ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

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ABSTRACT

Background Registry data on patients with type 1 diabetes mellitus who undergo pancreatic islet transplantation indicate that only 8 percent are free of the need for insulin therapy at one year.

Methods Seven consecutive patients with type 1 diabetes and a history of severe hypoglycemia and metabolic instability underwent islet transplantation in conjunction with a glucocorticoid-free immunosuppressive regimen consisting of sirolimus, tacrolimus, and daclizumab. Islets were isolated by ductal perfusion with cold, purified collagenase, digested and purified in xenoprotein-free medium, and transplanted immediately by means of a percutaneous transhepatic portal embolization.

Results All seven patients quickly attained sustained insulin independence after transplantation of a mean (±SD) islet mass of 11,547±1604 islet equivalents per kilogram of body weight (median follow-up, 11.9 months; range, 4.4 to 14.9). All recipients required islets from two donor pancreases, and one required a third transplant from two donors to achieve sustained insulin independence. The mean glycosylated hemoglobin values were normal after transplantation in all recipients. The mean amplitude of glycemic excursions (a measure of fluctuations in blood glucose concentrations) was significantly decreased after the attainment of insulin independence (from 198±32 mg per deciliter [11.1±1.8 mmol per liter] before transplantation to 119±37 mg per deciliter [6.7±2.1 mmol per liter] after the first transplantation and 51±30 mg per deciliter [2.8±1.7 mmol per liter] after the attainment of insulin independence; P<0.001). There were no further episodes of hypoglycemic coma. Complications were minor, and there were no significant increases in lipid concentrations during follow-up.

Conclusions Our observations in patients with type 1 diabetes indicate that islet transplantation can result in insulin independence with excellent metabolic control when glucocorticoid-free immunosuppression is combined with the infusion of an adequate islet mass. (N Engl J Med 2000;343:230-8.) ©2000, Massachusetts Medical Society.

ISLET transplantation has been investigated as a treatment for type 1 diabetes mellitus in selected patients with inadequate glucose control despite insulin therapy. However, the perennial hope that such an approach would result in long-term freedom from the need for exogenous insulin, with stabilization of the secondary complications of diabetes, has failed to materialize in practice. Of the 267 allografts transplanted since 1990, only 12.4 percent have resulted in insulin independence for periods of more than one week, and only 8.2 percent have done so for periods of more than one year.¹ In the majority of these procedures, the regimen of immunosuppression consisted of antibody induction with an antilymphocyte globulin combined with cyclosporine, azathioprine, and glucocorticoids.²,³

In the past 10 years, techniques for isolating large numbers of human islets have advanced, permitting renewed attempts at islet transplantation.²,³ With the increase in the availability of new and more potent immunosuppressive agents, strategies can now be developed specifically for islet transplantation that will provide greater immunologic protection without diabetogenic side effects.

For any type of transplantation procedure, a balance is sought between efficacy and toxicity. With respect to islet transplantation a further difficulty is that many of the current agents damage beta cells or induce peripheral insulin resistance.⁴ To address this problem, we developed a glucocorticoid-free immunosuppressive protocol that includes sirolimus, low-dose tacrolimus, and a monoclonal antibody against the interleukin-2 receptor (daclizumab) for use in a trial of islet transplantation alone for patients with...
brittle type 1 diabetes. Most previous islet transplantations have been performed in combination with kidney transplantation in patients with end-stage diabetic nephropathy. We limited our procedure to islet transplantation alone and in doing so selected patients who had severe hyperglycemia (defined as multiple hypoglycemic episodes) or uncontrolled diabetes despite compliance with an insulin regimen.

METHODS

Patients

Patients who were considered to have type 1 diabetes for more than five years on the basis of a stimulated serum C-peptide concentration of less than 0.48 ng per milliliter (0.16 nmol per liter) were eligible to undergo islet transplantation if their serum glucose concentrations remained uncontrolled despite exogenous insulin therapy. Patients also had to have recurrent severe hyperglycemia with coma or metabolic instability to such an extent that the global risk of transplantation and immunosuppression was judged to be less than the risk of continued uncontrolled diabetes. All protocols were approved by the health research ethics board of the University of Alberta, and each patient gave written informed consent.

Glucocorticoid-free Immunosuppression

Immunosuppression was initiated immediately before transplantation. Sirolimus (Rapamune, Wyeth–Ayerst Canada) was given orally at a loading dose of 0.2 mg per kilogram of body weight, followed by a dose of 0.1 mg per kilogram per day, with monitoring of drug levels to maintain the dose in the range of 12 to 15 ng per milliliter for the first three months and in the range of 7 to 10 ng per milliliter thereafter. Low-dose tacrolimus (Prograf, Fujisawa Canada) was given orally at an initial dose of 1 mg twice daily, and the dose was subsequently adjusted to maintain a trough concentration at 12 hours of 3 to 6 ng per milliliter (IMX enzyme immunoassay, Abbott). Daclizumab (Zenapax, Roche Canada) was given intravenously at a dose of 1 mg per kilogram every 14 days for a total of five doses. If the second transplantation procedure occurred more than 10 weeks after the first, the course of daclizumab was repeated. No glucocorticoids were given at any time during the trial.

Conditioning Regimen and Post-Transplantation Therapy

As soon as there were sufficient numbers of islets for transplantation, the patient was given intravenous antibiotics prophylactically (500 mg of vancomycin and 500 mg of imipenem), and oral supplementation with vitamin E (800 IU per day), vitamin B6 (100 mg per day), and vitamin A (25,000 IU per day) was initiated. Inhaled pentamidine (300 mg once a month) was given after transplantation to prevent infection with Pneumocystis carinii, and oral ganciclovir (1 g three times per day) was given for 14 days for a total of five doses. If the second transplantation procedure occurred more than 10 weeks after the first, the course of ganciclovir was repeated. No glucocorticoids were given at any time during the trial.

Glucose Challenge to Yield the Mean Insulin-Release Stimulation Index

Blood was drawn for an oral glucose challenge to yield the mean insulin-release stimulation index. In brief, the islets were incubated in CMRL 1066 medium with 10 percent fetal-calf serum and 25 mmol HEPES buffer. A known number of duplicate aliquots of islets were incubated in a low concentration of glucose (50 mg per deciliter [2.8 mmol per liter]) and a high concentration of glucose (360 mg per deciliter [20 mmol per liter]) for two hours, and the amount of insulin generated in response to the high-glucose challenge was divided by the amount generated by the low-glucose challenge to yield the mean insulin-release stimulation index.

Statistical Analysis

Results are expressed as means ± SD or, in the case of nonparametric variables, as medians and ranges. Analysis of variance was conducted with use of the SigmaStat program.
Figure 1. Length of Follow-up after the Initial Islet Transplantation and the Time at Which Subsequent Transplantations Were Performed.

Table 1. Characteristics of the Islet Allografts.

<table>
<thead>
<tr>
<th>Patient and Procedure No.</th>
<th>Age of Donor</th>
<th>Duration of Cold Ischemia</th>
<th>Immunohistochemical Analysis</th>
<th>Total Beta-Cell Mass per Transplant*</th>
<th>Total No. of Islets per Isolation</th>
<th>Total No. of Islets Transfused</th>
<th>Mean Insulin Release Stimulation Index‡</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>yr</td>
<td>hr</td>
<td>percent</td>
<td>×10^-6</td>
<td>IEµT</td>
<td>IE/kg of recipient’s body weight</td>
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<td>26</td>
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<td>Mean (±SD) values</td>
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<td>45.0±14</td>
<td>4.8±3</td>
<td>13.9±9</td>
<td>24±12</td>
<td>10±5</td>
<td>30±15</td>
</tr>
</tbody>
</table>

*The mean total beta-cell mass per transplant was based on the DNA content of the allografts (the DNA content of human islet cells is 6.0 pg per cell) and the percentage of insulin-positive cells in the allograft.†
†The islet equivalent (IE) is the standard unit used to report the volume of islets.
‡Values reflect the response of islet cells in vitro to a glucose challenge.
§Islets from two donors were used.
litus for a median of 35 years (range, 18 to 50) underwent islet transplantation between March 11, 1999, and January 23, 2000. As of June 2000, the median duration of follow-up was 11.9 months (range, 4.4 to 14.9). In all seven patients, exogenous insulin therapy quickly became unnecessary once sufficient numbers of islets were transplanted. At the time of the most recent follow-up, all patients remained free of the need for exogenous insulin. The patient who received the smallest number of islets (Patient 1) has briefly required 4 to 10 U of insulin per day on four occasions during times of stress from intercurrent illness. One patient required a total of 7 U of insulin on a single occasion during a two-day illness.

There have been no episodes of acute cellular rejection, as determined by measurements of glycemic control, serum insulin, and C peptide. None of the patients have died. Six of the seven required a second islet infusion from a second donor pancreas a median of 29 days (range, 14 to 70) after the first procedure (Fig. 1) to become insulin independent. One patient, the most obese (weight, 93 kg), required a third infusion to achieve insulin independence. The third infusion combined islets from two donors because of mechanical failure in one of the purification runs.

All patients had had repeated episodes of severe hypoglycemia before transplantation but have had no further episodes since transplantation. This change has dramatically improved their quality of life.

The mean (±SD) total number of islets required to induce insulin independence was 11,547±1604 islet equivalents per kilogram of the recipient’s body weight, with a mean total beta-cell mass per transplant of 132±67×10⁶ (Table 1). A mean packed-cell volume of 3.5±1.3 ml was infused, and this did not change the portal pressure significantly (mean increase, 0.8 mm Hg; P=0.8). The results of tests of liver function 24 hours after transplantation were within the normal range. Doppler ultrasonography demonstrated no evidence of thrombus within the portal vein in any of the patients. The patients were hospitalized for a median of 2.3 days (range, 0.5 to 14.7), and three patients who underwent transplantation most recently (40 percent) were discharged within 24 hours after the procedure.

Glycemic Control and Serum C-Peptide Concentrations after Islet Transplantation

Insulin requirements decreased in all patients after the first transplantation (Fig. 2). Computer analysis of data from capillary glucose meters showed a marked improvement in glycemic control in all patients. Overall mean serum glucose concentrations decreased and the mean amplitude of glycemic excursions decreased significantly with sequential islet transplantation (Fig. 2). The lability of glycemic control in a 24-hour period also decreased dramatically (Fig. 3). All patients had normal glycosylated hemoglobin values after transplantation (Table 2). Serum C-peptide concentrations were undetectable in all patients before transplantation (less than 0.48 ng per milliliter after an overnight fast and in response to the mixed-meal test). Three months and six months after transplantation all patients had detectable serum C-peptide concentrations (P<0.001 by analysis of variance for the comparison with values before transplantation), and the concentrations did not decrease over time: at three months, the mean fasting value was 2.4±0.3 ng per milliliter (0.8±0.1 nmol per liter), and the mean value after a meal was 5.7±0.9 ng per milliliter (1.9±0.3 nmol per liter); at six months, the mean fasting value was 2.5±0.2 ng per milliliter (0.8±0.1 nmol per liter), and the mean value after a meal was 5.7±0.6 ng per milliliter (1.9±0.2 nmol per liter).

Autoantibody Analyses

Serum was analyzed for anti-insulin antibody, islet-cell antibody 512, and glutamic acid decarboxylase antibody before and after transplantation.¹⁹ Mean serum anti-insulin antibody fell from 0.26±0.06 IU before transplantation to 0.07±0.03 IU after transplantation (P=0.04 by t-test); this change may represent a beneficial effect of systemic immunosuppression. Serum glutamic acid decarboxylase antibody was undetectable before and after transplantation. One of four patients for whom data were available was positive for islet-cell antibody 512 before transplantation and remained so after transplantation.

Assessments of Oral Glucose Tolerance, Mixed-Meal Tolerance, and Homeostasis

The results of oral glucose-tolerance tests, completed after insulin independence had been achieved, indicated that none of the seven patients met current American Diabetes Association criteria for diabetes (Table 2).²⁰ However, in five patients, the response to the test at 120 minutes was impaired (glucose, 142 to 195 mg per deciliter [7.9 to 10.8 mmol per liter]), and two had fasting glucose concentrations that were at or above the upper limit of the normal range (110 mg per deciliter [6.1 mmol per liter]).

We used the homeostatic model assessment¹⁸ to estimate insulin sensitivity on the basis of paired fasting glucose and insulin data from the transplant recipients after they had achieved insulin independence and from normal subjects without diabetes. The values in the two groups did not differ significantly (103±14 percent among transplant recipients and 118±12 percent among control subjects, P=0.43).

Transplantation-Related Complications

None of the patients have had cytomegalovirus infection, despite the fact that four were seronegative for the virus before transplantation and received an allograft from a seropositive donor. In the first 2 of
the 15 procedures, moderate bleeding occurred at the site of the transhepatic puncture and required transfusion. This complication was subsequently avoided by injecting a Gelfoam plug through the catheter and by reducing the intraportal dose of heparin from 5000 to 500 U.

All patients had minor, superficial ulcerations of the buccal mucosa that resolved after the dose of sirolimus was reduced and the capsule formulation of sirolimus was substituted for the liquid form. None of the patients had sirolimus-related cytopenia. After transplantation, there were no significant increases in lipid con-

Figure 2. Mean (±SE) 24-Hour Blood Glucose Concentrations (Panel A), Mean (±SE) Daily Insulin Requirements (Panel B), Mean (±SE) Amplitude of Glycemic Excursions (Panel C), and Mean Percentage of Glucose Values That Fell within a Given Range (Panel D) Three Days before the First Islet Transplantation, Three Days before the Second Transplantation, One Week after the Attainment of Insulin Independence, and at the Most Recent Follow-up Visit.

Each box in Panels A, B, and C represents the 95 percent confidence interval. P<0.001 (by analysis of variance) for each comparison of pretransplantation values with subsequent values. Blood glucose was measured seven times a day for the first four weeks, four times a day for the subsequent two months, and a minimum of four times a week thereafter. The mean amplitude of glycemic excursions is a measure of fluctuations in blood glucose concentrations. Values in Panel D were based on a computerized analysis of data from capillary glucose meters. For each value obtained after transplantation, there was a significant decrease in the percentage of glucose values that exceeded 200 mg per deciliter (11.1 mmol per liter) (P<0.001 by analysis of variance) and a significant increase in the percentage of values that were within the range of 60 to 140 mg per deciliter (3.3 to 7.8 mmol per liter) (P<0.001). To convert values for glucose to millimoles per liter, multiply by 0.0555.
centrations and no patient required lipid-lowering therapy (Table 2). There were no significant changes in serum concentrations of creatinine ($P=0.92$), cholesterol ($P=0.90$), or triglycerides ($P=0.46$) during follow-up (Table 2). As of this writing, there has been insufficient follow-up for us to perform a prospective evaluation of secondary diabetic complications.

**DISCUSSION**

We found that in patients with type 1 diabetes the use of a glucocorticoid-free immunosuppressive protocol in conjunction with islet transplantation quickly resulted in sustained freedom from the need for exogenous insulin. Our results represent an improvement in outcome as compared with previous reports. Transplantation of an initial, suboptimal islet mass halted the episodes of severe hypoglycemia in our patients. Sirolimus, low-dose tacrolimus, and daclizumab provided effective immunosuppression, with no apparent diabetogenic or toxic effects. Indeed, there were no clinically evident episodes of graft rejection, and this combination appears to be effective in preventing autoimmune recurrence of diabetes.

A recent review of the potential barriers to insulin
TABLE 2. RESULTS OF ASSESSMENTS OF ORAL GLUCOSE TOLERANCE, MIXED-MEAL TOLERANCE, GLYCOXYLATED HEMOGLOBIN VALUES, AND SERUM CREATININE AND LIPID CONCENTRATIONS BEFORE AND AFTER TRANSPLANTATION.*

<table>
<thead>
<tr>
<th>PATIENT NO.</th>
<th>DURATION OF FOLLOW-UP</th>
<th>GLUCOSE-TOLERANCE TEST†</th>
<th>MIXED-MEAL TEST‡</th>
<th>GLYCOXYLATED HEMOGLOBIN</th>
<th>CREATININE</th>
<th>CHOLESTEROL</th>
<th>TRIGLYCERIDE</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>AFTER Fasting</td>
<td>Glucose at 120 min</td>
<td>C Peptide at 0 min</td>
<td>Glucose at 90 min</td>
<td>Before Transplantation</td>
<td>At 3 mo</td>
</tr>
<tr>
<td>1</td>
<td>14.9 mo</td>
<td>103 mg/dl</td>
<td>130 mg/dl</td>
<td>3.6 ng/ml</td>
<td>5.7 ng/ml</td>
<td>150 mg/dl</td>
<td>7.2 mg/dl</td>
</tr>
<tr>
<td>2</td>
<td>12.8 mo</td>
<td>97 mg/dl</td>
<td>195 mg/dl</td>
<td>1.4 ng/ml</td>
<td>3.0 ng/ml</td>
<td>157 mg/dl</td>
<td>8.1 mg/dl</td>
</tr>
<tr>
<td>3</td>
<td>12.3 mo</td>
<td>108 mg/dl</td>
<td>142 mg/dl</td>
<td>1.6 ng/ml</td>
<td>3.6 ng/ml</td>
<td>182 mg/dl</td>
<td>9.0 mg/dl</td>
</tr>
<tr>
<td>4</td>
<td>11.9 mo</td>
<td>88 mg/dl</td>
<td>139 mg/dl</td>
<td>2.3 ng/ml</td>
<td>5.1 ng/ml</td>
<td>83 mg/dl</td>
<td>8.6 mg/dl</td>
</tr>
<tr>
<td>5</td>
<td>9.0 mo</td>
<td>110 mg/dl</td>
<td>150 mg/dl</td>
<td>2.8 ng/ml</td>
<td>4.8 ng/ml</td>
<td>106 mg/dl</td>
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<tr>
<td>6</td>
<td>5.5 mo</td>
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<td>157 mg/dl</td>
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<tr>
<td>7</td>
<td>4.4 mo</td>
<td>92 mg/dl</td>
<td>175 mg/dl</td>
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<td>4.8 mg/dl</td>
<td>153 mg/dl</td>
<td>8.5 mg/dl</td>
</tr>
</tbody>
</table>

Mean ±SD

| GLUCOSE | 101.7±10 | 155.2±23 | 2.3±0.8 | 4.5±1.0 | 138.4±37 | 8.4±0.6 | 5.7±0.2 | 13.2±0.4 | 12±0.6 | 193±33 | 196±43 | 105±37 | 119±29 |
|---------|----------|----------|---------|---------|----------|---------|--------|----------|--------|--------|--------|--------|--------|--------|

*Values were determined after insulin independence had been achieved. To convert values for glucose to millimoles per liter, multiply by 0.0555. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for C peptide to nanomoles per liter, multiply by 0.33. To convert values for cholesterol to millimoles per liter, multiply by 0.026. To convert values for triglyceride to millimoles per liter, multiply by 0.011.

†A total of 75 g of glucose in 300 ml of solution was given over a one-minute period after an overnight fast.

‡A total of 300 ml of a high-protein drink (Ensure) was given over a one-minute period.

§This patient had preexisting renal dysfunction, with a glomerular filtration rate of 46 ml per minute per square meter of body-surface area on radionuclide assay.

¶P<0.001 for the comparison with the value before transplantation by analysis of variance.
ISLET TRANSPLANTATION IN PATIENTS WITH DIABETES USING GLUCOCORTICOID-FREE IMMUNOSUPPRESSION

Our findings show that an infusion of islets from a single donor (a mean of $389,016 \pm 73,769$ islet equivalents in the first transplant) did not result in insulin independence. Since glucocorticoids were not used and thus did not exert any adverse effects on islet function, other factors must be involved. The quantity of islets required to achieve insulin independence is approximately double that reported previously.1 Recently, one center achieved insulin independence in 14.3 percent of patients after the transplantation of islets from a single donor, but insulin was not withdrawn until a mean of 10.6 months after transplantation.38 In our study the need for more than one donor pancreas per recipient may be interpreted as a drawback, given the shortage of donors. At present, however, less than one third of available cadaveric pancreases are actually transplanted (United Network for Organ Sharing Registry: unpublished data).

In patients with type 1 diabetes, glycemic control can also be achieved with intensive insulin therapy and pancreatic transplantation. Intensive insulin therapy does not normalize glycosylated hemoglobin values and may cause severe hypoglycemia.39 Pancreatic transplantation provides excellent glycemic control, and although the outcome of the procedure has improved dramatically over the past decade, it remains an invasive procedure with a substantial risk of morbidity and mortality.40 Our findings indicate that islet transplantation alone is associated with a minimal risk and results in good metabolic control, with normalization of glycosylated hemoglobin values and sustained freedom from the need for exogenous insulin.

Supported by the Alberta Foundation for Diabetes Research, by a grant from the Medical Research Council–Juvenile Diabetes Foundation, by the Alberta Health Services Research Innovation Fund, by institutional support from the University of Alberta Hospitals Capital Health Authority, by the Muttart Diabetes Research and Training Centre, and by the Edmonton Civic Employees Charitable Assistance Fund, by the C.F. (“Curly”) MacLachlan and Gladys B. MacLachlan Fund, and by the University Hospital Foundation. Drs. Lakey and Korbutt are recipients of scholarships from the Canadian Diabetes Association and the Alberta Heritage Foundation for Medical Research. Drs. Warnock and Kneteman are Senior Scholars of the Alberta Heritage Foundation for Medical Research.

We are indebted to Roche Canada, Wyeth–Ayerst Canada, and Fujijama Canada for their generous gifts of daclizumab, sirolimus, and tacrolimus, respectively; to all the technical staff members of the human islet transplant laboratory, including Dr. Tatsuya Kin, for their expertise; to Barbara Waters and Ingrid Larsen (islet transplantation coordinators) for excellent patient care; to Dr. Dalila Barama, Dawn Said, Sharleen Ines, and the staff members of the clinical investigation unit and the University of Alberta Hospitals metabolic center for assistance with metabolic monitoring of patients; to our colleagues in interventional radiology for their assistance; to the organ-procurement programs in Alberta and across Canada for identifying cadaveric donors; to Dr. George Eisenbarth, Barbara Davis Diabetes Center, Denver, for assistance with the evaluation of autoimmune markers; and to Dr. Jonathan Levy, Radcliffe Infirmary, Oxford, United Kingdom, for providing the HomaFak program.

REFERENCES