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Treatment of Isolated Pancreatic Islets to Reverse Pancreatectomy-Induced and Insulin-Dependent Type I Diabetes in Humans: A 6-Year Experience

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THE SUCCESSFUL isolation and subsequent autotransplantation of islets into pancreatectomized patients has promulgated the possible use of this procedure for the treatment of insulin-dependent type I diabetes (IDDM).[1,2] However, our inability to diagnose and promptly treat islet allograft rejection combined with the deleterious effects of currently used immunosuppressive agents have severely limited the clinical utility of this approach. In an attempt to evolve a universally applicable strategy for the surgical treatment of IDDM, we at the Thomas E. Starzl Transplantation Institute have performed, between January 1990 and May 1996, 42 pancreatic islet cell transplantations. We report herein, the results of our 6-year experience with this procedure in humans and discuss some of the approaches that we have evolved that may assist in the successful engraftment of allotransplanted islets.

MATERIALS AND METHODS

Patients

Between 1990 and 1996, 37 patients received pancreatic islet allotransplantation (Table 1). Additionally, during the same period, five patients underwent autotransplantation of islets isolated from pancreata retrieved from individuals undergoing total or partial resection (Table 1, group VIII). In an attempt to induce donor-specific tolerance, selected diabetic recipients of kidney and liver also received a perioperative infusion of 3 to 5 $\times$ 10^8 unmodified bone marrow (BM) cells/kg body weight (Table 1, groups IV and V). Furthermore, using the percutaneous portal vein approach, delayed (31 to 45 days post–organ transplantation) infusion of islets cultured in pyruvate-rich medium[3] was performed in some patients (Table 1, groups VI and VII). This latter approach was prompted with an objective to optimize graft acceptance in patients who were anticipated to be on relatively lower doses of immunosuppression (IS) with demonstrable immune modulation. For IS, recipients of cluster transplants (Table 1, group I) received tacrolimus alone, whereas all the other patients (except recipients of autografts) received tacrolimus and steroids. The function of transplanted islet cells was monitored by serial postoperative determinations of plasma glucose, C-peptide, and glycosylated hemoglobin (HbA_{1c}) levels. An intravenous glucose tolerance test or Sustacal challenge test was also performed at regular intervals was to ascertain the ability of transplanted islets to respond to stress. In selected cases, oral glucose tolerance tests were also performed.

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Table 1. Patient and Graft Survival and Insulin Freedom in Isolated Pancreatic Islet Cell Recipients

Group	Patients (*n*)		Follow-Up Range (Mo)	Primary Organ Tx	C-Peptide*	Insulin-Free
	Total	Alive (%)				
I	11	2 (18)	2–77	Cluster	55	6 (55%)
II	11	10 (91)	0–74	Kidney	45	0
III	4	1 (33)	1–69	Liver	33	1 (33%)
IV	1	1 (100)	34	Liver + BM†	0	0
V	6	6 (100)	26–37	Kidney + BM†	83	0
VI	2	2 (100)	2–12	Kidney + BM‡	100	0
VII	2	2 (100)	10–13	Kidney§	100	0
VIII	5	5 (100)	3–64	Autografts	100	4 (80%)

*Percent of recipients who exhibited normal levels of circulating C-peptide 30 days post-islet Tx.
†Simultaneous organ and BM Tx.
‡Simultaneous organ and BM Tx with delayed islet cell Tx.
§Delayed islet cell Tx.

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Islet Cell Isolation

Islets were isolated by a modification of the automated method detailed elsewhere.[4] Isolated cells were subsequently purified by velocity sedimentation on a discontinuous Euro-Collins–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 0.2 to 1.7 $\times$ 10^4 islets/kg body weight were infused into each patient.

Culture in Pyruvate-Rich Medium

For patients receiving delayed islet cell allografts, a known concentration (60 to 80 islets/mL) of isolated islets were cultured in pyruvate-enriched (5 to 7 mmol/L) medium supplemented with 5 mmol/L D-glucose, 5% to 10% fetal calf serum and 25 mmol/L HEPES (Gibco, Grand Island, NY). The cells were maintained at 37°C in 5% CO_2 in air until infusion.[3] Five days prior to and on the day of infusion, extensive microbiologic testing was performed to ensure the sterility of the infusate.

RESULTS AND DISCUSSION

A comprehensive account of the outcome in the first 37 successive cases has been published previously.[1,2] Although only 2 of 11 (18%) cluster transplant recipients are currently alive and insulin-dependent, it is nevertheless noteworthy that hyperglycemia was reversed in 6 of 11 (55%) patients who maintained an insulin-free existence until succumbing to recurrence of malignancy. Interestingly, included among them was the longest survivor who was insulin-free for 58 months after islet cell transplantation (Tx) until her demise which was a consequence of multiple system organ failure precipitated by the recurrence of primary malignancy.[5]

While four of five (80%) recipients of autografts (Table 1, group VIII), have attained an insulin-free existence, this favorable outcome has not been witnessed in patients in other groups (Table 1). It is, however, interesting to note that one kidney + islet BM recipient (Table 1, group VI) was free of exogenous insulin for 1 week at 4 months post-Tx, but evolving hyperglycemia prompted the reinitiation of insulin therapy. Notwithstanding that the recipients of delayed islet cell allografts are as yet insulin-dependent for the maintenance of euglycemia, it is nonetheless noteworthy that many have exhibited normal levels of circulating C-peptide in the 2 to 14 months of follow-up (Table 1, groups VI and VII); it still remains to be seen if any of these patients would ever achieve an insulin-free existence. Having already established the utility of this technique for the treatment of diabetes, it is our contention that the advent of improved and long-term culture techniques and the initial success observed following delayed islet cell Tx may allow for wider clinical application of this procedure toward reversal of this disease.

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