A New Combined Approach for Treatment of Type 1 Diabetes Mellitus By Immunomodulation and Beta Cell Regeneration

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Introduction: Type 1 Diabetes Mellitus (T1DM) is a metabolic disorder defined by hyperglycemia resulting from a defect in insulin secretion by β cells in the pancreas. T1DM results as a consequence of chronic destruction of pancreatic β cells by the immune system, leading to insulin deficiency and subsequent pathologies including neuropathies, nephropathies, retinopathies and cardiovascular diseases. Although the definite cause of immune attack on β cells remains unknown, the mechanisms of the immune attack on β cells have been thoroughly studied, and were shown to comprise of a type 1 T Cell-mediated inflammatory immune response. Several clinical trials have been conducted to manage T1D using various approaches, including insulin pumps, pancreatic transplantation, pancreatic encapsulation, islet cell regeneration, and gene therapy. However, until today, these approaches have not led to the complete rescue of β cells nor to stop the development of T1DM.Recent advances in stem cell research have shown promising therapies for several chronic and untreatable conditions. Stem cells from various sources and types, including autologous bone marrow, cord umbilical blood, and embryonic stem cells, have been utilized in several clinical trials to treat T1DM, with varying outcomes. Our team has developed a two-armed approach; the first arm is aimed at stopping the immune attack on β cells, while the second arm aims at regenerating lost β cells in the pancreas. Results showed decreased immune attack, and β cells regeneration, and subsequent insulin production.

Objective: In this study, we aimed at ceasing the immune attack on β cells through immunomodulation, and regenerating β cells by transplantation of autologous, purified stem cells into the pancreatic arteries.

Materials and Methods: This study consists of phase I and phase II. Phase I pilot study was from 2011-2015, and included four patients with confirmed T1DM, from 13-52 years old. Pre-operatively, patients had an average insulin intake of 50 units per day (20-80), average HbA1c of 9.0 (6.3-12.1), and Fasting Blood Sugar average of 350 (180-650); three patients had 0.00 C peptide, and the fourth (male, 32 years) had 0.23 C peptide. All patients were healthy, non-smokers, non alcoholics, except one (male, 32 years) with retrograde ejaculation. Patients received daily SC injections of 10ug/kg G-CSF (GeSysin, Filgrastim) for 5 days. On day 6, about 200 ml of peripheral blood mononuclear cells (PB-MNCs) were collected from peripheral blood. CD34+, CD133+, and CD271+ stem cells were isolated from PB-MNCs using the CliniMACS(R) System. The purified cell populations were injected into pancreatic arteries of patients using interventional radiology techniques. The remaining fraction of PB-MNCs that did not contain the above stem cell populations were co-cultured with adherent cord blood MSCs for 6 hours. After coculture, patient's autologous PB-MNCs (without MSCs) were injected back into the patient intravenously. Patients were then followed for up to 51 months (average 22 months), with measurements of C-peptide, insulin requirement, HbA1c, and FBS. **Phase II study started on 2015 and is planned to go until 2018.** Twenty-four patients were included in phase II study. Patients are currently enrolling in the study and are still being followed up.

Results: All patients in phase I and phase II studies tolerated the procedures well. For phase I patients, there were no complications over the follow up period (14-51 months). Three out of four patients (75%) in

the T1DM group completely stopped their insulin requirement at 6 month interval follow up. All 4 patients (100%) showed significant improvement in FBS (average 145, range 89-190). C peptide levels showed marked increase in all 4 patients (average 1.01, range 0.74-1.32). Similarly, 3 out of 4 patients showed significant improvement in measured HbA1c levels after 12 months (average 7.0, range 6.2-8.1). For phase II patients the study is still going on and it is too early to draw a meaningful conclusion; however, results are encouraging concerning HbA1c, C-peptide, Auto-antibodies, and Insulin intake.

Conclusion: Our protocol represents hopeful and promising potential for the use of SCT in the treatment of T1DM patients. Future randomized controlled trials are needed to support the results of our pilot study.