%**

Table 1: MNC count and viability of 20 patients.
(*Mononuclear Cells (MNC), Each frozen tube of umbilical cord derived MSC was thawed and the viability of thawed cells was evaluated with the trypan blue exclusion test. In average stem cells viability was 84,3% ± 0,42% (Descriptive statistics: Mean = 84,3%; Std error = 0,42%)).

Follow up protocols and questionnaires

At 0, 3, 6 month intervals the patient were interviewed and asked to fill out questionnaires. Analysis of different indicators of chronic inflammation and anti-aging included in initial, 24-hours, two weeks and three months protocols showed that stem cell treatment was safe for the patients; there were no adverse reactions. Moreover data from follow up protocols demonstrate significant improvement in some parameters (Table 3 and Figure 1).

Discussion

Early clinical data indicates that MSCs, either directly or by inducing an anti-inflammatory milieu, can be used for tissue repair in toxic injury or fistulas in Crohn's disease [19,20]. Clinical results of patients with neurological disorders such as amyotrophic lateral sclerosis or spinal cord injury seem to be encouraging as well [21,22]. In addition, MSC applications to promote wound healing have demonstrated safety and efficacy in published pilot studies [23,24].

Our study of blood test markers (general blood panel and specific biomarkers associated with inflammation) of 20 patients with chronic inflammation demonstrates that there is no significant changes before and after stem cell treatment and the stem cell treatment was safe for the patients. Moreover, ten patients showed significant improvement in some blood work panels (Figure 2).

Many clinical studies and animal experiments have confirmed that the injection of MSCs has favorable effects on wound repairing, immunomodulation, and anti-apoptosis via a paracrine effect or differentiation [25,26]. Recent studies also revealed that adipose-derived stem cells improve wrinkles resulting from photo-aging and promote collagen synthesis and epidermal thickening of photo-aged fibroblasts *in vitro* [27]. Nakagawa et al. suggest that hMSCs together with bFGF in a skin defect model accelerate cutaneous wound healing as the hMSCs transdifferentiate into the epithelium [28]. Zhang et al.

Blood Work Tests and Panels		N of patients	Normal blood test results with no changes	Abnormal blood test results with no improvement	Improved blood work results	
					N	Patients ID Number
Lipid Panel	Triglycerides	18	10 (55,6 ± 12,1%)	4	4	002-14 008-15 010-15 014-15
	Cholesterol/ HDL Ratio	7	6 (85,7 ± 14,3%)	0	1	002-14
	VLDL	8	7 (87,5 ± 12,5%)	0	1	010-15
Total: from 8 patients with abnormal blood test result 4 patients showed improvement (**50.0 ± 18,9%**)						
Liver Enzymes	AST	19	16 (84,2 ± 8,6%)	1	2	007-15 011-15
	ALT	19	17 (89,5 ± 7,2%)	1	1	010-15
Total: from 5 patients with abnormal blood test result 3 patients showed improvement **(54.8 ± 24,5%)**						
Comprehensive Metabolic Panel	Glucose Level	19	16 (84,2 ± 8,6%)	2	1	014-15
	Sodium Serum	18	16 (88,9 ± 7,6%)	0	2	011-15 029-15
	Bilirubin, Total	20	15 (75,0 ± 9,9%)	4	1	014-15
	BUN	19	17 (89,5 ± 7,2%)	1	1	033-15
Total: from 12 patients with abnormal blood test result 4 patients showed improvement **(33.3 ± 14,2%)**						
Complete Blood Panel	Lymphocytes	18	16 (88,9 ± 7,6%)	1	1	006-15
	Platelets	18	15 (83,3 ± 9,0%)	1	1	027-14
	Hematocrit	18	16 (88,9 ± 7,6%)	1	1	007-15
Total: from 6 patients with abnormal blood test result 3 patients showed improvement **(50.0 ± 22,4%)**						

Table 2: Description of blood work panels of patients with improved blood tests (From eight patients with abnormal Lipid Panel, four patients showed improvement (50.0 ± 18,9%). From five patients with abnormal Liver Blood Tests, three patients showed improvement (54.8 ± 24,5%). From twelve patients with Comprehensive Metabolic Panel, four patients showed improvement (33,3 ± 14,2%). From six patients with abnormal Complete Blood Panel, three patients showed improvement (50,0 ± 22,4%).)

Parameters	24 hours after treatment	2 weeks after treatment	3 months after treatment
Improved skin	5,3 ± 5,3	26,3 ± 10,4	42,1 ± 11,6
Accelerated hair and nails growth	-	15,8 ± 8,6	42,1 ± 11,6
Increased Energy Level Improved Libido Improved mood	57,9 ± 11,6	63,2 ± 11,4	73,7 ± 10,4
Improved sleep	-	10,5 ± 7,2	10,5 ± 7,2
Sleeping difficulties	21,1 ± 9,6	26,3 ± 10,4	31,6 ± 11.0
Pain relief	15,8 ± 8,6	21,1 ± 10,4	-

Table 3: Changes in indicators associated with chronic inflammation and anti-aging 24 hours, 2 weeks and 3 months after stem cell treatment (Follow up protocols from 20 patients showed increased energy level (73,7 ± 10,4), improved skin (42,1 ± 11,6) and accelerated hair and nails growth (42,1 ± 11,6)).

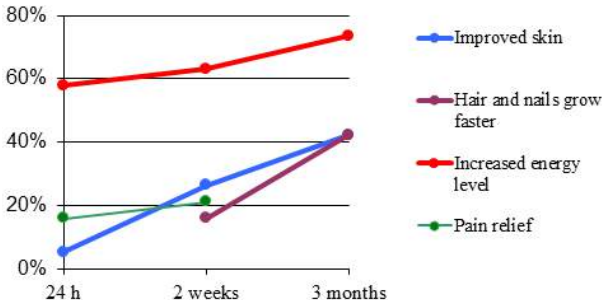

Figure 1: Changes in indicators associated with chronic inflammation and anti-aging 24 hours, 2 weeks and 3 months after stem cell treatment. Follow up protocols demonstrate significant improvement in energy level, skin condition, hair and nails growth.

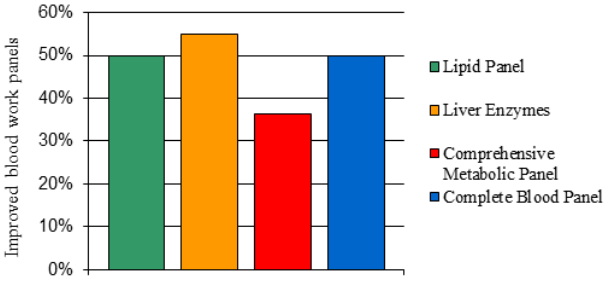

Figure 2: Improvement in blood work panels of 10 patients. Ten patients showed significant improvement in some blood work panels - Lipid Panel, Liver Blood Tests, Comprehensive Metabolic Panel and Complete Blood Panel.

demonstrated that MSCs may contribute to the regeneration of skin during aging [29]. Several interesting studies have been done in the last few years to investigate the role of stem cells in alopecia [30]. Fukuoka et al. demonstrated that hair regenerative therapy was effective for hair growth and is a potential alternative for hair regeneration in patients who are unwilling or unsuitable to undergo traditional surgical hair transplantation [31]. In our study, follow up protocols from 20 patients with chronic inflammation demonstrate that energy level, hair, nails and skin conditions may improve significantly following stem cell infusion (Figure 3).

In summary, intravenously administered human cord blood

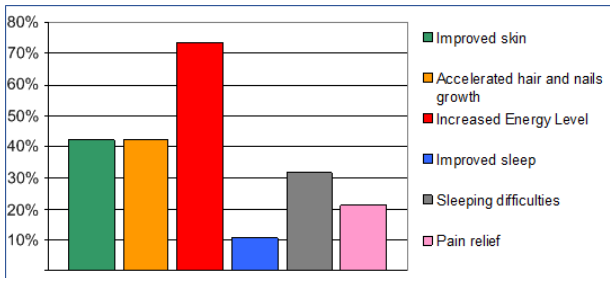

Figure 3: Significant improvement in energy level, skin condition, hair, nails growth following stem cell treatment. Analysis of different indicators of chronic inflammation and anti-aging included in initial, 24-hours, two weeks and three months follow-up protocols showed improved skin, accelerated hair and nails growth, increased energy level.

stem cells were safe for the treatment of symptoms related to chronic inflammation. Further close monitoring of 20 patients and inclusion of more patients with chronic inflammation are necessary to fully characterize the advantages of human cord blood stem cells application in treatment of symptoms related to chronic inflammation.

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