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An Attempt to Reverse Diabetes by Delayed Islet Cell Transplantation in Humans

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Although autotransplantation of islets has been shown to successfully reverse pancreatectomy-induced diabetes, such an outcome is rarely witnessed after islet cell allotransplantation.[1,2] To promote acceptance of islets in diabetic patients suffering from end-stage renal disease (ESRD), perioperative infusion of donor bone marrow (BM) to augment chimerism has already been attempted.[1,3] A less than desirable outcome of the latter approach has prompted the exploration of alternative strategies which would allow for successful islet cell transplantation (Tx). It has been previously shown that, unlike concomitant Tx, islets implanted subsequent to BM infusion in rodents results in indefinite reversal of streptozotocin-induced diabetes.[4] However, despite its uniqueness, the principal limitation for clinical application of this procedure was the unpredictable islet cell recovery encountered using contemporary culture and cryopreservation techniques. Recognizing this predicament, we embarked on developing a novel technique that allowed for prolonged islet cell culture with an acceptable loss of their viability and function.[5] This accomplishment motivated the initiation of a clinical trial for delayed islet cell infusion into diabetic kidney transplant recipients, who have exhibited demonstrable immune modulation and are maintained on relatively lower doses of immunosuppression (IS); reported herein is the clinical outcome in these patients.

MATERIALS AND METHODS

Patients

Since June 1995, four patients with insulin-dependent type I diabetic mellitus diagnosed with ESRD received cadaveric renal Tx (CRTx) with delayed (31 to 45 days post-CRTx) islet cell infusion. In two patients, chimerism was augmented with infusion of 6×10^8 unmodified BM cells/kg body weight that were obtained from the vertebral bodies of the cadaveric donor. Of these two recipients, one received BM as a single infusion at the time of organ Tx, whereas in the other, 1.2×10^8 cells/kg were infused over a period of 5 consecutive days beginning on the day of renal Tx. IS was with Tacrolimus, CellCept, and steroids.

Islet Cell Isolation, Culture, and Infusion

Islets were isolated from the pancreata obtained from the kidney donors by a modification of the automated method described elsewhere,[6] and subsequently purified by velocity sedimentation on a discontinuous Eurocollins-ficoll density gradient using a cell separator (COBE 2991, COBE Laboratories Inc, Lakewood, Colo). Islet number, purity, and viability were determined by dithizone staining and in vitro dynamic perifusion assay. A known concentration (60 to 80 IEq/mL) of isolated islets was cultured in pyruvate-enriched (5- to 7-mmol/L) medium supplemented with 5 mmol/L D-glucose, 5% to 10% fetal calf serum and

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25 mmol/L HEPES (GIBCO, Grand Island, NY). The cells were maintained at 37°C in 5% CO_2 in air until infused.[5] The day of the isolation, 5 days before, and on the day of the infusion, extensive microbiological testing was performed to ensure the sterility of the preparation. Additionally, on the day of the infusion, islet number and viability were again determined by dithizone staining and in vitro dynamic perifusion assay. At the time of Tx, a known concentration (0.3 to 1.3×10^6 IEq) of cultured islets was infused using the percutaneous portal vein approach. The function of the implanted islets was subsequently monitored by serial detection of blood glucose and plasma C peptide levels and by the requirement for exogenous insulin to maintain euglycemia.

RESULTS AND DISCUSSION

Infusion of delayed islets was uneventful and in all patients an initial increase in plasma C peptide activity was discerned. However, the necessity to reduce IS after cytomegalovirus infection in two patients (one each in study [Table 1] and control [Table 2] group) precipitated moderate acute cellular rejection on postoperative days (PODs) 112 and 70, respectively, resulting in a significant decrease in plasma C peptide levels. In one control patient (Table 2), a very high (2.9 pmol/L/mL) C peptide level was witnessed on POD 34 translating into a 40% reduction in the insulin requirement. Albeit during the period of follow-up (3 to 15 months), two recipients have maintained a relatively high level of plasma C peptide activity (Tables 1 and 2), all patients nevertheless remain insulin-dependent. It is therefore tempting to speculate that given the partial success witnessed in these patients with the possibility that some may ultimately achieve an insulin-free existence, a much wider clinical application of this procedure may be warranted.

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Table 1

Graft Function in BM-Augmented and Nonaugmented Kidney + Delayed Islet Cell Transplant Recipients: Kidney-Delayed Islet-BM*

		Follow-up (mo)		Graft Function	
Patient	Age (yr)/Gender	Kidney	Islet	Creatinine (mg/dL) Current	C-peptide (pmol/mL) Pre-Tx/Current
I	32/M	14	13	1.4	0.3/0.4
II	39/M	5	4	1.2	0.2/1.7

Abbreviations: BM, bone marrow: Tx, transplant.

*Average insulin requirement (IU): Pre-Tx = 50 ± 12 Post-Tx = 46 ± 10.

All patients are alive and remain insulin-dependent.

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Table 2

Graft Function in BM-Augmented and Nonaugmented Kidney + Delayed Islet Cell Transplant Recipients: Kidney-Delayed Islet*

		Follow-up (mo)		Graft Function	
Patient	**Age (yr)/Gender**	**Kidney**	**Islet**	**Creatinine (mg/dL) Current**	**C-peptide (pmol/mL) Pre-Tx/Current**
I	34/M	16	15	1.2	0.02/0.4
II	42/F	12	11	0.8	0.2/2.9

Abbreviations: BM, bone marrow: Tx, transplant.

*Average insulin requirement (IU): Pre-Tx = 57 ± 5 Post-Tx = 37 ± 4.

All patients are alive and remain insulin-dependent.

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