1447

Intrahepatic Human Islet Transplantation at the University of Pittsburgh: Results in 25 Consecutive Cases

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IN PATIENTS with type I diabetes, insulin production by pancreatic islets declines until several years after onset, and the majority have no demonstrable endogenous insulin secretion due to relentless autoimmune destruction of insulin-producing B cells. Before 1990, the lack of any successful islet cell transplants in humans was frustrating. With new developments in the techniques used to isolate and purify islets from the human pancreas, short and prolonged insulin independence has been reported following human islet transplantation in man. We report herein our initial experience in human islet allo- and autotransplantation in 25 patients.

METHODS

Twenty-five intrahepatic islet grafts were performed in 24 patients between January 10, 1990 and April 1, 1992.

Group 1 (Cluster-Islet Recipients)

Ten patients, aged 8 to 58 years, underwent combined liver islet allotransplantation following upper-abdominal exenteration for tumors requiring radical surgery that included total pancreatectomy, partial gastrectomy, splenectomy, lymphnode dissection, and liver transplantation. Detailed information on nine of these patients has been reported previously.[1,2] Immunosuppression was with FK 506 that began with IV doses of 0.075 mg/kg every 12 hours followed by 0.15 mg/kg BID when patients were taking oral feedings. The dose was adjusted on clinical grounds and by monitoring plasma levels.

Group 2 (Liver-Islet Recipients)

Three patients with type I diabetes and absent C-peptide to either glucagon or Sustacal underwent combined liver and islet transplantation for the indication of cirrhosis. One patient with a positive crossmatch died in the first 24 hours following the transplant due to hyperacute liver rejection and is not included in the data analysis. Immunosuppression in this group was also with FK 506 that was administered at a dose of 0.1 mg IV as a continuous infusion over 24 hours. In addition, these patients received a 1000-mg bolus of methylprednisolone during the operation, followed by a maintenance dose of 20 mg IV prednisolone until conversion to oral medications.

Group 3 (Islet Autograft Recipients)

Two patients underwent a near total pancreatectomy for the indication of severe recurrent pancreatitis with pain. One patient had pancreatitis due to lupus and the other due to alcoholic pancreatic disease. No immunosuppression was used in this group.

Group 4 (Kidney-Islet Recipients)

Nine patients underwent 10 kidney-islet grafts (one retransplant) for indications of end-stage renal disease due to type I diabetes. One patient died on the fifth postoperative day of aspiration pneumonia, and the data on this patient are not included for analysis. Immunosuppression in this group was with FK 506 given as in group 2. Following the intraoperative IV bolus of 1000 mg of methylprednisolone, a decreasing prednisone dose from 200 to 20 mg/d was given. The last three patients also received 200 mg Imuran/d with a tapering of mediations based on clinical criteria.

Islet Preparation and Administration

The human islets were obtained from pancreata that were harvested from multiorgan donors.[3,4] The human islets were obtained by a modification[2] of the automated method for human isolation.[5]

Metabolic Testing

Group 1 patients were followed with an intraoperative 1-mg glucagon stimulation test following the pancreatectomy that confirmed absent endogenous insulin secretion. Serial IV glucose tolerance tests (IVGTT) (0.5 g/kg) have been followed in this group. Groups 2 and 4 underwent screening IV glucagon or oral Sustacal (6 cal/kg) followed by postoperative assessment of function by serial oral Sustacal challenges. Group 3 patients underwent intraoperative sampling followed by postoperative IVGTTs as described above.

RESULTS

In group 1, six of ten (60%) patients achieved insulin independence for prolonged periods of time (29, 14, 22, 9, 10, and 13 months). Of these patients, only 2 had onset of hyperglycemia requiring insulin at 10 and 22 months. Recurrence of tumor has been a major problem in this group and occurred in 5 patients. Three patients are currently alive and back to full activities. Six of 10 patients had at least one episode of liver rejection documented by biopsy. One patient is still insulin independent at 29 months with HbA_{1c} 4.8 (nl: 3.9 to 5.9). This patient did not have any episodes of allograft rejection of liver or islets. Of interest in this patient with the longest graft survival in our series was the increase in mean pre- and postprandial glucose determinations that occurred at 17 months. This

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was accompanied by a rise in HbA_{1c} to 7.4%. No intervention was made and glycemic control normalized spontaneously. In group 2, no patients were insulin-free. Both patients had at least one liver rejection episode. One patient died of hepatitis B and sepsis 6 months after the procedure; the other patient has a stimulated C-peptide level >2.0 pmol/mL and a normal glycosylated hemoglobin on 18 U (0.38 U/kg) of insulin daily. In group 3, two of two patients are insulin-free at 7 and 17 months after islet autograft procedures and both have normal HbA1c values, normal glucose values, and normal IV glucose values. In group 4, zero of ten patients are insulin-free, although five of ten patients continue to have significant C-peptide production for up to 24 months following transplantation. All ten patients have had kidney rejection episodes in this group. Analysis of basal and stimulated C-peptide values show cluster > liver > autograft > kidney groups.

DISCUSSION

Several cases of intrahepatic human islet allografts have been reported with transient[6] or prolonged[1,7,8] insulin independence; however, insulin independence occurs in the few rather than the many patients who have undergone islet transplantation. Our data in cluster patients along with the data from other groups in type I diabetes confirm that islet cell transplantation is feasible in man. If there are no rejection episodes, one donor is enough in many patients to allow for insulin independence. What explains the excellent results in cluster patients compared to type I diabetic patients with liver or kidney transplantation? Differences in islet isolation and/or purification techniques cannot explain the inferior results in the combined kidney-islet and liver-islet groups, since the patients received islets using the same separation and purification procedure by the same islet group. The number of islet equivalents was higher in the kidney and liver-islet groups compared with those transplanted in the cluster and autograft groups which did much better clinically. The transplanted islet equivalents/kg was also similar in the groups. Possible explanations for the high success rate in cluster patients include: (1) less rejection episodes in this group; (2) the protective effect of donor islets transplanted into the donor liver; (3) native pancreatectomy in the cluster and autograft groups; (4) less diabetogenic immunosuppressive agents used in the cluster group; and (5) the absence of pre-existing vasculopathy in patients who do not have long-standing diabetes may allow for better islet engraftment. HLA matching was similar in the allograft groups and, therefore, cannot explain the observed results. The protective effect of donor islets into the donor liver cannot entirely explain the results since one patient in the cluster-islet group received third-party islets and achieved long-term insulin independence. This was never seen in the liver-islet group with the same advantage.

The major obstacle to applying islet cell transplantation to type I diabetes is rejection of islets. The exploration of alternative sites, mechanisms to induce tolerance in recipients, and brief pretreatment of islets to reduce immunogenicity and not sacrifice yield and barrier devices are currently under intense investigation. Application of these methods in human transplantation will allow for improved results in all groups of patients undergoing islet transplantation.

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