ELSEVIER

Outcomes of Simultaneous Kidney–Pancreas Transplantation With Positive Cross-Match

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ABSTRACT

We studied 72 consecutive simultaneous pancreas kidney transplant (SPKT) recipients. There were 14 patients with positive pretransplant cross-matches (positive CDC- B cell and/or positive flow T or B cross-match). The control group included all 58 SPKT recipients with a negative crossmatch. The study group received induction with low dose intravenous immunoglobulin (IVIg), rabbit antithymocyte globulin (rATG; total dose 6 mg/kg), or alemtuzumab (30 mg single dose) and maintenance with tacrolimus, mycophenolate mofetil (MMF), and corticosteroids. The control group was treated similarly, but with steroid avoidance and no IVIg. Biopsy-proven acute rejection (BPAR) of the kidney allograft occurred in 7 study patients (50%) compared with 10% in the control group (P = .022). One patient experienced acute cellular rejection (ACR); the other 6 (43%), antibody-mediated rejection (AMR). None of the cross-match negative patients had AMR (P = .001). The mean follow-up period was 18.7 months in the study group, and 18.3 months in the control group. The 1-year actuarial patient survival was 91.7% in the study group and 97% in the control group. Kidney allograft survival was 91.7% in the study group and 95.2% in the control group. Pancreas allograft survival was 76.9% in study group and 89.6% in the control group (P = .088). We concluded that patients with a positive pretransplant CDC-B cross-match and/or positive flow cross-match have an increased risk of AMR; more intensive desensitization is needed with low-dose IVIg and induction with either rATG or alemtuzumab.

IN RECENT YEARS, there has been growing experience with kidney transplantation for highly sensitized patients.[1–7] Many of these patients show a positive cross-match, which is usually related to donor-specific HLA antibodies.[5,6] The risk of antibody-mediated rejection (AMR) is significantly increased among these recipients.[6] Various treatments have been used to desensitize these patients, but there are no randomized studies to confirm efficacy.[5] In addition, various treatment modalities have been used to treat AMR, which usually produce a satisfactory short-term response.[6,7] However, AMR is associated with an increased risk of transplant glomerulopathy and diminished kidney allograft survival.[8]

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There has been a scattering of reports of AMR among pancreas transplant recipients.[9,10] A recent Banff consensus conference suggested that C4d staining should be performed on all pancreas allograft biopsies and that there are characteristic histologic findings of AMR in pancreas allografts.[11] However, there are no published data on the frequency and outcomes of AMR in pancreas transplant recipients.

The aim of this study was to compare the outcomes of simultaneous pancreas-kidney transplantation (SPKT) among patients with positive pretransplant CDC-B cell cross-matches and/or positive flow cross-matches with a control group of SPKT recipients with negative pretransplant cross-matches. Herein, we showed a significantly increased incidence of AMR but a good response to therapy at intermediate term follow-up.

METHODS

We studied 72 consecutive patients who received SPKT between January 2005 and March 2008. The study group included 14 patients with positive pretransplant cross-matches. We included all patients with positive pretransplant CDC-B cell and/or positive flow T or B cross-matches. Twelve recipients had positive cross-matches with the current specimens and 2 were positive with historic specimens but showed a negative cross-match with the current specimen. We did not transplant patients with positive AHG CDC–T-cell cross-matches. The control group included 58 SPKT recipients with negative pretransplant crossmatches.

Immunosuppression

The study group received induction with low-dose intravenous immunoglobulin (IVIg; 100 mg/kg daily for 3 consecutive days, with first dose given pretransplant) and rabbit antithymocyte immunoglobulin (rATG; total dose 6 mg/kg, usually in 4 divided doses, first dose given before reperfusion). Starting in January 2007, we switched induction to alemtuzumab (30 mg single dose) in all SPKT recipients. Maintenance immunosuppression included tacrolimus, mycophenolate mofetil (MMF), and corticosteroids. Tacrolimus was started when the urine output was adequate and when the serum creatinine had dropped by ≥30%. The goals for trough tacrolimus levels were 10 to 15 ng/mL for the first month, 8 to 10 ng/mL for 30 to 90 days, and 5 to 8 ng/mL after 90 days. MMF started at 2 g/d was adjusted as tolerated. Prednisone was tapered to 20 mg/d by postoperative day 30 and 5 mg/d by postoperative day 90.

The control group received induction with rATG or alemtuzumab as described. Tacrolimus and MMF were initiated and managed using an identical protocol. The control group received steroid avoidance immunosuppression. Corticosteroids used for induction were stopped after postoperative day 4.

Protocol kidney biopsies stained with C4d by immunoflorescence were performed at reperfusion and at 1, 4 and 12 months posttransplantation on both study and control patients. AMR was defined according to Banff criteria, which include typical histologic findings and diffuse peritubular C4d staining. AMR was treated with therapeutic plasma exchange (TPE; 1.5 plasma volumes, replaced with 5% albumin and IVIg 100 mg/kg, on 3 consecutive days), with solumedrol and with a single dose of rituximab (375 mg/m^2) after TPE was completed. If technically feasible, pancreas biopsies were done at 1, 4 and 12 months posttransplantation. C4d staining was not performed routinely on pancreas biopsies.

Statistics

We compared baseline recipient and donor characteristics among the groups using Student's t tests for continuous variables and Fisher exact tests for categorical variables. We compared graft and patient survivals with Kaplan-Meier curves and log-rank tests.

RESULTS

The groups showed similar baseline characteristics at the time of transplantation, as indicated by (positive cross-match vs controls): age (46.5 ± 10.2 vs 44.9 ± 11.1 years), preemptive transplant status (36% vs 31%), mean HLA mismatches (4.2 ± 1.4 vs 4.6 ± 1.1), and induction with alemtuzumab (50% vs 43%). Patients in the positive cross-match group were more likely to be females (71% vs 31%; $P = .012$), with a previous transplant (36% vs 2%; $P = .008$), and a panel reactive antibody (PRA) >80% (36% vs 0%; $P = .001$). No PRA was detected in 14% of the positive cross-match group, and 94% of the control group ($P = .001$).

Five patients displayed a positive CDC-B cell cross-match and 9 had a negative pretransplant CDC-B cross-match, but a positive flow T ($n = 6$) or B ($n = 8$) cross-match. A donor-specific antibody (DSA) was present in 2/5 of the positive CDC B-cell cross-match and 5/9 of the negative CDC B-cell cross-match cases.

One year after transplantation, there was no significant difference in kidney allograft function as indicated by mean serum creatinine, and Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (GFR) between the groups: study group vs control, (mean ± SD) were 1.00 ± 0.17 vs 1.41 ± 0.96 mg/dL and 75 ± 14.0 vs 64.5 ± 21.3 mL/min/1.73 m^2, respectively. In addition, the mean fasting glucose and C-peptide levels were not significantly different between the groups: study group vs control, fasting blood sugar (FBS) 108 ± 31.2 vs 100 ± 30.5 mg/dL and C-peptide 1.4 ± 1.5 vs 2.4 ± 1.9 ng/mL, respectively. The hemoglobin A1C was significantly higher among the study group (6.0 ± 1.2 vs 5.4 ± 0.5%; $P = .042$). The study group remained on low-dose corticosteroids, whereas the control group was largely steroid-free, which may explain this difference.

Complications after transplantation are shown in (Table 1). The incidences of cytomegalovirus (CMV) viremia (14% vs 19%) and BK nephropathy (0% vs 3%) were not

Table 1. Complications After Transplantation

	Positive Cross-Match ($n = 14$)	Negative Cross-Match ($n = 58$)	P
DGF	7%	5%	NS
Biopsy-confirmed acute rejection	50%	10%	.022
Subclinical rejection (protocol biopsy)	7%	6%	NS
Antibody-mediated rejection	43%	0%	.001
CMV infection	14%	19%	NS
BK nephropathy	0%	3%	NS