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COMBINATION BM-MSC WITH BM-MNC IS BETTER THAN BM-MNC ALONE IN RESOLUTION OF LARGE ISCHEMIC ULCERS: A PHASE II/III CLINICAL RANDOMISED STUDY

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Background: We previously demonstrated that combination bone marrow derived cultured mesenchymal stromal cell (BM-MSC) with bone marrow derived unselected mononuclear cell (BM-MNC) may help induce angiogenesis in diabetic patients with critical limb ischemia. In this new randomized Phase II/III clinical trial, we compared autologous BM-MSC with BM-MNC (Group A) versus BM-MNC alone (Group B) in severe lower limb ulcers secondary to critical limb ischemia with the aim of avoiding amputations.
Methodology: Seven consecutive patients were randomized and underwent bone marrow aspiration (BMA) to collect 500 mls that was then centrifuged and separated to obtain the unselected BM-MNC fraction. Group A (N = 3) patients underwent intra-muscular injection of the BM-MNC 1 hour after BMA on the affected limb, followed by intra-muscular injection of *in-vitro* expanded BM-MSC. Group B (N = 4) patients underwent injection of BM-MNC after BMA only. One patient in Group B had ulcers on each leg.
Results: All patients tolerated the BMA and injection well. The ulcer size at baseline, 1 month, 2 months and 5 months were as follows: Group A (22.5 ± 14.2 vs. 6.3 ± 10.1, 2.5 ± 3.5, 0.0 ± 0.0 cm^2; p = 0.066). Group B (25.4 ± 12.0 vs. 29.1 ± 22.8, 45.2 ± 41.7, 54.8 ± 52.7 cm^2; p = 0.842). All ulcers in Group A were completely healed by 5 months irrespective of baseline size (10–38 cm^2). In Group B, 2 ulcers (both smaller than 20 cm^2) resolved while 3 ulcers (all greater than 20 cm^2) enlarged in size. Digital subtraction angiography (DSA) showed restoration of peripheral blood flow in all Group A patients. However there were no difference in ankle brachial index at baseline to end of follow–up within both groups.
Conclusion: We have demonstrated that BM-MSC with BM-MNC is superior to BM-MNC alone in the resolution of severe foot ulcer secondary to critical limb ischemia, particularly for large ulcers.

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ALLOGENEIC CORD-DERIVED MSC INFUSION IS SAFE AND IMPROVES METABOLIC FUNCTIONS OF UNCONTROLLED DIABETES PATIENTS

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Background: Insulin resistance causes type II diabetes mellitus (DM) and is characterized by increased serum insulin and eventually insulin depletion. The initial increased insulin state results in increase in inflammation and deranged metabolic function.
Method: 65 patients with uncontrolled diabetes were recruited. Diet, exercise and medications were not altered unless in medical emergencies. Total 50–100 x10^6 C-MSC were infused over 1 or 2 sessions. Blood tests for glycated haemoglobin (Hba1c—marker of glycaemic control), high-sensitivity C-Reactive Protein (hs-CRP, marker of inflammation), fasting LDL cholesterol (LDL-Chol), triglyceride (TG), gamma-glutamyl transaminase and aspartate transaminase (GGT and AST, both markers of fatty liver infiltration), serum creatinine (a marker of renal dysfunction), systolic and diastolic blood pressure (SBP and DBP) were measured at baseline and 6 months. Serum total testosterone was also measured in men only.
Results: All patients tolerated the procedure well. There was significant improvement of Hba1c (7.9 ± 2.0 vs. 7.4 ± 1.7%; P = 0.001), TChol (4.7 ± 1.4 vs. 4.2 ± 1.0 mmol/L; P = 0.011), LDL-Chol (2.5 ± 1.3 vs. 2.1 ± 0.9 mmol/L; P = 0.009) and creatinine (107 ± 115 vs. 97 ± 92 umol/L; P = 0.025). In men, there was also significant improvement in total testosterone (10.3 ± 4.8 vs. 12.3 ± 6.0, P = 0.029). There were trends for improvement of hs-CRP, TG, AST and DBP. The reduction is Hba1c was most significant for very poorly controlled diabetics (9.4 ± 1.9 vs. 8.4 ± 1.8%; P < 0.001). There was a modest inverse correlation between HbA1c and total testosterone (r = –0.49, P < 0.001).
Conclusions: Allogeneic C-MSC infusion is safe in diabetes patients and is associated with improvement in their metabolic functions including cholesterol and renal function. Further study with increased number of infusions and longer observation period may be warranted to observe the sustainability of the response.

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WILL NOT BE PRESENTED

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RAPIDLY-GENERATED EBV-SPECIFIC T CELLS (EBVST-CELLS) TO TREAT TYPE 2 LATENCY LYMPHOMA

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Up to ~30% of Hodgkin and non-Hodgkin lymphomas carry the EBV genome and express the viral latency proteins EBNA-1, LMP-1, LMP-2 and BARF-1 in a pattern known as Type 2 latency. We have previously shown that EBVSTs specific for Type 2 latency antigens can be expanded from the peripheral blood of lymphoma patients by stimulation with dendritic cells and lymphoblastoid cell lines modified with an adenoviral vector encoding LMP1 and LMP2 and induce clinical responses in over 50% of patients with active disease (Bollard et al J Clin Oncol 2014). To broaden the applicability of this strategy we have sought to shorten the manufacture time and simplify the process, by removing viral-vector components from our manufacturing process and replacing these components with dendritic cells or peripheral blood mononuclear cells pulsed with peptide libraries (pepmixes) spanning the antigens of interest. Responder T-cells are subsequently expanded by restimulation with the same pepmixes presented on autologous, activated T-cells together with HLA-negative K562 costimulatory cells in the presence of cytokines. We initially used IL4 and IL7 but subsequently modified the manufacturing to use IL7 and IL15 with the goal of overcoming T-cell anergy and enhancing the specificity of patient-derived EBVSTs. EBVSTs manufactured using IL7/15 are polyclonal comprising both CD4+ and CD8+ cells and generate VSTs with enhanced proliferative capacity, antigen specificity, and cytotoxicity. The manufacturing time is 3–4 weeks compared with 3–4 months with the original product. We have infused EBVSTs manufactured using both cytokine combinations into 24 patients with multiply-relapsed, EBV-positive lymphoma as adjuvant therapy after stem cell transplantation or chemotherapy in 14 patients and as treatment for disease in 10 patients. No patients had any adverse events attributed to the cell infusion. Of patients in remission at the time of infusion, 2 with IL-4/7-grown EBVSTs and 12 with IL-15/7 grown EBVSTs remain in remission with follow up of 2 to 30 months. Of patients with disease at the time of infusion, one receiving IL-4/7-grown EBVSTs had stable disease and 3 had progressive disease, while of 6 patients with IL-15/7-grown EBVSTs, two had CRs (sustained for 18 + and 6 + months), two had PRs, one had stable disease and one progressed. We are continuing to enroll patients with IL7/15 product and plan to add PD-1 inhibition in patients who have partial responses.

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INTRAVENOUS ADMINISTRATION OF ALLOGENEIC MESENCHYMAL STEM CELLS IN PATIENTS WITH CEREBELLAR ATAXIAS: A PHASE I/IIA CLINICAL TRIAL

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Introduction: Mesenchymal stem cells (MSCs) are immune evasive and can be transplanted to HLA-unmatched allogeneic recipients. Animal studies indicated that transplantation of MSCs improved the motor function in SCA 2 transgenic mice. This is a phase I/II clinical trial aiming to evaluate the safety and efficacy of allogeneic mesenchymal stem cells (MSCs) for the treatment of cerebellar ataxia.
Materials and Methods: Adipose-derived MSCs product, Stemchymal®, was provided by Steminent Biotherapeutics Inc. 7 patients [6 spinocerebellar ataxia type 3 (SCA3) patients and 1 multiple system atrophy-cerebellar type (MSA-C)] were recruited in the trial and received single infusion of 7 × 10^7 cells with