Achievement of Insulin Independence via Pancreatic Islet Transplantation Using a Remote Isolation Center: A First-Year Review

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ABSTRACT

Background: Owing to advances in both immunosuppressive protocols and pancreatic islet isolation techniques, insulin independence has recently been achieved in type 1 insulin-dependent diabetics (IDDM) via pancreatic islet transplantation (PIT). Although the dissemination of immunosuppressive protocols is relatively easy, transferring the knowledge and expertise required to isolate a large number of quality human islets for transplantation is a far greater challenge. Therefore, in an attempt to centralize the critical islet processing needed for islet transplantation and to avoid the development of another islet processing center, we have established a collaborative islet transplant program between two geographically distant transplant centers.

Patients and Methods: Eleven consecutive type 1 IDDM patients with a history of severe hypoglycemia and metabolic instability underwent PIT at the Methodist Hospital (TMH) in Houston, Texas, utilizing pancreatic islets isolated at the Diabetes Research Institute (DRI) at the University of Miami in Miami, Florida between January 1, 2002 and June 31, 2003. Forty-one pancreata have been procured in the Houston area and have subsequently been transported for isolation at the DRI following enzymatic ductal perfusion by the automated method (Ricordi chamber). Following purification the islets were immediately transported back to TMH in Houston and transplanted via percutaneous transhepatic portal vein infusion. Immunosuppression regimen consisted of sirolimus, tacrolimus, and daclizumab.

Results: Following harvesting, donor pancreata arrived at the DRI for initiation of the isolation process within 6.5 hours of cross-clamping (median time 5.4 hours; range 4.8 to 6.5 hours). The islets were immediately transported back to TMH for final sterility and viability tests and transplanted via percutaneous transhepatic portal vein infusion. The harvesting of 41 pancreata has yielded a number of pancreatic islets sufficient for transplantation (>5000 IEQ/kg recipient body weight) 26 times (63% of harvested pancreata). Thus far, three patients have received three PITs and eight patients have received two PITs. Six remain insulin independent. All have experienced a decrease in serum hemoglobin A1c levels, and both basal and stimulated C-peptide levels have...
increased. There have been no major complications related to the procedure or the immunosuppressive regimen used.

Conclusions: Our series demonstrates that pancreatic islets isolated at a remote isolation center can successfully and safely be used for PIT and the achievement of insulin independence.

Because of an understanding that islets of Langerhans were responsible for the production of insulin and glucose homeostasis, clinicians and researchers have attempted to avoid whole-organ pancreas transplantation by isolating the islets. The results of pancreatic islet transplantation (PIT) in the 1990s were disappointing, with only 8% of patients achieving insulin independence 1 year after transplantation. In 2000 Shapiro et al. introduced several improvements to both the immunosuppression regimen and the isolation techniques, resulting in 80% of patients remaining insulin free 2 years after PIT. Although implementing an immunosuppression regimen is relatively easy, successful islet isolation requires highly trained laboratory personnel, expensive instrumentation, and FDA-approved and institution-specific protocols. For this reason we expanded the PIT program at the Baylor College of Medicine/The Methodist Hospital (Houston, Tex) to utilize a remote islet isolation center at the University of Miami, Diabetes Research Institute in Miami, Florida (DRI). By doing so we have successfully initiated a PIT program at an already established transplantation center while relying on the laboratory expertise of a remote center.

Methods
A total of 25 PITs have been performed for 11 patients between January 1, 2002, and June 31, 2003. All patients have type 1 insulin-dependent diabetes mellitus (IDDM) and severe metabolic instability in spite of maximal medical therapy and have developed hypoglycemic unawareness. Prospective recipients are required to have a body mass index of 26 or less.

Suitable donor pancreata were procured in the Houston area. Excised pancreata are stored using the standard two-layer static method, then transported to the DRI by chartered jet. In Miami the pancreata undergo enzymatic ductal perfusion by the automated Ricordi chamber method. After isolation the islets were transported to Houston for final sterility and viability testing, then preparation and packaging. The islets were then transplanted into the liver via ultrasound-guided percutaneous transhepatic infusion by a staff interventional radiologist. The patients are monitored in

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>IEQ per PIT</th>
<th>Total IEQ/kg</th>
<th>HbA1c—Pre- to Posttransplant Levels (%)</th>
<th>C-peptide (ng/mL)</th>
<th>Daily Insulin Requirements (U/d): Pre- and Posttransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1—1st PIT</td>
<td>36/F</td>
<td>395,567</td>
<td>18,599</td>
<td>8.7 to 5.7</td>
<td>&lt;0.5 to 1.8</td>
<td>30 → 15</td>
</tr>
<tr>
<td>2—1st PIT</td>
<td>47/F</td>
<td>394,381</td>
<td>19,703</td>
<td>9.1 to 5.9</td>
<td>&lt;0.5 to 1.8</td>
<td>44 → 0</td>
</tr>
<tr>
<td>3—1st PIT</td>
<td>42/F</td>
<td>563,206</td>
<td>25,060</td>
<td>12.0 to 5.2</td>
<td>&lt;0.5 to 1.6</td>
<td>39 → 0</td>
</tr>
<tr>
<td>4—1st PIT</td>
<td>37/M</td>
<td>768,132</td>
<td>56,295</td>
<td>10,644</td>
<td>8.1 to 5.9</td>
<td>0.5 to 1.1</td>
</tr>
<tr>
<td>5—1st PIT</td>
<td>62/M</td>
<td>746,480</td>
<td>26,704</td>
<td>9.1 to 6.0</td>
<td>&lt;0.5 to 1.4</td>
<td>20 → 10</td>
</tr>
<tr>
<td>6—1st PIT</td>
<td>42/F</td>
<td>394,122</td>
<td>12,935</td>
<td>7.0 to 6.4</td>
<td>&lt;0.5 to 1.6</td>
<td>15 → 0</td>
</tr>
<tr>
<td>7—1st PIT</td>
<td>39/M</td>
<td>973,133</td>
<td>18,122</td>
<td>7.3 to 5.9</td>
<td>&lt;0.5 to 0.9</td>
<td>33 → 10</td>
</tr>
<tr>
<td>8—1st PIT</td>
<td>40/F</td>
<td>330,667</td>
<td>20,121</td>
<td>8.3 to 7.6</td>
<td>&lt;0.5 to 0.9</td>
<td>25 → 0</td>
</tr>
<tr>
<td>9—1st PIT</td>
<td>37/F</td>
<td>459,784</td>
<td>13,707</td>
<td>8.5 to N/A</td>
<td>&lt;0.5 to 0.9</td>
<td>25 → 10</td>
</tr>
</tbody>
</table>

Table 1. Characteristics and Results of PIT Recipients
the intensive care unit for at least 1 night and are discharged after a color Doppler ultrasound is done to rule out intrahepatic hematoma or portal vein thrombosis. The immunosuppressive regimen used consists of sirolimus, tacrolimus, and daclizumab.

RESULTS

Between January 1, 2002, and June 31, 2003, we harvested and transported 41 pancreata to the DRI for islet isolation. The isolation process began within 6.5 hours of cross clamping in all patients (median delivery time was 5.4 hours, with range of 4.8 to 6.5 hours). Of the 41 pancreata transported to the DRI, 26 (63%) have yielded a number of islets sufficient for transplantation. With these islets we have performed 25 consecutive transplants in 11 patients (8 women, 3 men; mean age 43 years, range 33 to 66 years). Three patients have received three preparations and nine have received two preparations, with one patient having received islet cells from two donors in a single setting. The mean number of islet equivalents transplanted per infusion was 477,688 islet cell equivalents (IEQ) (range 246,000 to 973,133 IEQ) for a mean IEQ/kg of body weight of 17,717 (range 10,664 to 26,704 IEQ/kg body weight). Seven patients have achieved insulin independence. Although most remain insulin independent, one patient now requires insulin at 50% of the pretransplant dose. The remaining four patients are awaiting transplantation of additional islets. Median length of hospitalization is 1 day (range 0.5 to 5.0 days). Hemoglobin A1c levels have decreased in all 11 patients (Table 1). All patients have also been shown to produce C-peptide at both a basal and simulated level. The mean amplitude of glycemic excursions (MAGE) have decreased from a mean of 215 mg/dL before transplantation (range 197 to 245 mg/dL) to a mean of 114 mg/dL following transplantation (range, 108 to 162 mg/dL). There have been no major complications related to the transplant. No patient developed any posttransplant infection, including recipients negative for cytomegalovirus (CMV) of islets from CMV donors. Minor complications have included a transient elevation of serum transaminases, nausea, and abdominal pain (Table 2).

CONCLUSION

Our series has demonstrated that PIT utilizing a remote isolation center is safe and effective for treatment of type 1 IDDM. Pancreatic islets remain viable following shipment to remote transplant centers, demonstrating that a small number of regional facilities could possibly supply islets to several remote centers.

REFERENCES