Benefits and Risks of Solitary Islet Transplantation for Type 1 Diabetes Using Steroid-Sparing Immunosuppression

The National Institutes of Health experience

BOAZ HIRSHBERG, MD[1]
KRISTINA I. ROTHER, MD[1]
BENIGNO J. DIGON, III, MD[1]
JANET LEE, MD[2]
JASON L. GAGLIA, MD[1]
KENNETH HINES, BS, MT (ASCP)[2]
ELIZABETH J. READ, MD[2]
RICHARD CHANG, MD[3]
BRADFORD J. WOOD, MD[3]
DAVID M. HARLAN, MD[1]

OBJECTIVE — The aim of this study was to describe the National Institutes of Health's experience initiating an islet isolation and transplantation center, including descriptions of our first six recipients, and lessons learned.

RESEARCH DESIGN AND METHODS — Six females with chronic type 1 diabetes, hypoglycemia unawareness, and no endogenous insulin secretion (undetectable serum C-peptide) were transplanted with allogenic islets procured from brain dead donors. To prevent islet rejection, patients received daclizumab, sirolimus, and tacrolimus.

RESULTS — All patients noted less frequent and less severe hypoglycemia, and one-half were insulin independent at 1 year. Serum C-peptide persists in all but one patient (follow-up 17–22 months), indicating continued islet function. Two major procedure-related complications occurred: partial portal vein thrombosis and intra-abdominal hemorrhage. While we observed no cytomegalovirus infection or malignancy, recipients frequently developed transient mouth ulcers, diarrhea, edema, hypercholesterolemia, weight loss, myelosuppression, and other symptoms. Three patients discontinued immunosuppressive therapy: two because of intolerable toxicity (deteriorating kidney function and sirolimus-induced pneumonitis) while having evidence for continued islet function (one was insulin independent) and one because of gradually disappearing islet function.

CONCLUSIONS — We established an islet isolation and transplantation program and achieved a 50% insulin-independence rate after at most two islet infusions. Our experience demonstrates that centers not previously engaged in islet transplantation can initiate a program, and our data and literature analysis support not only the promise of islet transplantation but also its remaining hurdles, which include the limited islet supply, procedure-associated complications, imperfect immunosuppressive regimens, suboptimal glycemia control, and loss of function over time.

Diabetes Care 26:3288–3295, 2003

From the [1]Transplantation and Autoimmunity Branch, National Institutes of Health/Department of Health and Human Services, Bethesda, Maryland; the [2]Clinical Center Department of Transfusion Medicine, National Institutes of Health/Department of Health and Human Services, Bethesda, Maryland; and the [3]Special Procedures–Diagnostic Radiology Department, National Institutes of Health/Department of Health and Human Services, Bethesda, Maryland.

Address correspondence and reprint requests to David M. Harlan, MD, Chief, Transplantation and Autoimmunity Branch, NIDDK, National Institutes of Health/Department of Health and Human Services, Building 10, Room BN307, Bethesda, MD 20892. E-mail: davidmh@intra.niddk.nih.gov.

Received for publication 23 May 2003 and accepted in revised form 26 August 2003.

Abbreviations: GCSF, granulocyte colony stimulating factor; IEQ, islet equivalent; NIH, National Institutes of Health.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Although it is well established that individuals with immune-mediated type 1 diabetes can minimize their risk for long-term complications by maintaining near-normal blood glucose (1,2), it is equally well established that maintaining normal blood glucose concentrations is often quite difficult (3), with one price of such efforts being a threefold greater risk for serious hypoglycemia (4). Currently, pancreas transplantation can restore insulin independence in up to 90% of patients 1 year after surgery, but the procedure is technically demanding and is associated with serious complications and high mortality. In fact, our recent analysis suggests that solitary pancreas transplantation may decrease overall survival for those patients with normal kidney function (4a). Because many of the postsurgical complications are attributable to the non–insulin-producing pancreatic exocrine tissue (5), investigators have asked whether transplanting just the insulin-producing islets might be similarly effective but safer (6,7). Thus, since early reports of islet transplantation restoring euglycemia in rats (8), the procedure has been pursued as a simpler and potentially safer means to transfer homeostatically regulated insulin-producing cells into insulinopenic recipients. Yet, the field languished for years as insulin independence was infrequently achieved (9,10). Interest in islet transplantation was rejuvenated by encouraging human transplantation results (11) as well as long-term insulin independence achieved in a clinically relevant nonhuman primate islet transplantation model (12). In a landmark study, investigators from Edmonton reported that glucocorticoid-free immunosuppression, islets transplanted from two to four donors, and improved islet isolation methods restored long-term insulin independence in seven consecutive patients (13,14).

In this context, the National Institutes of Health (NIH) launched the Transplantation and Autoimmunity Branch in May 1999 with an important goal to establish islet transplantation as a clinical research protocol and to test whether the Edmonton results could be reproduced in a new islet transplantation center. We now report our initial islet transplantation experience in six diabetic patients who all had marked hypoglycemia unawareness.

RESEARCH DESIGN AND METHODS

Patients

Patients with type 1 diabetes for at least 5 years and with undetectable arginine-stimulated serum C-peptide were enrolled. The main inclusion criterion was severe hypoglycemia. Patients with significant associated medical conditions were excluded. The institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases of NIH approved the study, and written informed consent was obtained from all patients.

Islet preparation

Pancreata were obtained from regional organ procurement organizations and the United Network for Organ Sharing after signed informed consent was attained for islet transplantation from the donors' relatives. All organs used for islet isolation were deemed unsuitable for solid organ transplantation due to donor age or pancreas quality (specific causes being that the pancreas was encased in fat or showed signs of obvious trauma as reflected by an intraparenchymal hematoma) (Table 1). The organs were shipped in ice-cold University of Wisconsin solution to the NIH islet isolation laboratory and processed using a modification of the automated Liberase-based human islet isolation method (12,15–17). Briefly, the spleen, attached duodenum, and surrounding tissues were dissected from the pancreas, and the pancreatic ducts were perfused with cold Liberase (Roche, Montclair, NJ). The "inflated" gland was cut into 9–13 pieces and then loaded into a Ricordi chamber to chemically and mechanically disrupt the pancreas into fragments small enough to pass through a screen filter. This digest was collected on ice and then loaded onto a continuous bioficoll gradient and centrifuged in a COBE 2991 blood cell processor (COBE, Lakewood, CO). To determine islet number, volume, and purity, a 50-μl sample taken from the 50-ml islet suspension was stained with dithizone and then counted and graded for purity. These data were mathematically converted to the total number of islets with an average diameter of 150 μm, expressed as islet equivalents (IEQs) (18).

Islet transplantation

Islet preparations fulfilling standard release criteria for sterility and viability and with at least 4,000 IEQ/kg of the recipient's body weight (for a first islet dose) or a number sufficient to reach a total of at least 10,000 IEQ/kg per recipient weight for a second transplant dose were infused. We infused only islet preparations with a maximal packed tissue volume of ≤7 ml and with islet purity of at least 30%. We assessed islet viability (release criteria of ≥70%) by suspending islets with 10 μl propidium iodide (0.5 mg Sigma P-4170/ml) and 10 μl fluorescein diacetate in acetone (10 μg Sigma F-7378/ml). The ratio of red (necrosis) versus green (viable) was scored in 50 islets using an axiovert 35 fluorescent microscope (Zeiss, Thornwood, NY). Other testing required before product release included a negative gram stain and endotoxin levels <5 EU/ml. The islets were suspended in 50 cc of medium 199 that contained 500 units/kg of heparin for the first two patients and 35 units/kg of heparin of the recipient weight for the subsequent four patients (two-thirds of the dose was given as a bolus into the portal vein and one-third with the islet preparation).

Patients were transferred to the interventional radiology suite where they received standard conscious sedation, local anesthesia, and underwent hemodynamic and oxygen saturation monitoring. Glucose meter readings were performed every 15 min during the procedure. A peripheral portal vein that provided a relatively straight access to the main portal-splenic vein confluence was identified with ultrasound and fluoroscopy. A 21- or 22-gauge needle was first placed in a peripheral portal vein tributary, followed by a 3-French/4-French 20-cm coaxial micropuncture dilator set. This modified Seldinger technique was used to place a 4.1-French Kumpe catheter (Cook Medical, Bloomington, IN) with side holes cut near the tip. Contrast portal venography was performed to position the catheter tip in the main portal vein. Islets were slowly infused via syringe over 60–90 min. Portal venous pressures were monitored before and every 5 min during the infusion. At the conclusion of the procedure and to promote hemostasis, collagen gel foam pledgets were injected just below the hepatic capsule into the parenchymal track.

Immunosuppression

Once it was determined that the islet preparation was adequate for transplantation, immunosuppression was initiated immediately before the portal vein cannulation procedure. The patients were given sirolimus (Rapamycin; Wyeth-Ayerst) using a loading dose of 0.2 mg/kg body wt and subsequently in a dose adjusted to maintain drug levels of 10–15 ng/ml for the first 6 months and 6–10 ng/ml thereafter. Tacrolimus (Prograf, Fujisawa) was given orally twice daily in a dose adjusted to maintain a 12-h trough concentration of 3–6 ng/ml. Daclizumab (Zenapax; Roche) was administered at 1 mg/kg i.v. on the day of transplantation and every 2 weeks for a total of five doses after each islet infusion. All patients received oral Gancyclovir at a dose of 1 g three times per day after each islet infusion for 14 weeks. Cotrimoxazole (sulfamethoxazole/trimethoprim; Septra) was given at a dose of one single-strength tablet three times per week for 1 year as prophylaxis against pneumocystis pneumonia. Patients (three of six) reporting sulfa allergy or unable to tolerate the drug were treated instead with inhaled Pentamidine at a dose of 300 mg per month for 1 year.

Glycemia control and assessment of islet function after islet transplantation

Exogenous insulin was discontinued 24 h after 10,000 IEQ/kg body wt were transplanted or in one patient (#4) immediately after transplant because any exogenous insulin resulted in hypoglycemia. Patients remained off insulin unless the serum glucose rose to >180 mg/dl. After the initial transplant using at least 4,000 IEQ/kg body wt, insulin doses were adjusted to maintain blood glucose levels in the 70- to 140-mg/dl range. We followed the arginine-stimulated C-peptide secretory response as a functional measure of β-cell mass (19). After an overnight fast, blood samples were collected at 5 and 0 min before the infusion of 5 g arginine (as a 10% solution) by intrave-

Table 1—*Characteristics of the islet allograft*

Patient and infusion procedure number	Age of donor (years)	Donor's BMI (kg/m^2)	Cause of donor death	Duration of cold ischemia (hours) from cross clamping to islet isolation	Total islet infused (IEQ)	Pellet volume (cc) (pure fraction/less pure fraction)*	Purity % (pure fraction/less pure fraction)	Islet viability % (pure fraction/ less pure fraction)
Patient 1								
1	43	28.4	Intracerebral hemorrhage	5.1	276,333	1.5	85	91 ± 10
						2.0	65	91 ± 17
2	53	30.2	Intracerebral hemorrhage	6.5	316,933	2.3	70	87 ± 13
						2.0	40	90 ± 10
Patient 2								
1	59	23.7	Stroke	3.2	337,848†	0.8	70	90 ± 19
						7.0	35	87 ± 17
Patient 3								
1	64	26.6	Intracerebral hemorrhage	2.6	244,580	2.0	90	79 ± 33
						1.5	40	91 ± 9
2	34	34.0	Trauma	6.3	316,160	2.0	70	81 ± 27
						3.0	30	85 ± 25
Patient 4								
1	53	29.7	Intracerebral hemorrhage	7.2	317,272	1.5	70	84 ± 25
						2.5	60	77 ± 30
2	39	32.3	Intracerebral hemorrhage	4.8	509,000	2.0	90	87 ± 13
						3.0	45	87 ± 20
Patient 5								
1	61	19.6	Intracerebral hemorrhage	3.25	298,500	2.0	85	91 ± 12
						3.0	30	91 ± 15
2	47	34.0	Intracerebral hemorrhage	6	361,000	3.0	75	87 ± 16
Patient 6								
1	41	27.7	Trauma	7.5	435,482	3.0	80	87 ± 18

*The calculated volume of 300,000 efficiently packed IEQs is ~1 cm^3. One can thus double-check microscopically determined IEQ counts by using the packed cell volume and the purity assessment. For instance, the islet preparation for patient #6 was estimated to contain, by sampling and physical counting, 435,482 islets. The islet cell pellet was measured as being ~3.0 ml (or cm^3) with an ~80% purity, and as such another way of estimating that recipient's islet dose would be (3.0 ml × 300,000 IEQ/ml × 80%) or 720,000 IEQ. Islet isolation experts recognize the considerable inaccuracy inherent when calculating IEQs and by convention have used the manual count IEQ determination. The higher numbers calculated by cell pellet volume and estimated islet purity are thought to reflect an overestimation of visually determined islet purity. †Due to abdominal pain and increased portal pressure, only 270,000 islets were infused.

nous infusion into a cephalic vein. Subsequent samples were collected from the contralateral cephalic vein at 2, 3, 4, 5, 7, 9, and 10 min after the arginine infusion. Peak minus baseline differences were calculated by subtracting the mean C-peptide level at −5 and 0 min from the mean of the three highest stimulated values.

RESULTS

Patients

Six female patients underwent islet transplantation between 29 December 2000 and 14 June 2001. They ranged in age from 39 to 63 years and had type 1 diabetes for 13–50 years. Their mean BMI was 21.7 ± 3 kg/m^2, and the trial inclusion indication for each was severe hypoglycemia events secondary to hypoglycemia unawareness. Protocol enrollees had no measurable basal- or arginine-stimulated C-peptide secretion before transplantation. The follow-up period was 17–22 months (Fig. 1). All patients demonstrated arginine stimulatable C-peptide levels for more than a year after transplantation, and all reported improved glycemia control. The mean hemoglobin A1c fell in our patients from 8.2 ± 1.2% to 6.04 ± 0.6% a year after transplantation, and the average glucose levels (determined by calculating the mean fasting and several 2-h postprandial sugars recorded by each patient) declined from 183 ± 45 mg/dl to 125 ± 22 mg/dl a year later. Whereas all patients had repeated severe hypoglycemia episodes before islet transplantation (indeed, this was an inclusion criterion), none of the patients suffered severe hypoglycemia requiring the assistance of others after islet transplant, including those still requiring exogenous insulin.

As shown in Fig. 1*A*, three patients (patients #1, 4, and 6) remained insulin independent for >1.5 years once an adequate islet number was infused (two patients required two infusions, and one patient required only one). Several other observations from Fig. 1*A* warrant comment. First, the glycemia control appears to gradually worsen over time. One patient (#1) returned to insulin therapy 18 months after the islet transplantation when she developed sirolimus-induced pneumonitis and immunosuppressive agent doses were first decreased then discontinued. Two others (patients #4 and 6) have required oral insulin sensitizer therapy to maintain euglycemia. Second, the glycemia control achieved is marginal with fasting blood glucose concentrations typically in the impaired glucose tolerance range and skirting the diagnostic threshold for diabetes. This marginal glycemia control is consistent with reports from Edmonton (13,20). Third, Fig. 1*A* also clearly demonstrates the marked improvement in HbA_{1c} achieved in these patients and that islet function, as assessed by arginine-stimulatable C-peptide production, appears to be sustained so long as immunosuppressive drug levels can be maintained. Notably, the one patient (#1) who elected to discontinue immunosuppressive therapy due to unacceptable toxicity appeared to lose nearly all (but not all) islet function within 6 weeks.

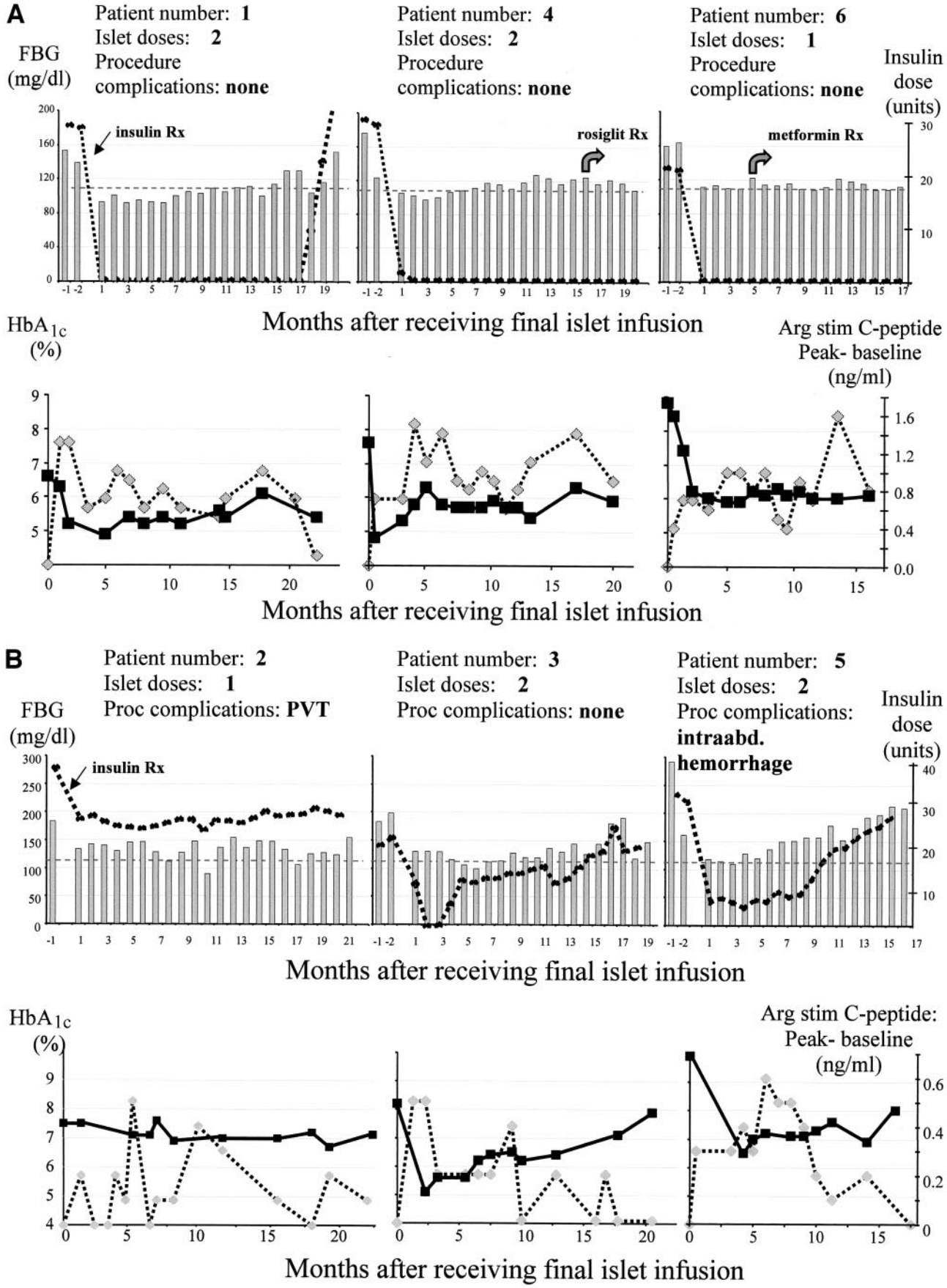
As shown in Fig. 1*B*, three patients remained insulin dependent after their islet allograft infusion. Of them, one patient (#3) remained insulin independent for 6 weeks after her second islet infusion before mild hyperglycemia prompted a return to exogenous insulin but for many months at one-half her previous insulin dose. This patient subsequently discontinued immunosuppressive therapy due to fatigue, diarrhea, weight loss, and worsening kidney function; but now >6 months after discontinuing immunosuppression, she also continues to have measurable serum C-peptide levels. One patient (#2) received only a partial islet dose because her portal vein pressure increased during the first infusion, and she subsequently presented with a partial portal vein thrombosis; thus she was precluded from additional islet infusion. Edmonton also recently reported that 2 of their first 26 islet transplant recipients suffered a partial portal vein thrombosis (21). This patient continues to display islet function as assessed by C-peptide production, diminished insulin requirements, and improved glycemia (as assessed by HbA_{1c}) >18 months after her islet infusion. The third patient (#5) with data depicted on Fig. 1*B* had an intra-abdominal hemorrhage after her second islet infusion requiring a four-unit transfusion of packed erythrocytes. This patient demonstrated markedly improved glycemia control as assessed by her average monthly fasting blood glucose levels and by her HbA_{1c} and a diminished insulin requirement. Of the patients we have studied, her glycemia control was the worst, mostly due to her fear of hypoglycemia and her reluctance to take suggested insulin doses. Interestingly, she is our only patient who lost all evidence of islet function, at which time immunosuppressive agents were withdrawn.

Transplantation-related complications

As reported above, one patient (#2) developed a symptomatic partial portal vein thrombosis 8 days after the abrogated infusion of an islet isolation preparation. A second patient (#5) became hypotensive due to intra-abdominal bleeding after her second islet infusion and was transfused with four units of packed erythrocytes. Both events were considered life threatening and required stabilization in an intensive care setting.

Immunosuppressive agent-related complications

All patients experienced side effects deemed secondary to the immunosuppressive medications (Table 2). All reported recurrent oral ulcers, although their frequency declined over time. Other common side effects included episodic diarrhea (6/6), leg edema (5/6), and generalized fatigue (5/6). Two patients developed at least temporary severe neutropenia (absolute neutrophil counts <500/mm^3) and were treated with granulocyte colony stimulating factor (GCSF). One of these patients' neutrophil counts responded to discontinuing sulfamethoxazole plus trimethoprim therapy after just one GCSF dose, the other required repeated GCSF doses after transplant (~1–2 per month) until she discontinued immunosuppression 18 months after her second islet infusion. All patients developed normocytic anemia, and four have had at least transient mild thrombocytopenia. Although five of the six patients lost weight after transplant (mean weight before transplant 60.8 ± 6.5 kg and 1 year after transplant 57.8 ± 8.3 kg), several of the patients attributed their weight loss, at least in part, to the reduced need to snack to avoid hypoglycemia. None of our patients have developed cytomegalovirus infection, although all four cytomegalovirus-negative recipients received islets from cytomegalovirus-positive donors. One patient (#6) did, however, develop a Pitisporidium skin infection, and another patient (#1) developed recurrent urinary tract infections during the fol-


A
Patient number: 1
Islet doses: 2
Procedure complications: none
Patient number: 4
Islet doses: 2
Procedure complications: none
Patient number: 6
Islet doses: 1
Procedure complications: none
FBG (mg/dl)
Insulin dose (units)
insulin Rx
rosiglit Rx
metformin Rx
Months after receiving final islet infusion
HbA1c (%)
Arg stim C-peptide Peak- baseline (ng/ml)
Months after receiving final islet infusion
B
Patient number: 2
Islet doses: 1
Proc complications: PVT
Patient number: 3
Islet doses: 2
Proc complications: none
Patient number: 5
Islet doses: 2
Proc complications: intraabd. hemorrhage
FBG (mg/dl)
Insulin dose (units)
insulin Rx
Months after receiving final islet infusion
HbA1c (%)
Arg stim C-peptide: Peak- baseline (ng/ml)
Months after receiving final islet infusion

low-up period. One patient (#1) developed sirolimus-induced interstitial pneumonitis 18 months after her second islet infusion. Her sirolimus treatment was discontinued, and she appeared to reject the allogeneic islets within 6 weeks, although interestingly, she continues to display minimal islet function. One patient (#3) with clearly measurable islet function but requiring exogenous insulin elected to discontinue immunosuppression 15 months after her second islet infusion due to intolerable diarrhea, fatigue, weight loss, and deteriorating renal function. This patient, too, continues to display continued islet function as reflected by measurable circulating C-peptide. The third patient (#5), now off immunosuppressive therapy, discontinued the therapy 18 months after receiving her second islet dose when studies indicated loss of all islet function.

Table 2—*Immunosuppressive agent associated toxicity*

	Patient number					
Complication descriptor	1	2	3	4	5	6
Oral ulcers	X	X	X	X	X	X
Peripheral edema	X	X	X	X		X
Neutropenia*	X				X	
Anemia†	X	X	X	X	X	X
Thrombocytopenia‡	X		X	X		
Weight loss	X		X	X	X	X
Headache				X		
Acne				X		
Menstrual irregularity		X		X		X
Tremor	X					
Pneumonitis	X					
Worsening kidney function		X	X		X	
Hematuria	X		X			
Hypertension§	X	X	X			X
Hyperlipidemia‖	X			X		X
Episodic diarrhea	X	X	X	X	X	X
Fatigue	X	X	X	X	X	
Skin infection						X

*White blood cell count <1,000 K/Ul; †hemoglobin <11.1 g/dl; ‡platelets <165 K/mm^3; §blood pressure >135/80 mmHg; ‖direct LDL cholesterol >130 mg/dl or triglycerides >150 mg/dl.

CONCLUSIONS — Since December 2000, our program transplanted 10 cadaveric donor islet allografts into six patients with long-standing and brittle type 1 diabetes, and consistent with Edmonton's success, we observed 1-year islet allograft function in all six. Of note, and different from the Edmonton group, we used only organs that had been rejected for whole organ transplantation. Our efforts have shown that a center previously not engaged in islet isolation and transplantation can successfully, and in a relatively short period (18 months), initiate those efforts assuming excellent preexisting infrastructure like the NIH's cell processing facility and input from existing centers (as we enjoyed from both the University of Miami's Diabetes Research Institute and the University of Alberta programs).

The proportion of our patients achieving insulin independence at 1 year is lower than that reported from Edmonton. We propose several perhaps overlapping explanations. First, our protocol limited patients to islet infusions from only two donors, whereas the Edmonton group infused islets from three or more donors in 30% of recipients (20). If 30% of our recipients (that is two of the six) had received a third islet dose, they too may have been rendered insulin independent. Second, one of our patients suffered a partial portal vein thrombosis after her first islet infusion (indeed, even that infusion was stopped early due to an increase in her portal pressure during the infusion) and that complication precluded her from receiving a second, possibly curative islet dose. Third, it is possible that the islets we isolated were less viable or functional in vivo than those isolated by the Edmonton group. Arguing against the latter interpretation, however, is that all our patients had measurable C-peptide production for at least 1 year after transplantation.

Although our results thus confirm that islet cell transplantation can effectively restore insulin independence for patients with brittle type 1 diabetes, we have also observed that the procedure is not benign, that the glycemia control achieved is often imperfect and tends to deteriorate over time, and that the immunosuppressive regimen required to prevent rejection can result in significant toxicity. The immunosuppressive agent–associated complications we noted are not unique to islet transplantation recipients, but are typical as reported in other transplant settings (22). Consistent with the Edmonton group report (13,14), we too have observed potentially life-threatening procedure-related complications: a partial portal vein thrombosis in one patient and a significant intra-abdominal hemorrhage in another.

Indeed, our experience with islet cell transplantation has prompted us to re-

Figure 1—*A: Patients insulin independent at least 1 year after allogeneic islet transplantation. Data from each islet recipient are represented in a chart in the top row and another below it. The number of islet infusions is also shown. In the top row of charts, the gray bars indicate the average monthly fasting blood sugars both before islets were infused and after islet infusions were complete. The black dotted line in the upper row of charts indicates the average daily insulin doses administered during that month. In the lower row of charts, the bold black squares and line represent HbA_{1c} values (4.8–6.4%), and the gray symbols connected by the dotted lines represent the arginine-stimulated C-peptide values. In our experience, an arginine-stimulated C-peptide of at least 0.5 ng/ml appeared to correlate with insulin independence. The time line for the upper and lower charts differ some but have been aligned as closely as possible. B: Patients remaining insulin dependent after allogeneic islet transplantation. See the legend for* A. *Noteworthy points include the complications suffered by two patients shown: one a partial portal vein thrombosis and the other an intra-abdominal hemorrhage requiring a four unit transfusion of packed erythrocytes. FBG, fasting blood glucose; PVT, portal vein thrombosis.*

evaluate the risk-benefit analysis of a transplant-based treatment for patients with type 1 diabetes. Transplantation for several medical conditions is now appropriately considered a life-saving therapy. Indeed, mortality for patients on waiting lists for liver or heart transplantations (23–26) remains high such that for these patients, transplantation represents a miraculously health-restoring therapy. This also holds for patients with end-stage renal disease (mortality is distressingly common with a "listed" 20- to 59-year-old patient awaiting a transplant having a 4.3–6.5 per 100 patient-years estimated mortality risk) (27), and dialysis-dependent patients suffer with the malaise and inconvenience associated with chronic dialysis therapy (28). Compared with heart, liver, and kidney failure patients, individuals with type 1 diabetes represent a population for whom current therapies are constantly improving (29). Although we have confirmed that patients with type 1 diabetes can be restored to insulin independence after an islet allograft, we also find that the regimen has significant associated problems and that although islet transplantation is less invasive than pancreas transplantation, both procedures are associated with significant risk. While working to further develop transplant-based therapies for type 1 diabetes, we challenge the community to develop criteria for identifying those patients with "end-stage" diabetes for whom the therapy's risks are most likely to improve long-term outcome.

We were surprised to find that two of our three patients who stopped immunosuppressive therapy continued to display islet function (as assessed by measurable C-peptide production) >6 months later. We can think of two possible explanations. One, some allogeneic islets may have escaped immune-mediated destruction, but both patients developed anti-HLA antibodies (data not shown), clearly indicating an allogeneic immune response. Two, the prolonged immunosuppression, alone or in combination with the improved glycemia control afforded by the islet transplant, allowed some endogenous pancreatic islet function to recover. In conclusion, we have established an islet isolation and transplantation program and have by and large replicated Edmonton's results. Although our data support islet transplantation as a possibly viable future treatment for type 1 diabetes, significant hurdles remain, including the limited islet supply and complications associated with both the procedure and the required lifelong immunosuppression. Therefore, we argue that this procedure can only be justified in a very select patient cohort (i.e., patients with severe metabolic instability despite compliance with an optimized diabetes regimen using best current dietary, blood glucose monitoring, and insulin delivery systems).

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