Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
markers, including CRP, ferritin, D-dimer, IL-6, LDH, platelet count, and lymphocyte count, all showed various levels of improvement at day 7 after SBI-101. A comprehensive profiling of 200 exploratory biomarkers and immune cell subsets over time points pre- and post-treatment will be presented to characterize the pharmacokinetic and pharmacodynamic effects of SBI-101 on the immune system. Overall, these preliminary results suggest ex vivo MSC therapy carries significant promise and warrants further study in the treatment of patients with severe COVID-19 requiring CRRT.

Abstracts / Cytotherapy 23 (2021) S17–S207

S21

markers, including CRP, ferritin, D-dimer, IL-6, LDH, platelet count, and lymphocyte count, all showed various levels of improvement at day 7 after SBI-101. A comprehensive profiling of 200 exploratory biomarkers and immune cell subsets over time points pre- and post-treatment will be presented to characterize the pharmacokinetic and pharmacodynamic effects of SBI-101 on the immune system. Overall, these preliminary results suggest ex vivo MSC therapy carries significant promise and warrants further study in the treatment of patients with severe COVID-19 requiring CRRT.

10 Somatic Stem Cells: Mesenchymal Stem/Stromal Cells

MESENCURE—AN ENHANCED CELL THERAPY EXPLICITLY DEVELOPED FOR TREATING ACUTE RESPIRATORY DISTRESS IN COVID-19: FROM BENCHTOP TO BEDSIDE

T. Bronshtein1, D. Ben David1, A. Novak1, V. Kivity1, S. Hamoud4, T. Hayek4, S. Meretzki2

1Research and Development, Bonus BioGroup, Haifa, Israel; 2Bonus BioGroup, Haifa, Israel; 3Regulatory and Clinical Affairs, Bonus BioGroup, Haifa, Israel; 4Department of Internal Medicine E, Rambam Health Care Campus, Haifa, Israel.

Keywords: COVID-19, ARDS, Mesenchymal stromal cells.

Background & Aim: Mesenchymal stromal cells (MSC) have attracted much attention for treating pulmonary manifestations of Covid-19, for which they are already tested in clinical studies. These efforts are, nonetheless, overshadowed by studies predating the pandemic that failed to show MSC efficacy in treating acute respiratory distress syndrome (ARDS). Also, concerns regarding the hemocompatibility of MSCs were raised vis-à-vis their source tissue and administration route, especially in coagulopathic Covid-19 patients. With this in mind, and relying on years of MSC-related experience and manufacturing capacity of clinical-grade material, and technologies developed for the efficient and standardized isolation and cultivation of MSCs, Bonus BioGroup has developed MesenCure—an enhanced allogeneic MSC product for intravenous (IV) injection designed to treat ARDS in Covid-19 patients.

Methods, Results & Conclusion: MesenCure is based on adipose stromal cells (ASC) primed by a combination of biological and physical conditions to improve their potency, stability, and safety. Our data shows that MesenCure, but not unprimed ASCs, have alleviated edema in an acute lung injury (ALI) model by 60% (Fig. 1A) and reduced the leukocytes’ counts in the lung fluids by 40% (Fig. 1B–1E). Three IV administrations of MesenCure were shown to rescue animals from a lethal ALI (Fig. 2). In vitro, MesenCure inhibited the proliferation of activated T cells by >83% compared to <15% inhibition by unprimed ASCs (Fig. 3). Under refrigeration, MesenCure cells retained their immunomodulatory capacity longer than unprimed ASCs representing a more stable product for transplantation with a longer shelf-life. MesenCure cells’ hemocompatibility was found to resemble that of bone marrow MSCs, regarded as safe for IV injection. This was evidenced by 50% lower levels of coagulation factor 3 at the mRNA, protein, and activity levels, as well as a >2-fold higher level of tissue factor pathway inhibitor, expressed on MesenCure cells compared to unprimed ASCs. A GLP toxicity study found MesenCure to be well-tolerated.

Fig. 1 (abstract 10). MesenCure effect in ALI model animals. MesenCure was injected 6 hours post-induction of an ALI model in C57BL mice by IT injection of LPS. Animals were sacrificed 18 hours post-treatment. (A) The effect of MesenCure on the lungs’ weights was measured following lung harvesting from treated model animals compared to lungs harvested from healthy non-treated animals and model animals injected with Vehicle Control or unprimed ASCs. (B–E) The effect of MesenCure on the leukocytes’ counts in the lung fluids was measured on bronchoalveolar lavage fluids (BALF) harvested from treated model animals and subjected to complete blood count protocol in comparison to BALF harvested from healthy non-treated animals, as well as model animals injected with the Vehicle Control item. Results are presented for (B) total white blood cells (WBC), (C) lymphocytes, (D) neutrophils, and (E) monocytes.

Fig. 2 (abstract 10). The effect of repeated MesenCure administrations in a lethal ALI model. MesenCure was injected thrice in 48 hours’ intervals starting 6 hours (0.25 days) post model induction and two and four days after that (arrows designate administrations). Animals’ survival, weights, and clinical scores were recorded until complete recovery was measured on Day 7, three days after the final injection. Results are presented as (A) individual and averaged weight changes (%) in respect to Day 0, as well as (B) individual and median clinical scores reflecting the animals’ overall health as a combination of their appearance, activity, response, and respiratory quality.
Based on our promising preclinical results, Bonus BioGroup has initiated a Phase I/II clinical study to assess the safety and efficacy of MesenCure for treating pulmonary manifestations of Covid-19 in up to 35 severe patients hospitalized at the Rambam Health Care Campus (Haifa, Israel). Encouraging preliminary results have already been obtained and will be presented, emphasizing MesenCure’s potential in Covid-19 and ARDS management.

**Results:**

**Keywords:** Mesenchymal stromal cells, COVID-19, Phase I trial.

**Background & Aim:** Approximately 20% of Ontario hospitalized patients require ICU admission for management of acute respiratory distress syndrome (ARDS) and mortality rates remain high. To date few studies evaluating different treatment options for COVID-19 associated ARDS have shown meaningful clinical impact. Mesenchymal stromal cells (MSCs) are rapidly emerging as promising therapeutics for ARDS due to their immunomodulatory effects, including selective downregulation of major pro-inflammatory cytokine pathways, and enhanced pathogen clearance in septic and ARDS animal models. We conducted a Phase I dose escalation trial of IV infusion of freshly cultured umbilical cord (UC) derived MSCs in adults with COVID-19 induced ARDS to assess its safety and tolerability.

**Methods, Results & Conclusion:** Eligible ICU patients were enrolled within 96hrs of ARDS onset (P/F ratio <300 with PEEP ≥5cm H₂O or on high flow nasal cannula, minimum total flow rate of 40 lpm). There were 3 UC-MSC dose cohorts, with 3 participants per cohort. Participants received repeated doses of UC-MSCs over 3 consecutive days (24±4 hours) according to one of the following dose panels: Panel 1: 25 million MSCs/dose (cumulative dose: 75 million MSCs); Panel 2: 50 million MSCs/dose (cumulative dose: 150 million MSCs); Panel 3: 90 million MSCs/dose (cumulative dose: 270 million MSCs). Participants were monitored for pre-specified MSC transfusion associated AEs or serious unexpected AEs.

Nine participants were enrolled with median age of 68 yrs (range: 57 to 78); median Apache II score of 15 (range: 12 to 17); and median P/F ratio 102 (range 57 to 163). Median time of UC-MSC infusion from ICU admission was 48h17 (range 21h27 to 91h57). The UC-MSCs had a viability of >95%, endotoxin levels of <0.2 EU/mL and were free of any bacterial contaminants. All 3 panels were well tolerated with 0 pre-specified MSC transfusion associated AEs or serious unexpected AEs considered related to the MSCs.

A cumulative dose of 270 million freshly cultured UC-MSCs infused into COVID-19 induced ARDS participants appears safe. These results support the feasibility of our multi-site, blinded, RCT to examine efficacy of UC-MSCs in COVID-19 associated ARDS.