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Safety study of cultured human Wharton's Jelly mesenchymal stem cell therapy for multiple indications – a retrospective descriptive study

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Abstract

Objective: **Human umbilical cord Wharton's Jelly derived MSCs (WJ-MSCs) are reported as the most potent cell source of mesenchymal stem cells, however they remain understudied in comparison to autologous sources. This study aimed to evaluate the safety of WJ-MSC therapy for a range of conditions and administration routines, including intravenous, intrathecal, and intraarticular delivery.**

Patients and Methods: **22 subjects were retrospectively evaluated for adverse events following treatment with 1x10^8 WJ-MSCs for a range of conditions including neurological and osteoarthritic indications. Subjects were treated at Blue Horizon International (BHI) clinical sites; 13 subjects at BHI Slovakia (Nemocnica Malacky hospital, Slovakia) and 9 subjects were treated at BHI Jamaica (Montego Bay St. James and Ochos Rios, Jamaica) between 2018 to 2021. Subjects received 1 – 3 dosages of WJ-MSC via intravenous, intrathecal, or intraarticular administration depending on the indication.**

Results: **Subjects were followed on for 6-months and the incidence of adverse events recorded. In total this study reported AEs in 3 subjects from the 32 doses administered in this study, resulting in an AE rate of 9.3%. Reported AEs consisted of chills and headaches both transient and mild, and resolved without concern. Blood profiling of 75 markers for health and disease in a single subject reported that WJ-MSC treatment poses no hematological safety concern, with only one dietary related marker showing marked change during the follow up period. In contrast, several out of reference hematological markers were corrected 8-months after WJ-MSC therapy.**

Conclusions: **We highlight the minimal occurrence of adverse reactions, most commonly chills and headache associated with intrathecal administration, following WJ-MSC therapy. Overall, this study supports the use of WJ-MSC therapy for various indications and provides safety data for future prospective studies.**

Introduction

Mesenchymal stem/stromal cells (MSCs) are the leading candidate for regenerative medicine applications due to their established immunomodulatory ability, hypo-immunogenicity, regenerative capabilities and proven clinical safety. MSCs are multipotent, non-hematopoietic and have the capability for self-renewal and differentiation. MSCs can be isolated from many different tissues, most commonly bone-marrow, adipose, or umbilical cord (cord blood or Wharton's Jelly) origins[1-4]. The therapeutic

effect of MSC therapy arises largely through immunomodulatory repair mechanisms. MSCs detect and home to sites of inflammation and damage[5,6], where they exhibit a dose-dependent antiproliferative effect on T and B lymphocytes, dendritic cells and natural killer cells[7,8]. The reduction in local inflammation at the injury site provides a suitable environment for repair, which is furthered by secretion of trophic factors from MSCs that promote cell survival[9], angiogenesis[10] and accelerate tissue regeneration[11]. The pharmacokinetic characteristics and *in vivo* biodistribution of intravenous MSC delivery is well defined and non-toxic in many species, including dogs[12], rat[13], mice[14], sheep[15], and non-human primates[5,16,17]. These studies have characterized how MSCs distribute immediately under normal physiological conditions to the lungs after intravenous infusion, and later are found in the liver, spleen, bone marrow and kidneys[13,14,17]. If injury or inflammation is present, MSCs will subsequently migrate to the leading areas of damage, as identified in the injured muscle, skin, bone marrow, thymus and gut following total body irradiation in non-human primate[5,16,17].

Safety is the paramount concern during the development of any new therapeutic intervention. Human MSC (hMSC) therapy presents an impeccable safety profile. A meta-analysis of 36 clinical trials of human MSC therapy reported no serious adverse reactions, including no association with acute toxicity, thromboembolism, abnormal cell growths, neurological deterioration, or death[18]. This study reported the only adverse reaction as transient fever occurring in a subset of patients to a particular preparation of MSCs, with no long-term health concern. Further studies exemplify the safety of hMSC therapy which is routinely used with no severe adverse reactions reported[19-24]. Further, hMSC therapy presents no health concerns over long term follow ups. A 5-year study post hMSC treatment in stroke patients has reported no significant adverse reactions observed in the treatment group versus the control[25].

Blue Horizon International (BHI) has to date treated thousands of patients with hMSCs without any serious adverse events. Published research from BHI treatments continues to contribute to the expanding safety data supporting the use of hMSCs for a range of human conditions. We recently published a retrospective cohort study to evaluate the safety and efficacy of adipose tissue derived MSC therapy for osteoarthritis[26]. Evaluation of 350 patients receiving the therapy showed a significant improvement in pain levels and mobility, and critically, reported no severe adverse events or complications. Prior, we published data on the safety of MSC-containing cord blood therapy in 30 patients with spinal cord injury[27]. No subjects developed adverse reactions, further demonstrating the safety of hMSC therapy. Our clinical trial data for autologous MSC therapy as a spinal cord injury treatment in 20 patients reported no severe adverse effects[28]. The most common adverse event, fever, and headache disappeared without treatment within 24 to 48 hours. To provide further safety and immunogenicity data, we characterized the blood profile and immune response in 29 patients receiving human umbilical cord blood derived MSC treatment for chronic inflammation[29,30]. Our data demonstrated that no essential changes in blood markers (including general health blood test panel and inflammatory markers) occurs following stem cell treatment and when followed up for 3 months.

The use of allogenic Wharton's Jelly derived MSCs (WJ-MSCs) has many advantages over autologous MSCs in which a patient's own cells are harvested from bodily stores. This includes circumventing the pain and healing process of invasive stem cell harvesting from a patient. Furthermore, MSCs of umbilical cord Wharton's Jelly origin offer the highest level of potency for therapeutic benefit as they exist in a more naive state than adult MSCs, and thus exhibit increased proliferation ability and anti-inflammatory effects[31]. Specifically, WJ-MSC administration is safe and effective for many indications, including in COVID-19[32], acute graft versus host disease[33], and type 2 diabetes[34], with long term safety confirmed over a 3 year follow on. Further, WJ-MSCs illicit no infusion-related toxicity, no development of treatment related adverse events, nor ectopic tissue formation even at high dosages[33,35]. In this study, we confirm the safety of human allogeneic WJ-MSCs delivered at a high dose (administration of 1 x 10^8 cells total), via multiple delivery routes (intravenous (IV), intrathecal (IT) or intraarticular (IA)), and in conjunction with Mannitol in some cases, for the treatment of various indications. Mannitol is a blood-brain barrier permeabilizer that can facilitate intravenously delivered stem cells to exert therapeutic benefits on the central nervous system, significantly improving recovery in pre-clinical stroke and traumatic brain injury[36-41]. Therefore, Mannitol provides a useful adjunct for subjects unable to tolerate intrathecal administration.

Patients and Methods

Study Subjects and Procedures

This retrospective study of 22 subjects that were treated with allogeneic human WJ-MSCs at BHI clinical sites between 2017 to 2021. All patients that were treated with human WJ-MSCs for any indication were included in the study. Participants were to be excluded if they had an active systemic infection or an active malignancy during the treatment phase. 13 subjects were treated at BHI Slovakia (Nemocnica Malacky Hospital, Slovakia) and 9 subjects were treated at BHI Jamaica (Montego Bay St. James and Ochos Rios, Jamaica) who were included in the study. Subjects were followed up to a minimum of 6 months post treatment.

Grouped subject characteristics are detailed in Table **1**. Of the 13 subjects treated at BHI Slovakia, 10 were male (77%) with mean age of 42 (range 24 – 78), and 3 were female (23%) with a mean age of 62 (range 59 – 64). Of the 9 subjects treated at BHI Jamaica, 7 were male (77.8%) with mean age of 40 (range 25 – 59), and 2 were female (22.2%) with a mean age of 50 (aged 48, 51). Subject specific characteristics, indications and treatment modalities are listed in Table 2.

The study was approved by the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (IRCM-2022-313, IRCM-2022-330, IRCM-2022-331, approved April 28, 2022) and by the Ministry of Health of the Slovak Republic. The BHI Jamaica clinic and internal research studies are licensed with approval from the Minister of Health of Jamaica. 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 2013[42]. All subjects provided written informed consent for inclusion in the study.

Cell isolation and expansion

WJ-MSCs were isolated from the Wharton's Jelly fraction of umbilical cord tissue donated with consent of the mother following live birth. The umbilical tissue was cleaned and placed in cultivation medium (79% DMEM (low glucose), 20% FBS, 1% Penicillin-Streptomycin) and incubated at 37°C, 5% CO2, 90% humidity for 21 days. Cultivation medium was changed on day 7, 10 and 15. After 21 days, the cell culture was quality checked for blood cell cultivation and sterility. The WJ-MSCs were

Table 1. Grouped indication characteristics and AEs.

Indication	N	Sex	Mean Age (range)	#Doses	Delivery Route	Adverse Reaction
BHI Slovakia						
Osteoarthritis (total)	6	4M, 2F	47 (24 – 78)	1	IA	No
Knee	4	M	39 (34 - 43)	1	IA	No
Hip	1	F	43	1	IA	No
Knee & Hip	1	F	59	1	IA	No
Stroke	2	1M, 1F	62.5 (61, 64)	2	IV + IT	Headache (F)
Stroke with MI	1	M	58	2	IV + IT	No
Spinal cord injury	2	M	25 (24, 26)	2	IV + IT	No
Hypoxic brain injury	1	M	3.5	2	IV + IT	No
Vascular insufficiency with diabetic wounds	1	M	78	2	Locally + IV	No
BHI Jamaica						
Osteoarthritis	1	M	54	2	IV	Chills
Muscular weakness	1	M	41	1	IV + Mannitol	Chills, Headache
Neurological spasms	1	F	51	1	IV + Mannitol	No
Age-related decline	2	M	35 (29, 40)	1	IV, IV + Mannitol	No
Multiple Sclerosis	1	F	48	3	IV + IT	No
Stroke	1	M	59	3	IV + IT	No
Hip pain	1	M	30	1	IV	No
Knee pain	1	M	25	2	IV	No

M = Male, F = Female, IA = Intraarticular, IV = Intravenous, IT = Intrathecal, MI = Myocardial Infarction

Table 2. Grouped indication characteristics and AEs.

Subject ID	Age	Sex	Diagnosis	Doses	Delivery	Adverse events
SK1	78	M	Vascular insufficiency, diabetic wounds	2 (6 months apart)	Locally + IV	No
SK2	24	M	Spinal cord injury	2 (3 months apart)	IV + IT	No
SK3	64	F	Stroke	1	IV + IT	Headache
SK4	61	M	Stroke	1	IV + IT	No
SK5	58	M	Stroke, Myocardial infarction	2 (6 months apart)	IV + IT	No
SK6	3.5	M	Hypoxic brain injury	2 (3 months apart)	IV + IT	No
SK7	26	M	Spinal cord injury	2 (7 months apart)	IV + IT	No
SK8	63	F	Knee Osteoarthritis	1	IA	No
SK9	59	F	Knee & Hip Osteoarthritis	1	IA	No
SK10	56	M	Knee Osteoarthritis	1	IA	No
SK11	43	M	Hip Osteoarthritis	1	IA	No
SK12	34	M	Knee Osteoarthritis	1	IA	No
SK13	41	M	Knee Osteoarthritis	1	IA	No
JM1	41	M	Muscular Weakness	1	IV + Mannitol	Chills, headache
JM2	54	M	Osteoarthritis	1	IV	Chills
JM3	51	F	Neurological Spasms	1	IV + Mannitol	Chills, slight headache
JM4	40	M	Age-related decline	1	IV + Mannitol	No
JM5	48	F	Multiple Sclerosis	3 (3 days between doses 1 and 2, then 4 months)	IV + IT	No
JM6	59	M	Stroke, left arm and left leg weakness	3 (5 days apart)	IV + IT	No
JM7	25	M	Knee pain	2 (3 months apart)	IV	No
JM8	30	M	Hip pain	1	IV	No
JM9	29	M	Age-related decline	1	IV	No

M = Male, F = Female, IA = Intraarticular, IV = Intravenous, IT = Intrathecal, MI = Myocardial Infarction

dissociated using trypsin and cryopreserved at passage 4 in 10% DMSO. Cells were characterized for positive expression of CD29, CD44, CD73, CD90, CD105, CD166 markers and negative for non-MSC markers CD11b, CD14, CD19, CD31, CD34, CD45, CD79 and HLA-DR[43]. WJ-MSCs were collected and processed under current good manufacturing practice (cGMP) and current good tissue practice (cGTP) specifications and follows a routine protocol across study sites. WJ-MSCS underwent initial pathogen testing for a range of infectious agents prior to cryopreservation or administration. Cell viability, identity and safety was confirmed following low-passage expansion.

Cell Infusion

Cells were thawed in a water bath, centrifuged, and resuspended for infusion. At the Jamaica site, cells were resuspended in 50 mL of normal saline solution. In the Slovakian site, the patient's own platelet rich plasma (PRP) was combined with saline to make a 20% PRP solution. For intravenous delivery, the cell suspension was filtered through a 170 to 260-micron filter to remove clots and infusion was maintained at a rate of 100 milliliters per hour. For IV delivery only, 1 x 10^8 cell dosage was administered. For intrathecal administration, 2.5 mL of WJ-MSC infusion solution was administered consisting of 1.0 mL patients own PRP (Slovakia) or saline (Jamaica) and 1.5 mL WJ-MSC suspension. Subjects were placed in the lateral position and a board-certified anesthesiologist sterilized the lumbar area prior to injection of 2% lidocaine for anesthesia. A spinal needle was inserted under sterile technique into the spinal canal and 2.5 mL of cerebral spinal fluid was aspirated, and the volume replaced with the corresponding infusion of WJ-MSCs. For IV and intrathecal delivery, 7.5 x 10^7 cells are administered intravenously, and 2.5 x 10^7 cells were delivered by intrathecal injection (total cell dosage delivered across both delivery routes amounts to 1 x 10^8 cells). Where intrathecal administration was not tolerated by the subject, 1 x

Table 3. Hematological safety evaluation of subject JM4 pre and post WJ-MSC treatment.

Marker	Pre-Treatment	Flag	Post-Treatment	Flag (+7 months)	Reference Interval/ Units
Hematocrit	52.5	High	51.3	High	37.5 - 51 %
Creatinine	1.58	High	1.3	High	0.76 - 1.27 mg/dL
A/G ratio	2.3	High	2.4	High	1.2 - 2.2
Hemoglobin	18	High	17	In reference	13 - 17.7 g/dL
BUN	27	High	24	In reference	06 to 24 mg/dL
AST	62	High	36	In reference	0 - 40 IU/L
Triglycerides	184	High	51	In reference	0 -149 mg/dL
eGFR	54	Low	68	In reference	>59 mL/min/1.73
Protein	1+	Abnormal	trace	In reference	Negative - trace
Ketones	Trace	Abnormal	Negative	In reference	Negative
Occult Blood	Trace	Abnormal	Negative	In reference	Negative
Specific Gravity	>1.030	Abnormal	>1.030	Abnormal	1.005 - 1.030
Hep B Core Ab	Positive	Abnormal	Positive	Abnormal	Negative
T Pallidum Ab	Reactive	Abnormal	Reactive	Abnormal	Non-reactive
LDL Cholesterol	82	In reference	114	High	0 - 99 mg/dL

A/G = albumin/globulin, BUN = Blood urea nitrogen, AST = aspartate aminotransferase, eGFR = Estimated glomerular filtration rate.

10^8 cells was administered by IV infusion following pretreatment with Mannitol. At minute zero 25% mannitol was introduced into 100 cc of saline solution. The Mannitol solution was infused by intravenous injection over a 10- to 15-minute timeframe, followed immediately by IV infusion of WJ-MSCs as described above. For intraarticular injection, 2.5 x 10^7 cells are injected directly into the affected joint in combination with 7.5 x 10^7 cells administered intravenously as previously described (total cell dosage by both delivery routes amounts to 1 x 10^8 cells).

Statistical Analysis

No statistical analysis was performed in this study as it is a descriptive reporting of cases. Age was reported as mean with range for grouped subjects.

Results

Adverse events and safety evaluation

In total, 22 subjects treated for a range of conditions were assessed for serious (SAE) or mild adverse events (AE) (Table 2). In the Slovakian cohort of 13 subjects, a single AE was reported as a transient headache in one stroke patient (ID: SK3, female, 64 years old) that received IV and IT administration of WJ-MSCs. This AE was deemed related to the administration procedure, as headache following IT administration has been reported in 2% of subjects elsewhere[22]. The AE was transient and self-resolved without clinical concern.

In the Jamaican cohort of 9 subjects, 2 subjects reported AEs. One subject (ID: JM2, male, 54 years of age) who received a single IV infusion of WJ-MSCs for osteoarthritis experienced chills persisting for 45 minutes post administration. Chills is a relatively common reaction to cell administration (see discussion) and this AE resolved without clinical concern. Another subject (ID: JM3, female, 51 years of age) who received a single IV infusion of WJ-MSCs for neurological spasms experienced transient chills and a slight headache immediately post administration. Both AEs self-resolved without clinical concern.

In total this study reported AEs in 3 subjects from the 32 doses administered in this study, resulting in an AE rate of 9.3%. Notably, most of these AEs were both transient and mild, and resolved without concern.

Single Subject Case Study

Complete blood profiling was conducted pre- and post-treatment to assess changes in blood markers that may be associated with the cell treatment. Here, we report interim results composed of a single subject case study (subject ID: JM4, male, 40 years old). This case study evaluated changes in the blood profile of a subject that received one administration of WJ-MSCs by IV infusion in conjunc-

tion with Mannitol, for age-related decline. The subject reported no AEs during or post treatment. Blood markers flagged as outside of their respective reference intervals pre- or post-treatment were noted and compared to the alternative time point. Fourteen blood markers were flagged as high, low, or abnormal to the reference range in the subject prior to WJ-MSC administration (Table 3). When evaluated at 7-months post cell therapy, 8 of these out-of-reference blood markers (hemoglobin, BUN, eGFR, AST, protein, ketones, occult blood and triglycerides) were corrected to within normal reference intervals. Of the remaining 6 out-of-reference markers; 2 were improved towards the normal reference interval (hematocrit, creatinine), 2 were infectious disease antibody tests (HepB, T Pallidum), and 1 marker was elevated slightly (A/G ratio). Only 1 blood marker associated with diet, LDL cholesterol, was elevated to outside of the normal reference interval in the post-treatment assessment *vs.* pre-treatment.

Therefore, blood profiling of 75 markers for health and disease in these subject reports that WJ-MSC treatment poses no hematological safety concern, with only one dietary related marker showing marked change during the follow up period which is likely unrelated to the cell administration.

Discussion

Evaluation of reported adverse events

Two incidents of headaches following cell administration were reported by 2 subjects in this study. These AEs occurred following administration via the intrathecal or intravenous in combination with Mannitol routes. Headaches are a common side effect of intrathecal catheter insertion with "headache attributed to intrathecal injection" included in the International Classification of Headache disorders since its second edition[44]. Their incidence is well documented in literature concerning chemotherapy, pain management and lumbar punctures. It is widely accepted that risk for headache appears to be related to the size of the needle, age and sex of the patient, number of dural punctures (attempts), previous spine surgery, and direction of the bevel[45]. It is hypothesized that a headache occurs due to leak of CSF from the subarachnoid space, causing a drop in intracranial pressure[46,47]. Research estimates that up to a third of chemotherapy patients and lumbar puncture patients will experience these headaches post-catheter insertion and although bothersome, this effect is typically short-lived and easily managed by analgesia and fluid intake[48,49]. Previous literature does not indicate any significant correlation between dosage of cells and incidence of headache. Headache has been reported as an AE post intrathecal administration of a range of lesser doses that are utilized in this study. Doses of 4.2 x 10^6 cells, 3×10^7 cells, 5.3 x 10^6 cells and 1×10^6 cells per kg have each been associated with incidence of headache post-administration of stem cells via intrathecal catheter[21,22,50-52]. Therefore, it can be deemed that the occurrence of headaches is not associated with the increased dosage of 1 x 10^8 cells delivered in the current study. Additionally, headache is a commonly accepted side effect of intravenous Mannitol treatment[53]. Considering the prevalence and acceptance of this reaction across other intrathecal procedures, dosages and Mannitol use, the incidence of headache in this study is non-remarkable. Further, the occurrence of headache may be a result of the intrathecal administration route or Mannitol use rather than the WJ-MSC therapy.

Two incidents of subjects experiencing chills post treatment were observed in this study. Current cell practice uses dimethyl sulfoxide (DMSO) as a protective agent to maintain cell viability in the cryopreservation process. However, studies have demonstrated a link between DMSO toxicity and incidence of chills in patients who receive cryopreserved cells as opposed to cells that have been freshly harvested prior to transplantation or transfusion[54-56]. In a study directly comparing the incidence of AE's in patients receiving cryopreserved cells or freshly harvested cells, chills were reported in 31.1% of patients transfused with cryopreserved marrow, compared to 1.4% of those who received fresh allogeneic marrow[57]. In the current study, chills were only experienced by a small percentage of subjects in the Jamaica cohort who received cells that were not washed prior to infusion. Without placebo control it is difficult to determine which element caused the reaction, such as the cells or the procedure. However, previously reported evidence of DMSO toxicity and chills associated with cryopreservation suggests that this could be a defining factor. At present, further investigation is being conducted into the cause of reported chills.

Case study evaluation

No safety concerns were highlighted upon review of the single case study described above. Of the 14 abnormal blood markers identified, eight were improved and corrected inside reference intervals when assessed 7 months post treatment. The most dramatic change that occurred was that of the triglycerides. Although some markers such as hemoglobin, hematocrit and protein were only fractionally elevated at pre-treatment, levels of triglycerides were significantly raised. This measure was comfortably within normal range 7 months post-treatment. Derived from glycerol and three fatty acids, triglycerides are a type of lipid found in the blood, with elevated levels of this component contributing to cardiovascular risk[58]. As hypertriglyceridemia is typically associated with poor diet, lifestyle factors or poorly controlled diabetes, it is difficult to evaluate or ascertain the impact of the MSC treatment versus potential lifestyle changes employed by the subject post-administration. However, research has indicated that MSC therapy has the potential to reduce lipid imbalance in the blood with promising results emerging from clinical trials. Cell therapy has been found to be beneficial in altering a dyslipidemic profile, with documentation of the use of bone-marrows MSCs and adipose-derived MSCs for this purpose[59-61].

With regard to the single case study, there were some abnormalities specific to liver enzymes pre-treatment. Aspartate aminotransferase (AST) was elevated outside normal parameters during the pre-treatment blood analysis, indicating a mild increase in the amount of liver enzymes being excreted into the bloodstream. Liver damage is typically investigated and characterized through comparison of the ratio of liver enzymes, naming AST and alanine aminotransferase (ALT). In this patient, ALT was measured within normal limits, suggesting an element of liver damage or mild cirrhosis. It is important to note that this patient additionally tested positive for Hepatitis B core antibodies, an infection which can cause a degree of liver damage. Irrespective of the determinant for the elevated AST marker, post-treatment the patient experienced corrected regulation of this enzyme level. Although some aspects of the MSCs ability to repair liver cirrhosis remain unclear, clinical trials utilized MSCs have demonstrated 25-37% reduction in fibrosis and improvement in serum total bilirubin and model for end-stage liver disease scores[62,63]. Further trials are warranted to better understand the correlation between WJ-MSC administration and improvement of these measured hematological markers.

Conclusions

This study reports the safety (up to 6 months post treatment) of hWJ-MSCs when delivered via intravenous (including in combination with mannitol), intrathecal or intraarticular administration for a range of indications. We highlight the minimal occurrence of mild adverse reactions, most commonly chills and headache, following high dosage of $1x10^8$ hWJ-MSCs. Notably, these adverse events were transient and resolved without concern. Hematological profiling of a single subject pre- and post-treatment reports no blood abnormalities and, in the contrary, correction of several biomarkers to within the normal range. We aim to further characterize the long-term safety and efficacy of hWJ-MSC in future studies.

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Ethics approval:
The study was approved by the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (IRCM-2022-313, IRCM-2022-330, IRCM-2022-331, approved April 28, 2022). 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 2013[42].

Informed consent:
All subjects provided written informed consent for inclusion in the study.

Availability of data and material:
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest:
BM, DS, RM and KN are employed by Blue Horizon Therapeutic Sciences. EOG, GSM CT and RG are paid contractors of Blue Horizon Therapeutic Sciences.

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Author Contributions:

BM conceived, designed the study, and treated patients. DS, KN and RM set up the study, obtained the ethical approval, managed the patients, and collected data. DCW prepared the cell product. GS, CT and RG administered the cell therapies and monitored patients. EOG analyzed the data, interpreted results, and wrote the manuscript. RR processed patients. All authors read and approved the final version of the manuscript.

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