Simultaneous Islet and Kidney Transplantation in Seven Patients With Type 1 Diabetes and End-Stage Renal Disease Using a Glucocorticoid-Free Immunosuppressive Regimen With Alemtuzumab Induction

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OBJECTIVE—The aim of this study was to evaluate the efficiency and safety of simultaneous islet and kidney transplantation in patients with type 1 diabetes and end-stage renal disease using a glucocorticoid-free immunosuppressive regimen with alemtuzumab induction.

RESEARCH DESIGN AND METHODS—Seven patients with type 1 diabetes and end-stage renal failure were transplanted with allogenic islets and kidneys procured from brain-dead donors. To prevent organ rejection, patients received alemtuzumab for induction immunosuppression, followed by sirolimus and tacrolimus. No glucocorticoids were given at any time.

RESULTS—The median duration of follow-up was 18.3 months (range 13–31). Kidney survival was 100%. Four patients became insulin independent at 1 year. The other three reduced insulin use to less than 25% of the amount required before transplantation. Serum C-peptide levels were significantly greater posttransplant in all patients, indicating continued islet function. No major procedure-related complications were observed.

CONCLUSIONS—Our results demonstrate that a steroid-free immunosuppressive regimen consisting of alemtuzumab, sirolimus, and tacrolimus is feasible for simultaneous islet and kidney transplantation. The question of whether this induction regimen is superior to more standard induction deserves large studies.
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Type 1 diabetes remains a therapeutic challenge. Although intensive diabetes treatment reduces incidence and delays progression of long-term complications, including retinopathy, nephropathy, and neuropathy, the benefits of intensive diabetes treatment come with the price of severe hypoglycemia and increased body weight (1). Islet transplantation represents a most impressive recent advance in the search for better type 1 diabetes treatment, with an encouraging rate of insulin independence, normalization of blood glucose, and lowered A1C levels and improved quality of life after either pancreas or islet transplantation (2–7).

Type 1 diabetes can itself impair kidney function. It is therefore generally accepted to perform combined pancreas/kidney transplantation rather than kidney transplantation alone for patients with brittle diabetes and end-stage kidney disease because pancreas transplantation can improve kidney graft survival (8). Unfortunately, the positive impact of pancreas transplantation on the native kidney has been counterbalanced by the toxicity that steroids and calcineurin inhibitors pose to islet cells and the serious complications of pancreas transplantation.

In 2000, using a glucocorticoid-free immunosuppressive protocol that included sirolimus, low-dose tacrolimus, and a monoclonal antibody against the interleukin-2 receptor (IL-2R) (daclizumab), Shapiro et al. (9) carried out islet transplantation alone for seven patients with type 1 diabetes and a history of severe hypoglycemia and metabolic instability. They demonstrated 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. This treatment became known as the Edmonton Protocol. As of 1 November 2004, 65 patients have received islet transplants at the University of Alberta, and results have been promising: the majority (80%) of the recipients have had C-peptide present following islet transplant. Unfortunately, the median duration of insulin independence has been 15 months, and only a minority (10%) have maintained insulin independence 5 years following islet transplant (10).

Alemtuzumab (Campath-1H) is a 150-kDa humanized IgG1 monoclonal antibody that targets the CD52 antigen, a glycoprotein found on the cell surface of many cell types, including lymphocytes and monocytes. Alemtuzumab is currently approved for the treatment of β-cell chronic lymphocytic leukemia in patients who have been previously treated with an alkylating agent and who have failed to benefit from fludarabine therapy (11). Alemtuzumab has been used off label in solid-organ transplantation extensively, especially as an induction agent (12). Prolonged lymphocyte depletion can be expected following alemtuzumab treatment with 30 mg intravenous dose. The majority of alemtuzumab use experience in solid-organ transplantation has been in kidney transplantation; there is more limited experience in islet transplantation. In an observational cohort study, 75 pancreas/kidney and pancreas-only recipients received alemtuzumab and mycophenolate mofetil for induction and maintenance therapy;

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TABLE 1
Recipient characteristics for each of seven pretransplant islet recipients

	Recipient						
	1	2	3	4	5	6	7
Age (years)	34	44	43	40	32	46	39
Sex	F	F	F	M	M	M	F
Body weight (kg)	45	54	46	55	70	68	51
BMI (kg/m^2)	18.8	21.1	19.7	21.0	23.7	22.0	20.4
Diabetes duration (years)	13	15	25	14	15	9	13
Daily insulin (IU/day)	54	64	36	52	60	48	54
A1C (%)	8.0	7.8	8.8	9.5	8.9	10.0	9.5
Baseline glucose level (mmol/l)	7.8	8.0	8.5	8.7	8.0	8.9	8.5
Hemodialysis (months)	6	3	19	4	8	24	6
Serum creatinine (μmol/l)	453	427	460	403	615	558	424
Panel reactive antibodies (%)	0	0	2.5	0	2.5	0	2.5
HLA mismatch* (A, B, DR)	3	3	2	3	2	3	3

*HLA mismatch between the recipient and the kidney donor, who was also the donor of the first islet in case of multiple islet transplantation. F, female; M, male.

Gruessner et al. (13) showed that the combination of alemtuzumab and mycophenolate mofetil was associated with an acceptable rejection rate, a good safety profile, and a trend toward higher modification of renal disease levels. Kaufman et al. (14) reported that alemtuzumab induction followed by steroid-free maintenance therapy with a tacrolimus/sirolimus-based immunosuppression regimen is effective and safe in simultaneous pancreas/kidney transplantation compared with rabbit antithymocyte globulin induction. Here we report the 13- to 31-month follow-up of seven patients with type 1 diabetes and end-stage diabetic nephropathy receiving simultaneous islet and kidney transplantation in which alemtuzumab was used for induction immunosuppression.

RESEARCH DESIGN AND METHODS

This was a single-center pilot trial conducted from June 2005 to December 2006. A total of seven patients (four women and three men) with end-stage renal disease and type 1 diabetes with serum C-peptide level <0.3 ng/ml were enrolled. The main inclusion criterion was severe hypoglycemia (blood glucose level <50 mg/dl) during the past 3 years that required infusion of glucose. The mean age of the patients was 39.7 years (range 32–46) and duration of diabetes 14.8 years (9–25). Patients had undergone hemodialysis dialysis treatment for 10 months (3–24). Detailed recipient characteristics are shown in Table 1. The specificity of the anti-HLA antibodies was determined by ELISA (Lambda Antigen Tray, LAT 1240, lot 6#; One Lambda, Canoga Park, CA). The study protocol was approved by the ethics review committee of our hospital, and written informed consent was obtained from all participants.

Islet preparation. Islets were isolated from pancreata obtained from cadaveric multiorgan donors using a modified method described previously (15). Briefly, human cadaveric pancreata were removed from brain-dead donors after they had been pronounced brain dead in our hospital. The causes of death of the organ donors were traffic accidents. Cold-ischemia time of the 16 pancreata averaged 5.7 h (range 2–10.4). The pancreatic duct was perfused with a cold enzyme (Liberase human islet; Roche Diagnostics, Indianapolis, IN). The pancreas was enzymatically and mechanically dissociated before the islets were separated on a refrigerated Cobe 2991 centrifuge (Cobe BCT, Lakewood, CO). Purification was performed by centrifugation on continuous Ficoll gradients (Seromed-Biochrom). Islets were cultured in CMRL1066 medium (Mediatech-Cellgro) supplemented with 0.5% human serum albumin and incubated at 37°C in 5% CO_2 and 95% humidified air for 12–24 h. Islet numbers were quantified in duplicate with the use of an islet standard diameter of 150 μm and tested for sterility, endotoxin, and mycoplasma.

Transplantation procedures. The protocol was approved by the ethics review committee of our hospital. Kidney transplantation was performed in a routine procedure of our hospital, which has carried out more than 3,000 cases of kidney transplantation. Islets were infused in the liver as previously described (9), with modifications. Briefly, under local anesthesia (a mixture of 50% lidocaine [2%] and 50% ropivacaine [1%]), a 5-cm incision was made in the upper abdomen to expose the umbilical vein, which was usually 4 cm above the navel. A small incision was made in the umbilical vein. Then, a 7F biliary bougie was inserted. The tip of the bougie was directed toward the liver. The bougie was replaced by a 16F catheter when it reached the sagittal sinus. After the position of the catheter was confirmed to be correct by portography, the islets in 250 ml medium in an intravenous fluid bag were allowed to infuse for 30 min. Portal pressure was monitored during and after infusion, which was in the range of 7–11 mm H_2O. The catheter was then secured to the skin so that multiple deliveries of islets could be achieved later.

Immunosuppression. All patients were treated according to the Edmonton Protocol (9), with some modifications. Briefly, the protocol includes *1*) alemtuzumab (induction immunosuppression), administered by intravenous infusion at a dose of 15 mg 24 h before transplantation and repeated 24 h after islet infusion, with patient's peripheral blood lymphocyte count <50 cells/ml; *2*) sirolimus at 0.2 mg/kg for the first 10 days with target plasma levels of 12–15 ng/ml followed by a maintenance dose of 0.1 mg/kg once daily, with target plasma levels of 10–12 ng/ml for the next 30 days; and, following dose adjustment to achieve target plasma levels of ~7 ng/ml, *3*) tacrolimus at 2–3 mg/day adjusted to achieve a target plasma level of 3–5 ng/ml. No glucocorticoids were given at any time during the trial.

Other medications. Short-term antibiotic prophylaxis was administered immediately before and after islet infusion (intravenous ceftazidime, 1 g t.i.d. for 1 day). For 3 months after islet infusion, patients were treated with trimethoprim (800 mg/day), sulfamethoxazole (1,000 mg, twice a week), and Valcye (450 mg b.i.d.) to prevent *Pneumocystis carinii* and cytomegalovirus infection. During the first 3 days after islet infusion, insulin was administered intravenously using an infusion pump and then subcutaneously until withdrawal.

Postprocedural monitoring and management. Glucose was monitored every 2–4 h in the first 2 days posttransplant. After a normal diet was resumed, the patients were monitored for glucose levels preprandially, 2 h postprandially, and before sleep. Fasting and postprandial C-peptide levels, blood tests and liver and kidney functions were evaluated weekly. Glycated hemoglobin and anti-insulin antibody were checked monthly. Serum concentrations of immunosuppressants were checked weekly after transplantation and 1–2 times monthly when they reached the targeted concentrations. Sera of all subjects were monitored for islet cell antibodies, anti-insulin autoantibodies, and GAD glutamic acid decarboxylase antibodies using the ELISA technique. Cutoff values of <1.00, 1.00–1.050, and >1.050 units/m were considered negative, indeterminate, or positive, respectively.

Therapeutic efficacy. The primary end points were the proportion of recipients who achieve insulin independence in the first year, kidney graft loss, doubling of serum creatinine, or death. We defined recipients as insulin independent if they maintained fasting blood glucose levels <126 mg/dl (7.0 mmol/l) and 2-h postprandial levels <180 mg/dl (10.0 mmol/l) after discontinuation of insulin.

Statistical analysis. Statistical analysis was performed using SPSS for Windows (version 10.1; SPSS, Chicago, IL). Data are presented as means ± SD. Data were analyzed using one-way ANOVA. If the F ratios were significant, post hoc tests were applied to assess significance ($P < 0.05$).

TABLE 2
Donor characteristics

Patient and infusion procedure no.	Age (years)	BMI (kg/m^2)	Duration of cold ischemia (hours)	Weight of pancreas (g)	Islet yield (IEQ)	Islet viability (%)	Stimulus index	Cross-match (%)
Patient 1								
1	33	24	5	95.8	460,733	94	2.47	2
2*	34	21.4	2	84	387,000	95	2.15	3
2*	42	22.0	7	92	240,000	93	2.23	2
3	36	23.5	3.75	100.4	628,200	95	3.05	3
Patient 2								
1	38	23.4	8.3	95.6	587,467	95	2.48	3
2*	31	23.7	5	90.8	226,650	95	2.37	3
2*	37	22.0	9.5	93	429,200	95	2.18	2
Patient 3								
1	43	24	6	95	495,600	95	2.27	3
Patient 4								
1*	32	23.7	5	130.8	314,958	92	2.12	2
1*	36	20.4	10.4	93.1	385,567	95	2.58	3
2*	28	21.8	4.5	97	325,044	94	2.24	2
2*	34	24	8	113.7	382,733	93	2.10	2
Patient 5								
1	39	24.3	7	94	587,950	92	2.32	3
2	43	24.5	2	133.7	669,400	95	2.27	3
Patient 6	35	23	3.5	123.2	760,517	95	2.55	3
Patient 7	35	23.3	4.25	94.2	559,267	96	2.17	3

*Islets from two donors were infused in the same procedure for each patient.

RESULTS

Characteristics of the patients. Seven consecutive patients (median age 39.7 years [range 32–46]) who had type 1 diabetes for a median of 14.8 years (9–25) and end-stage renal disease underwent combined islet and kidney transplantation between June 2005 and December 2006. As of January 2008, the median duration of follow-up was 18.3 months (13–31). Detailed recipient and donor characteristics are shown in Tables 1 and 2.

Transplantation. The number of islets harvested was 450,000–760,000 islet equivalents (IEQs). Islet purity and viability were 94.3% (range 92–96) and 91.6% (91–93), respectively. The stimulation index, defined as the ratio of secreted insulin from the high-glucose to the low-glucose incubation, was 2.33 (2.1–3.05). No viruses or bacteria were detected in either islet preparation.

Therapeutic efficacy. The number of islets infused was 11,820 IEQ/kg (range 10,000–15,556 IEQ/kg of the recipient's body weight). Three of the seven patients received only one islet transplantation (patients 3, 6, and 7). Patient 3 become insulin independent at 34 days posttransplantation and remained free of the need for exogenous insulin thereafter. Patients 6 and 7 did not receive a second islet infusion because of islet shortage, and they did not become insulin independent, but both of them decreased their insulin dose by more than 60%. Three patients (patients 2, 4, and 5) required a second islet infusion from a second donor pancreas a median of 45 days (30–90) after the first procedure. Patients 2 and 4 became insulin independent thereafter, but patient 5 required 8 IU insulin per day. Patient 1 required three islet infusions to achieve insulin independence. Thus, four (57.1%) of the patients became insulin independent, and insulin requirements decreased in all patients after the first transplantation (Table 3). All patients attained near-normal A1C values after transplantation (Table 4 and Fig. 1).

Serum C-peptide concentrations were <0.1–0.25 ng/ml before transplantation. During the follow-up period, persistent C-peptide secretion was evident. One month after transplantation, all patients had serum C-peptide concentrations above 0.5 ng/ml, and the concentrations did not decrease over time: at three months, the mean fasting

TABLE 3
Procedural characteristics after the last transplantation

Subject	Baseline insulin requirement (IU/day)	Total transplantations	Insulin requirement after the last transplantation (IU/day)					Insulin independent time (months)
			1 month	2 months	3 months	6 months	12 months	
1	54	3	12	0	0	0	0	20
2	64	2	16	10	0	0	0	21
3	36	1	10	0	0	0	0	19
4	52	2	16	12	8	8	0	10
5	60	2	28	18	12	12	8	13%*
6	48	1	16	20	20	16	12	25%*†
7	54	1	24	26	26	18	14	26%*†

*Insulin use after the last transplantation as a percentage of the amount required before transplantation. †Patients 6 and 7 had only one islet infusion each because of nonavailability of additional islets.

TABLE 4
A1C and C-peptide levels after islet transplantation

	A1C	C-peptide before meal (ng/ml)	C-peptide after meal (ng/ml)
Pretransplantation	8.93 ± 0.81	0.06 ± 0.08	0.11 ± 0.09
1 month posttransplantation	6.59 ± 0.64*	0.84 ± 0.25*	1.18 ± 0.31*
3 months posttransplantation	5.96 ± 0.42*	1.00 ± 0.29*	1.65 ± 0.37*
6 months posttransplantation	6.14 ± 0.72*	1.30 ± 0.56*	1.71 ± 0.44*
12 months posttransplantation	6.31 ± 0.82*	1.42 ± 0.49*	2.33 ± 0.57*
Last examination	6.31 ± 0.82*	1.33 ± 0.39*	2.50 ± 0.71*

Data are means ± SD. *$P < 0.01$ compared with pretransplantation.

value was 1.00 ± 0.29 ng/ml and the mean value after a meal was 1.65 ± 0.37 ng/ml; at six months, the mean fasting value was 1.30 ± 0.56 ng/ml and the mean value after a meal was 1.71 ± 0.44 ng/ml; at twelve months, the mean fasting value was 1.42 ± 0.49 ng/ml and the mean value after a meal was 2.33 ± 0.57 ng/ml. Thus, all patients were C-peptide positive (>0.5 ng/ml) during the first year posttransplant (Table 4 and Fig. 1).

Sera of all subjects were monitored for islet cell antibodies, anti-insulin autoantibodies, and GAD antibodies using the ELISA technique. According to the considered cutoff point for positivity, none of the patients tested positive for these antibodies. All patients 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.

Renal and liver function. Kidney function became normal 5 days after transplantation (with a serum concentration of creatinine ~100 μmol/l) and remained normal thereafter (Fig. 1). The time course of glomerular filtration rate largely mirrored that of serum creatinine concentration. Glomerular filtration rate significantly increased to near normal posttransplant (~56–85.6 ml/min; Fig. 2). Doppler ultrasonography demonstrated no evidence of thrombus within the portal vein in any of the patients. The patients were hospitalized for a median of 21 days (range 15–28). No acute graft rejection or graft loss occurred during the 1 year of follow-up. The results of tests of liver function 24 h before and after transplantation were within the normal range for all patients and remained normal thereafter.

Other biochemical parameters. None of the patients had overt proteinuria at baseline or developed proteinuria thereafter. In all study groups, there was no significant change in serum cholesterol level compared with baseline values. Mean values of serum sodium and potassium concentrations (data not shown) were comparable before and at the end of the study period in all groups.

Safety. The packed cell volume ranged from 0.8 to 2.5 ml. The infused volume was ~250 ml for each islet preparation, and this did not change the portal pressure significantly (mean increase 1–2 cm H_2O). The portal vein pressure ranged from 7 to 11 cm H_2O after islet infusion. Mouth ulcerations were observed in two patients and cystitis in two patients. None of the patients had cytomegalovirus infection or sirolimus-related cytopenia. There have been no episodes of acute rejection of kidney or islets as determined by measurements of creatinine, glycemic control, serum insulin, and C-peptide. None of the patients have died.

DISCUSSION

In this report, we describe—for the first time—the results of simultaneous islet and kidney transplant in patients who have received a glucocorticoid-free immunosuppressive protocol that consisted of sirolimus, low-dose tacrolimus, and a monoclonal antibody against CD52 antigen (alemtuzumab). For patients with brittle diabetes and end-stage renal disease, survival is extremely poor, and kidney transplantation does not completely improve the situation (16–18). Sequential kidney and islet transplantation has been carried out with good results. In this situation, steroids were withdrawn in kidney recipients before islets were transplanted. The foremost challenge in simultaneous transplantation of islet and kidney is to

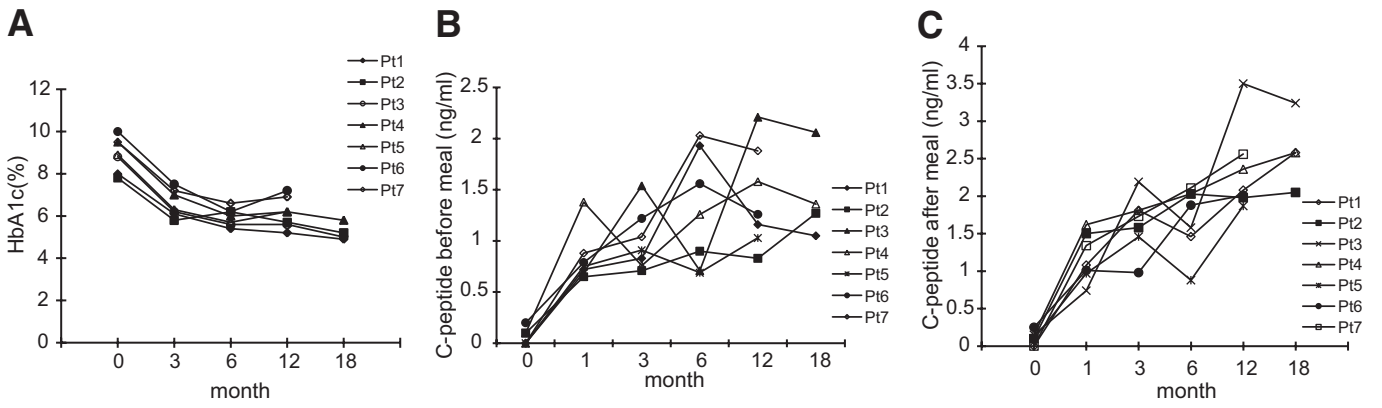

FIG. 1. Metabolic control and islet graft function after transplantation. Values of A1C data (*A*) show improvement in all patients after islet transplantation. Results of premeal (*B*) and postmeal (*C*) C-peptide values demonstrate the benefits of the transplant on metabolic control during the follow-up period.

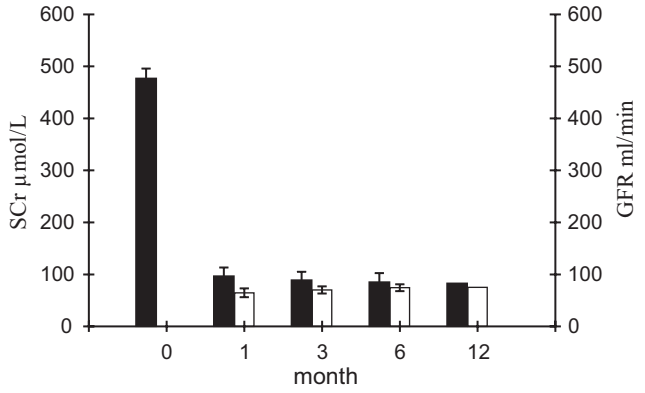

FIG. 2. Renal function of the recipient. Serum concentrations of creatinine after transplantation (□) are significantly lower than those before transplantation (■) ($P < 0.01$). Glomerular filtration rate increases to near normal posttransplant.

prevent alloreactivity and recurrence of autoimmunity against β-cells without the use of steroids in the immunosuppression regimen because steroids are considered favorable for prevention of organ rejection but harmful for islets (19,20). Recently, monoclonal antibodies directed against specific T-cell surface molecules have been developed for clinical use as immunosuppressants. One of these is anti-CD25 (daclizumab), a humanized IgG1 monoclonal antibody directed against the low-affinity IL-2R α-chain (21). This antibody is supposed to solely affect activated T-cells. It has been used in simultaneous kidney and pancreas/islet transplantation with or without steroids (22,23). Although glucocorticoid-free immunosuppression containing daclizumab has greatly contributed to the success of islet transplantation, in the case of simultaneous islet and kidney transplantation it is still a great risk to use a glucocorticoid-free immunosuppression regimen. The recipients may run the genuine risk of jeopardizing the function of their kidney grafts at the time of switching immunosuppression and/or the weaning of steroids. This happened, unfortunately, in the pilot study reported by Toso et al. (24), in which one patient lost his kidney graft several months after islet-after-kidney transplantation. In fact, even in kidney transplant recipients receiving an immunosuppression regimen containing daclizumab, cyclosporine, azathioprine, and prednisone, the proportion of recipients who had biopsy-confirmed episodes of acute rejection still reached 22% (25).

Alemtuzumab (Campath-1H), a 150-kDa humanized IgG1 monoclonal antibody that targets the CD52 antigen, has been used extensively in solid-organ transplantation, especially in kidney transplantation, with the aim of allowing steroid-free and/or calcineurin-free or sparing maintenance immunosuppressive protocols (12,26,27). Alemtuzumab is an attractive agent for induction. It produces profound and long-lasting lymphopenia. In an attempt to reduce both initial and long-term (nephrotoxic) calcineurin inhibitor maintenance dosage and totally eliminate maintenance corticosteroids, Ciancio et al. used alemtuzumab as induction therapy first in cadaver and then in non–HLA-identical living-donor renal transplantation. No corticosteroids were given after the first week posttransplant. In 44 de novo renal allograft recipients, patient and graft survival rates were each at 100% during a median follow-up of 9 months (27). Biopsy-proven acute rejection was diagnosed in four patients. Their results demonstrated that the combination of alemtuzumab, low doses of tacrolimus and mycophenolate mofetil, and avoidance of maintenance corticosteroid is safe and effective for kidney transplant recipients. Several other studies also demonstrated that when alemtuzumab was used for induction immunosuppression for kidney recipients, patients might be maintained on steroid-free immunosuppressive regimens (28–29). Simultaneous pancreas/kidney transplantation using alemtuzumab as a means of induction immunosuppression has also been performed (30,14). In the study by Kaufman et al. (14), alemtuzumab induction followed by steroid-free maintenance therapy with a tacrolimus- and sirolimus-based immunosuppression regimen was shown to be effective and safe. In the study by Gruessner et al. (13), only alemtuzumab and mycophenolate mofetil were included in the immunosuppression regimen, which resulted in a higher, but still acceptable, incidence of a first reversible rejection episode for simultaneous pancreas/kidney recipients compared with solitary pancreas recipients. Although the question of whether alemtuzumab is more effective than thymoglobulin or antiIL-2R receptor antibodies cannot be answered at this time, it appears that the incidence of acute rejection is low after induction with alemtuzumab, and there is no apparent increase in infection (26).

Based on these observations, we chose a steroid-free regimen that contained alemtuzumab, sirolimus, and minimal-dose calcineurin inhibitor. Alemtuzumab was used instead of daclizumab in the Edmonton Protocol. During a mean follow-up time of 18.3 months (range 13–31), four patients became insulin independent and three patients reduced insulin dose to about 75% the amount required before transplantation. The serum concentrations of C-peptide were all above 0.5 nmol/l. All patients had near-normal A1C values after transplantation. No acute and chronic rejections were observed for the transplanted kidney, as indicated by the normal kidney function. Another important finding is that none of the recipients had a percentage of panel reactive antibodies above 5% over follow-up. Also, none of the patients became antibody positive for islet cells.

Although the number of patients limits definite conclusions, this study demonstrates that a glucocorticoid-free immunosuppressive protocol that includes alemtuzumab, sirolimus, and minimal dose of calcineurin inhibitor is effective and safe for simultaneous kidney and islet transplantation. It provides clear benefits for patients with type 1 diabetes and end-stage renal disease in terms of improving variations in blood glucose and alleviating problematic hypoglycemia. The net harm versus benefit of simultaneous kidney and islet transplantation has not yet been established and will require further studies with larger numbers of enrolled subjects. Also, our induction regimen cannot be directly compared with the Edmonton Protocol or other more standard induction (for example, thymoglobulin or antiIL-2R therapy) because the dataset is small. Studies to analyze the benefit of the present induction regimen in a longitudinal follow-up are necessary.

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