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Insulin-secreting adipose-derived mesenchymal stromal cells with bone marrow–derived hematopoietic stem cells from autologous and allogenic sources for type 1 diabetes mellitus

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Abstract

Background aims. Stem cell therapy (SCT) is now the up-coming therapeutic modality for treatment of type 1 diabetes mellitus (T1DM). *Methods.* Our study was a prospective, open-labeled, two-armed trial for 10 T1DM patients in each arm of allogenic and autologous adipose–derived insulin-secreting mesenchymal stromal cells (IS-AD-MSC)+bone marrow–derived hematopoietic stem cell (BM-HSC) infusion. Group 1 received autologous SCT: nine male patients and one female patient; mean age, 20.2 years, disease duration 8.1 years; group 2 received allogenic SCT: six male patients and four female patients, mean age, 19.7 years and disease duration, 7.9 years. Glycosylated hemoglobin (HbA1c) was 10.99%; serum (S.) C-peptide, 0.22 ng/mL and insulin requirement, 63.9 IU/day in group 1; HbA1c was 11.93%, S.C-peptide, 0.028 ng/mL and insulin requirement, 57.55 IU/day in group 2. SCs were infused into the portal+thymic circulation and subcutaneous tissue under non-myelo-ablative conditioning. Patients were monitored for blood sugar, S.C-peptide, glutamic acid decarboxylase antibodies and HbA1c at 3-month intervals. *Results.* Group 1 received mean SCs 103.14 mL with 2.65 $\pm$ 0.8 $\times$ 10^4 ISCs/kg body wt, CD34+ 0.81% and CD45–/90+/73+, 81.55%. Group 2 received mean SCs 95.33 mL with 2.07 $\pm$ 0.67 $\times$ 10^4 ISCs/kg body wt, CD34+ 0.32% and CD45–/90+/73+ 54.04%. No untoward effect was observed with sustained improvement in HbA1c and S.C-peptide in both groups with a decrease in glutamic acid decarboxylase antibodies and reduction in mean insulin requirement. *Conclusions.* SCT is a safe and viable treatment option for T1DM. Autologous IS-AD-MSC+ BM-HSC co-infusion offers better long-term control of hyperglycemia as compared with allogenic SCT.

Key Words: *C-peptide, glycosylated hemoglobin, insulin requirement, insulin-secreting cells, mesenchymal stromal cells, stem cell therapy, type 1 diabetes mellitus*

Introduction

Type 1 diabetes mellitus (T1DM) is the second most common chronic disease of childhood, believed to be autoimmune in nature, characterized by irreversible destruction of insulin-secreting pancreatic β-islet cells and requiring life-long exogenous insulin therapy. Symptoms appear when insulin making the β-cell mass gets reduced by approximately 90%, leading to severe insulin deficiency and hyperglycemia [1]. The incidence of diabetes mellitus (type 2 DM) has been increasing in an epidemic-like fashion in the past two decades globally. India is expected to become the world capital of DM by year 2030 [2–4]. Sporadic cases of hematopoietic stem cell transplantation (HSCT) have been reported with limited success [5]. Stem cell therapy (SCT) offers great promise for cure of many autoimmune diseases, including T1DM. Insulin-secreting cells (ISC) generated from SC represent an attractive alternative [6]. Mesenchymal stromal cells (MSC) have remarkable paracrine effects that can be divided into trophic (“nurturing”), immunomodulatory, anti-scarring and chemoattractant [7]. We have successfully generated insulin-secreting adipose tissue–derived MSCs (IS-AD-MSCs) *in vitro* [8]. We now present our experience of insulin replacement therapy in T1DM patients by co-infusion of *in vitro*–generated IS-AD-MSCs and bone marrow (BM)-derived HSCs. In the

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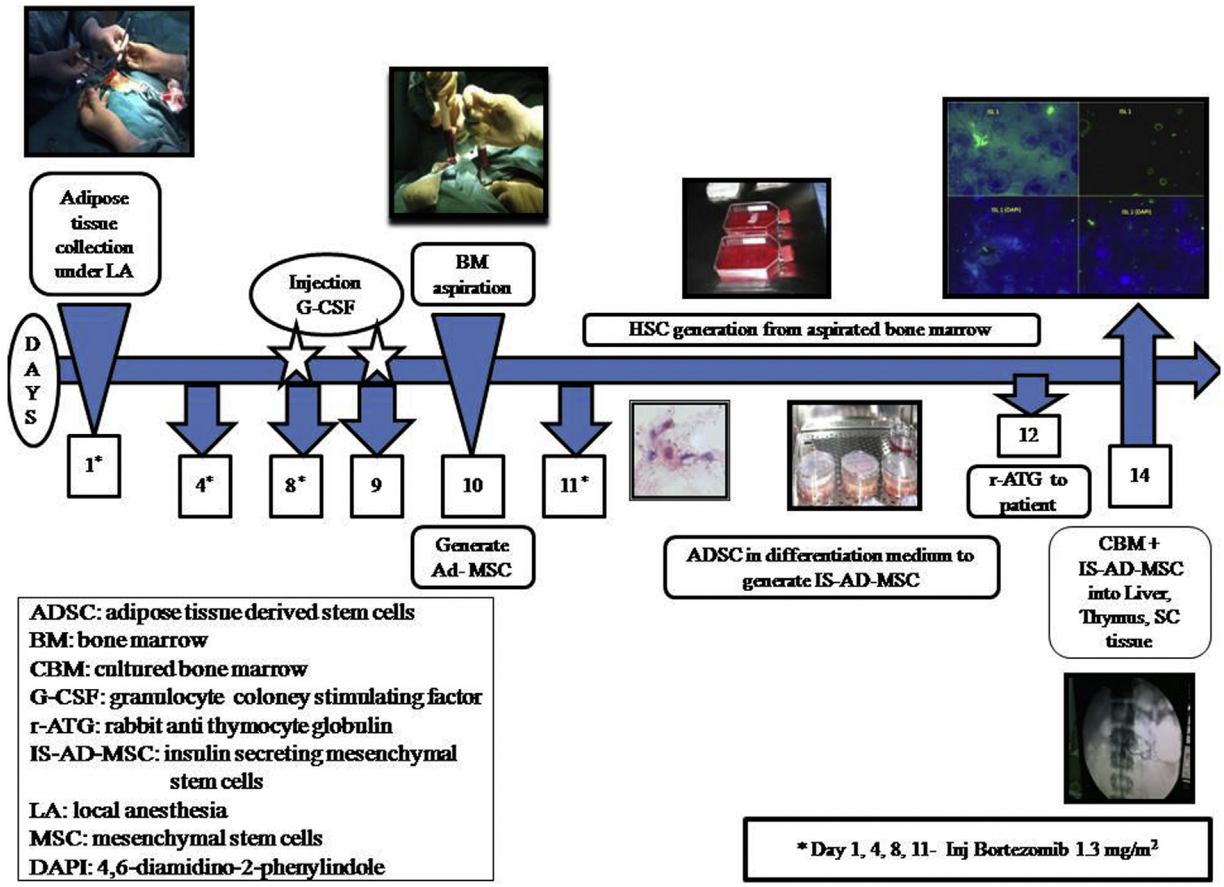

Figure 1. Protocol of stem cell therapy.

present study, we compared the results of autologous SCT with allogeneic SCT. We assessed the safety and efficacy of SCT.

Methods

This study was approved by our Institutional Review Board. Inclusion criteria were T1DM of >12 months' duration with the presence of glutamic acid decarboxylase (GAD) antibodies and age group of 8 to 45 years with low serum (S.) C-peptide levels. Exclusion criteria were positive serology for hepatitis C/hepatitis B/human immunodeficiency virus infection, other systemic infections/disorders, malignancy and pregnancy. Diabetic ketoacidosis (DKA) was not a contraindication to SCT.

Key end points of the study were morbidity, mortality, untoward side effects from SCT and changes in exogenous insulin requirements. Secondary end points were GAD antibodies, S.C-peptide levels with mixed-meal tolerance test and glycosylated hemoglobin (HbA1c). Monitoring was done at 3-month intervals.

Group 1 included autologous SCT in which patients' own abdominal fat and BM were used. Group 2, with allogenic SCT, included healthy non-diabetic volunteer donors from a family of recipients with compatible blood group who were willing to donate fat and BM without objections after written informed consent.

Patient data

This was a prospective, open-labeled, two-armed clinical trial. Group 1 had nine male patients and one female patient, with mean age of 20.2 ± 6.9 years, mean disease duration of 8.1 ± 3.4 years, mean fasting blood sugar (FBS) of 269 ± 93.04 mg/dL, mean post-prandial BS (PPBS) of 372 ± 68.3 mg/dL, mean HbA1c of 10.99% ± 2.1 %, mean GAD antibody of 327.8 ± 652.0 IU/day, mean S.C-peptide of 0.22 ± 0.2 ng/mL and mean insulin requirement 63.9 ± 20.95 IU/day.

Group 2 had six male patients and four female patients with a mean age of 19.7 ± 9.96 years, mean disease duration of 9.9 ± 7.1 years, mean FBS of 309.5 ± 67 mg/dL, mean PPBS of 334.7 ± 72.1 mg/dL, mean HbA1c of 11.93% ± 1.9%,