Transpl Int (2001) 14: 396–404

ORIGINAL ARTICLE

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Initial clinical experience with interleukin-2 receptor antagonist induction in combination with tacrolimus, mycophenolate mofetil and steroids in simultaneous kidney-pancreas transplantation

Received: 4 July 2000
Revised: 15 January 2001
Accepted: 3 September 2001

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Abstract Since 1996, our standard immunosuppressive protocol for simultaneous kidney-pancreas transplantation (SKPT) has been tacrolimus (TAC), mycophenolate mofetil (MMF) and steroids without antibody induction. When basiliximab and daclizumab, monoclonal antibodies directed against the interleukin-2 receptor (IL-2R), became available, we selectively added these agents to our standard protocol. The purpose of this prospective, open-label study was to evaluate the safety and efficacy of IL-2 receptor antagonists in SKPT. From April 1998 to August 1999, 35 SKPTS were performed. One patient with delayed graft function received Thymoglobulin and was excluded; 17 received no induction, and 17 received IL-2R antagonists (9 basiliximab, 8 daclizumab) as induction. Demographic- and transplant characteristics were similar between the two groups. At 6 months, patient survival was 88% (15/17) in the induction arm compared to 100% (17/17) in the no-induction arm, P = NS. The 2 causes of death were sepsis and hemolytic uremic syndrome, and both patients died with functioning grafts. Death-censored pancreas and kidney graft survival rates in the induction and the no-induction groups were 88% vs. 100% respectively, in both groups. The incidence of acute rejection (kidney or pancreas) at 6 months did not differ between the two groups (35% in both groups). Biopsy proven pancreas and kidney acute rejections were 35% vs. 24% and 12% vs. 12% in the induction- and no-induction groups, respectively. The incidences of major infection and readmission did not differ between groups. TAC trough levels and mean daily doses of TAC, MMF and steroids did not differ between the two groups at 1, 3, and 6 months. The incidence of event-free survival (no death, rejection, or graft loss) at 6 months was 59% (10/17) in the induction and 65% (11/17) in the no-induction group. Basiliximab and daclizumab appear to be safe in SKPT. However, the preliminary results of this study do not demonstrate a significant benefit in either reducing the incidence of acute rejection or improving outcomes at 6 months. Larger studies with longer follow-up are needed to confirm these findings.

Keywords Daclizumab · Basilixmab · Kidney-pancreas transplantation · Outcome · Rejection

Abbreviations *CMV* Cytomegalovirus · *IL-2R* Interleukin-2 Receptor · *MMF* Mycophenolate Mofetil · *POD* Post-Operative Day · *SKPT* Simultaneous Kidney-Pancreas Transplantation · *TAC* Tacrolimus · *UNOS* United Network for Organ Sharing

Introduction

In the recent past, the majority of simultaneous kidney-pancreas transplant (SKPT) recipients experienced at least one episode of acute cellular rejection, and most of these events occurred within the first 3 months post-transplant [5, 21]. With the evolution of immunosuppressive protocols, immunologic outcomes following SKPT have improved. However, there is no consensus as to the optimal immunosuppressive regimen for preventing rejection and improving graft survival. Most pancreas transplant centers utilize quadruple drug immunosuppression consisting of an anti-T lymphocyte agent for induction in combination with a calcineurin inhibitor, an anti-proliferative agent, and corticosteroids [5, 21]. Before the introduction of tacrolimus (TAC) and mycophenolate mofetil (MMF), cyclosporine-based therapy with azathioprine and corticosteroids was the standard immunosuppressive regimen in SKPT and was associated with an acute rejection rate of 50–80% [5, 21]. With increasing experience with the use of TAC and MMF in SKPT coupled with a lower rate of acute rejection reported in clinical trials, TAC and MMF have supplanted cyclosporine and azathioprine as maintenance immunosuppressive agents [2, 5, 6, 8, 11, 13, 14, 20, 21, 22]. Because of the improved outcomes reported with the combination of TAC and MMF, the need for anti-T lymphocyte induction has been questioned because of the lack of long-term benefits, the added costs, and the potential for serious adverse events [3, 4, 17, 18].

The introduction of monoclonal antibodies directed against the interleukin-2 receptor (IL-2R) such as basiliximab and daclizumab offers another alternative for the prevention of acute rejection in SKPT recipients [1, 12, 15, 24, 25]. These IL-2R antagonists have several advantages over traditional anti-T cell antibodies including the lack of cytokine release syndrome, absence of xenosensitization, longer half-life, and no increased risk of post-transplant infections [1, 10, 12, 15, 24, 25]. The purpose of this study was to evaluate if the addition of IL-2R antagonists for induction therapy in combination with TAC, MMF, and steroids would improve clinical outcomes without the penalty of added toxicity.

Materials and methods

Study population and design

From April 1998 to August 1999, we performed 35 simultaneous kidney-pancreas transplants (SKPT) at our center. These SKPT recipients received either induction with basiliximab, daclizumab, or no antibody induction. One patient with delayed graft function, defined as the need for dialysis within 48 h post-transplant, received Thymoglobulin induction therapy and was excluded.

This was a prospective, open-labeled, comparative study. The primary endpoints were patient-, kidney-, and pancreas graft survival rates, and the incidence of biopsy-proven acute rejection at 6 months and at the end of follow-up. Kidney graft loss was defined as return to dialysis; transplant nephrectomy, or return to pre-transplant serum creatinine level, and pancreas graft loss was defined as the need for continuous insulin therapy or transplant pancreatectomy.

Laboratory measures of kidney and pancreas functions including serum creatinine, fasting serum glucose, serum amylase and lipase were determined and compared at 1, 2, 4, 8, 12 weeks and 6 months post-transplant. Fasting C-peptide and hemoglobin A_1C levels were determined at 4, 8, 12 weeks and 6 months post-transplant. Daily tacrolimus (TAC) doses and 12-hour trough levels and daily mycophenolate mofetil (MMF) and prednisone doses were also determined and compared at 1, 2, 4, 8, 12 weeks and 6 months post-transplant.

Immunosuppression and prophylaxis regimens

All patients received TAC, MMF and steroids for maintenance immunosuppression. TAC was started at 0.1 to 0.2 mg/kg orally in two divided doses, and the 12-hour trough level was maintained at 15–20 ng/ml (IMX assay) for the first 3 months after transplantation. After 3 months, TAC levels were maintained at 10–15 ng/ml in the absence of rejection. Oral MMF was started immediately after transplant at 2 g/day, in two to four divided doses with dosage adjustment based on adverse effects such as gastrointestinal toxicity or myelosuppression. No attempt was made to intentionally lower the MMF dose in the absence of toxicity. Corticosteroids were administered as methylprednisolone 500–1000 mg intraoperatively, and 250 mg on postoperative day 1 and then tapered to oral prednisone 30 mg/day by day 7–10.

For patients randomized to IL-2R antagonist induction, basiliximab 20 mg was administered intravenously over 15–30 min via a peripheral or central vein within 24 h of transplantation, and a second dose of basiliximab 20 mg was administered on post-operative day (POD) 4. Two dosing regimens of daclizumab (2 dose or 5 dose) were used in this study. For the 2-dose regimen, daclizumab 2 mg/kg (total body weight) was administered within 24 h of transplantation, and a second dose of daclizumab 2 mg/kg was administered intravenously over 15–30 min via a peripheral or central vein on POD 14. For the 5-dose regimen, daclizumab 1 mg/kg was administered intravenously over 15–30 min within 24 h of transplantation and then every 14 days (POD 14, 28, 42, and 56) for a total of 5 doses.

The diagnosis of rejection was based on clinical criteria, renal allograft dysfunction, serum amylase and lipase levels, serum glucose levels, and renal- or pancreas allograft histopathology [16, 17]. Renal allograft rejection was suggested by an unexplained rise in serum creatinine of 0.3 mg/dl or greater and confirmed by ultrasound-guided percutaneous biopsy. Pancreas allograft rejection was suggested by an unexplained elevation in serum amylase, lipase, or glucose and confirmed by ultrasound-guided percutaneous biopsy [16, 17]. The severity of rejection was defined according to the Banff criteria for kidney biopsies and by a modification of the Maryland classification of allograft rejection for pancreas biopsies. Mild renal or pancreas allograft rejection was treated with intravenous methylprednisolone 500–1000 mg/day for 3 doses. Anti-lymphocyte therapy with OKT3, ATGAM, or Thymoglobulin for 5–10 days was used as the initial treatment for moderate or severe renal allograft rejection or pancreas allograft rejection. Steroid-resistant mild renal or pancreas allograft rejection was also treated with anti-lymphocyte therapy.

All study patients received intravenous ganciclovir (2.5 mg/kg every 12 h adjusted for renal function) during the initial hospital-

Table 1 Demographic and transplant characteristics

	IL-2R antagonist induction	No induction	*P*-value
Number of patients	17	17	
Duration of follow-up (months)	12 ± 6	17 ± 4	
Recipient demographics			
Age (years)	39 ± 9	39 ± 8	NS
Male	11 (65%)	12 (71%)	NS
African-American	3 (18%)	5 (29%)	NS
Weight (Kg)	77 ± 14	75 ± 14	NS
Duration of diabetes (years)	22 ± 7	23 ± 7	NS
Type II diabetes*	2 (12%)	2 (12%)	NS
Hepatitis C positive	1 (6%)	2 (12%)	NS
Duration of dialysis (months)	15 ± 10	11 ± 9	NS
Hemodialysis	9 (52%)	7 (41%)	NS
Peritoneal dialysis	5 (30%)	6 (35%)	NS
No dialysis	3 (18%)	4 (24%)	NS
Previous kidney transplantation	1 (6%)	2 (12%)	NS
CMV serology			
CMV donor + /recipient–	3 (18%)	4 (24%)	NS
CMV donor + /recipient +	7 (41%)	6 (35%)	NS
CMV Donor-/recipient +	3 (17%)	3 (17%)	NS
CMV Donor-/Recipient–	4 (24%)	4 (24%)	NS
Transplant characteristics			
Any pre-transplant blood transfusion	6 (35%)	7 (41%)	NS
PRA > 20%	0 (0%)	1 (6%)	NS
HLA mismatches			
A, B	3.3 ± 0.8	2.8 ± 0.8	NS
DR	1.6 ± 0.5	1.3 ± 0.7	NS
Total	4.9 ± 0.8	4.1 ± 1.2	NS
Cold ischemic time (h)			
Kidney	16.8 ± 4.9	14.0 ± 3.4	0.07
Pancreas	16.4 ± 4.9	14.0 ± 2.5	0.09
Surgical technique			
Portal-enteric	9 (53%)	9 (53%)	NS
Systemic-enteric	8 (47%)	8 (47%)	NS

* Type II diabetes is defined as pre-transplant fasting C-peptide ≥ 0.8 pmol/dl
Mean ± SD

ization followed by oral ganciclovir therapy (1 g three times daily, adjusted for renal function) for 3 months. Cytomegalovirus (CMV) seronegative patients receiving CMV seropositive organs received 6 months of oral ganciclovir therapy and selective CytoGam® therapy. All patients received sulfamethoxazole/ trimethoprim (Septra®) single strength daily for 12 months for *Pneumocystis carinii* prophylaxis and oral fluconazole 200 mg daily for 3 months for fungal prophylaxis. Patients with sulfa allergy were treated with inhaled pentamidine 300 mg once a month for 12 months.

Statistical analysis

Data are reported as mean ± standard deviation. Univariate analysis was performed by the Student's *t*-test for continuous variables, the chi-square test for categorical variables and Fisher's exact test when data were sparse. A *P*-value of less than 0.05 was considered significant.

Results

Patient characteristics

Of the 34 SKPT patients included in the study, 17 patients received no induction and 17 patients received IL-2R antagonist induction (9 basiliximab, 8 daclizumab). All patients were followed for a minimum of 6 months. Demographic, immunological and transplant characteristics were similar between the IL-2R antagonist induction and the no-induction groups. (Table 1).

Patient and graft survival

At the end of follow-up, the patient survival rate was 88% in the IL-2R antagonist induction group compared to 100% in the no-induction group, P = NS. In the IL-2R antagonist induction group, one patient expired 23 days post-transplant due to sepsis, and the other pa-

Table 2 Results

	IL-2R antagonist induction	No induction	*P*
Number of patients	17	17	
Duration of follow-up (months)	12 ± 6	17 ± 4	
Survival at the end of follow-up			
Patient survival	15 (88%)	17 (100%)	NS
Pancreas graft survival	13 (76%)	15 (88%)	NS
Kidney graft survival	15 (88%)	17 (100%)	NS
Censored pancreas graft survival*	13/15 (87%)	15/17 (88%)	NS
Censored kidney graft survival*	15/15 (100%)	17/17 (100%)	NS
Biopsy-proven acute rejection at the end of follow-up			
Pancreas allograft rejection	6 (35%)	4 (24%)	NS
Kidney allograft rejection	2 (12%)	2 (12%)	NS
Pancreas or kidney allograft rejection	6 (35%)	6 (35%)	NS
Mean time to first rejection (days)	54 ± 44	114 ± 110	
Survival at 6 months			
Patient survival	15 (88%)	17 (100%)	NS
Pancreas graft survival	14 (82%)	17 (100%)	NS
Kidney graft survival	15 (88%)	17 (100%)	NS
Biopsy-proven acute rejection at 6 months			
Pancreas allograft rejection	6 (35%)	3 (17%)	NS
Kidney allograft rejection	2 (12%)	2 (12%)	NS
Pancreas or kidney allograft rejection	6 (35%)	5 (29%)	NS
Renal function			
Serum creatinine (mg/dl)			
1 month	1.3 ± 0.5	1.2 ± 0.6	NS
3 months	1.4 ± 0.5	1.4 ± 0.5	NS
6 months	1.5 ± 0.5	1.5 ± 0.6	NS
Pancreas function			
Fasting serum glucose (mg/dl)			
1 month	99 ± 17	89 ± 35	NS
3 months	106 ± 40	99 ± 27	NS
6 months	98 ± 24	100 ± 58	NS
C-Peptide (pmol/ml)			
6 months	2.2 ± 1.8	2.1 ± 0.9	NS
Hemoglobin A_1C (%)			
6 months	6.4 ± 1.0	6.1 ± 1.1	NS
Composite endpoint			
Event-free survival[a]	10 (59%)	11 (65%)	NS

* Excludes death with functioning graft
[a] No death, graft loss, or biopsy-proven rejection
Mean ± SD

tient expired 18 days post-transplant due to systemic hemolytic uremic syndrome. Both patients died with functioning grafts. The pancreas graft survival rate in the IL-2R antagonist induction group was 13/17 (76%). There was one immunological graft loss at 11 months, one pancreas graft loss at 3 months due to persistent pancreatic fistula requiring transplant pancreatectomy, and two deaths with functioning pancreas allografts. The pancreas graft survival rate in the no-induction group was 15/17 (88%). Both pancreas graft losses were due to acute- and chronic rejection at 13 and 16 months. The kidney graft survival rate in the IL-2R antagonist induction group was 15/17 (88%), and both grafts were lost due to death with functioning graft. There was no kidney graft loss in the no-induction group. There were no differences in kidney- and pancreas graft survival rates between the two groups at 6 months or after censoring for death with functioning grafts (Table 2).

Biopsy-proven acute rejection

The incidence of biopsy-proven acute rejection was comparable between the two groups. At 6 months and at the end of the follow-up, the incidence of biopsy-proven acute renal allograft rejection was 12% in the IL-2R antagonist induction group (2 rejection episodes; one treated with steroids and one with Thymoglobulin) compared to 12% in the no-induction group (2 rejection episodes; one treated with steroids and one with OKT3). The incidence of biopsy-proven acute pancreas allograft rejection was 35% in the IL-2R antagonist induction group and 24% in the no-induction group

Table 3 Immunosuppression

	IL-2R antagonist induction	No induction	*P*-value
Number of patients	17	17	
Tacrolimus			
At 1 week			
Daily dose (mg/day)	7 ± 2	7 ± 3*	NS
12-h trough level (ng/ml)	15.7 ± 5.2	19. 6 ± 6.4	0.08
At 1 month			
Daily dose (mg/day)	10 ± 2	11 ± 6	NS
12 hour trough level (ng/ml)	18.9 ± 5.1	20.2 ± 5.7	NS
At 3 months			
Daily dose (mg/day)	8 ± 4	9 ± 4	NS
12-h trough level (ng/ml)	15.9 ± 4.8	19.9 ± 5.8	0.07
At 6 months			
Daily dose (mg/day)	11 ± 4	8 ± 4	NS
12-h trough level (ng/ml)	15.7 ± 5.3	15.3 ± 6.8	NS
Mycophenolate Mofetil			
At 1 month			
Daily dose (mg/day)	1800 ± 386	1821 ± 359	NS
At 3 months			
Daily dose (mg/day)	1633 ± 582	1661 ± 651	NS
At 6 months			
Daily dose (mg/day)	1500 ± 603	1286 ± 788	NS
Prednisone			
At 1 month			
Daily dose (mg/day)	23 ± 5	26 ± 6	0.07
At 3 months			
Daily dose (mg/day)	14 ± 3	16 ± 4	0.08
At 6 months			
Daily dose (mg/day)	11 ± 3	10 ± 2	NS

*Three patients received intravenous FK for 24–48 h immediately post-transplant.
Mean ± SD

($P = 0.45$) at the end of follow-up. Six patients in the IL-2R antagonist induction group experienced 8 episodes of acute pancreas allograft rejection. All patients received pulsed methylprednisolone therapy, and Thymoglobulin was used in two steroid-resistant rejection episodes. Four patients in the no-induction group experienced five episodes of acute pancreas allograft rejection. One patient received pulsed methylprednisolone therapy, 2 patients received OKT3 therapy, and one patient received 2 courses of Thymoglobulin therapy. In the IL-2R antagonist induction group, all episodes of acute rejection occurred within the first 6 months post-transplant. In the no-induction group, all but 1 episode of acute pancreas rejection occurred in the first 6 months post-transplant (Table 2). Event-free survival (no death, graft loss, or rejection) was 59 % in the IL-2R antagonist induction group compared to 68 % in the no-induction group.

Renal and pancreas graft functions

There were no differences in renal- and pancreas functions between the two groups at 1, 3, and 6 months as assessed by serum creatinine, serum amylase and lipase, fasting serum glucose, fasting C-peptide levels, and hemoglobin A_1C levels (Table 2). One patient in the IL-2R antagonist induction group and 2 patients in the no-induction group are receiving oral hypoglycemic agents.

Immunosuppression

Seventeen patients received IL-2R antagonist induction (9 patients received basiliximab, 3 patients received the 5-dose regimen of daclizumab, and 5 patients received the 2-dose regimen of daclizumab), and 17 patients received no induction. There were no significant differences in the 12-h trough TAC levels, TAC doses, daily MMF doses and daily prednisone doses at the specific time points of the study. However, there was a trend towards higher TAC levels at 1 week post-transplant in the no-induction group than the IL-2R antagonist induction group, 19.6 ng/ml vs. 15.1 ng/ml, respectively ($P = 0.08$). (Table 3).

Subgroup analysis

When the results were analyzed based on specific IL-2R antagonist induction agent, patient, kidney, and pancreas graft survival rates at the end of follow-up were similar between the basiliximab and daclizumab treated pa-

Table 4 Subgroup analysis at the end of follow-up

	Basiliximab	Daclizumab	No Induction	*P*-value
Number of patients	9	8	17	
Patient survival	8 (89%)	7 (88%)	17 (100%)	NS
Pancreas graft survival	7 (78%)	6 (75%)	15 (88%)	NS
Kidney graft survival	8 (89%)	7 (88%)	17 (100%)	NS
Censored pancreas graft survival*	7/8 (88%)	6/7 (86%)	15/17 (88%)	NS
Censored kidney graft survival*	8/8 (100%)	7/7 (100%)	17/17 (100%)	NS
Pancreas allograft rejection	3/9 (33%)	3/8 (38%)	4 (24%)	NS
Kidney allograft rejection	1/9 (11%)	1/8 (13%)	2 (12%)	NS
Pancreas or kidney allograft rejection	3/9 (33%)	3/8 (38%)	6 (35%)	NS
Serum creatinine (mg/dl)				
1 month	1.2 ± 0.6	1.4 ± 0.4	1.2 ± 0.6	NS
3 months	1.3 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	NS
6 months	1.4 ± 0.5	1.6 ± 0.5	1.5 ± 0.6	NS
Fasting serum glucose (mg/dl)				
1 month	101 ± 21	97 ± 11	89 ± 35	NS
3 months	112 ± 50	99 ± 28	99 ± 27	NS
6 months	95 ± 29	101 ± 17	100 ± 58	NS
C-peptide (pmol/ml)				
6 months	1.1 ± 0.3	2.9 ± 2.10	2.1 ± 0.9	NS
Hemoglobin A_1C (%)				
6 months	6.1 ± 0.5	7.1 ± 1.4	6.1 ± 1.1	NS
Event-free survival[a]	6/9 (67%)	4/8 (50%)	11 (65%)	NS

* Exclude death with functioning graft
[a] No death, graft loss, or biopsy-proven rejection
Mean ± SD

tients (Table 4). The incidence and severity of acute rejection episodes were also similar between patients treated with either basiliximab or daclizumab (Table 4). There were no differences in renal or pancreas functions or event-free survival rates based on the method of induction.

Adverse events

Both basiliximab and daclizumab were well-tolerated, and no specific adverse events were attributed to IL-2R antagonist therapy. There were no differences in the duration of hospital stay (initial and subsequent) and in the number of and the reasons for readmissions during the first 6 months post-transplant. At 6 months, 9 patients (53%) were readmitted in the IL-2R antagonist induction group, compared to 10 patients (59%) in the no-induction group, P = NS. The most common reasons for readmission in the IL-2R antagonist induction group were rejection (18%), operative complication (12%), and infection (12%). The most common reasons for readmission in the no-induction group were infection (23%), dehydration (18%), and operative complication (12%). The number of patients with any infectious episode (47%) was the same between the two groups. One patient in the IL-2R antagonist induction group developed Cytomegalovirus (CMV) colitis and one patient in the no-induction group developed CMV pneumonitis.

Discussion

According to United Network of Organ Sharing (UNOS) Registry data, approximately three-fourths of SKPT patients have received anti-T cell agents for induction therapy [5]. However, kidney- and pancreas graft survival rates were not significantly different between recipients with or without either polyclonal or monoclonal anti-T cell induction therapy, with one-year pancreas graft survival rates of 85% in the most recent era [5]. The registry data is in accordance with the preliminary results from our study, which showed no added benefits of IL-2R antagonists in either reducing the incidence of acute rejection or improving short-term graft survival rates.

The introduction of TAC and MMF has revolutionized immunosuppressive therapy in SKPT recipients. Initial experience with TAC as induction, maintenance,

and rescue therapy in pancreas transplantation has been favorable [8, 11]. Improved outcomes in pancreas transplantation with the use of TAC and MMF in combination have also been reported in the literature [14, 22]. Stratta *et al* conducted a survey of 12 pancreas transplant centers to evaluate the clinical outcomes of 102 SKPT recipients receiving TAC and MMF [22]. Thirty patients received TAC and MMF as primary therapy, and 72 patients received TAC and MMF for conversion therapy. At 6 months, patient-, kidney-, and pancreas graft survival rates were 100%, 97%, and 97% respectively, in patients receiving TAC and MMF as primary therapy, and 97%, 94%, and 96% respectively, in patients receiving TAC and MMF for conversion therapy. In a cohort of 50 SKPT patients receiving Atgam induction with TAC, MMF, and steroids, Kaufman *et al* reported an overall acute rejection rate at 6 months of 16% [14]. Nine patients in this cohort were converted to Neoral, and the acute rejection rate after conversion was 44%, compared to an acute rejection rate of 10% in patients that remained on TAC [14]. However, in a randomized, prospective trial comparing Neoral/ MMF with TAC/MMF in 36 SKPTs with OKT3 induction, Stegall *et al* reported no differences in patient and graft survival rates or the incidence of rejection between the two groups with limited follow-up [20].

Numerous groups have reported successful pancreas transplantation without antibody induction under TAC-, MMF- and steroid immunosuppression [3, 4, 17, 18] Reddy *et al* reported one-year actuarial patient-, kidney- and pancreas graft survival rates of 93%, 93% and 90% respectively, in 30 SKPT patients receiving TAC, MMF, and steroids without antibody induction [17]. The incidence of acute rejection was 30%. Corry *et al* reported their findings in a group of 123 pancreas transplant recipients, including 104 SKPTs [4]. All patients received intravenous TAC as induction, followed by oral TAC and steroids in combination with either azathioprine or MMF. Despite the high incidence of acute rejection (64%), the one-year actuarial patient-, kidney-, and pancreas graft survival rates were 98%, 95%, and 83% respectively. Moreover, only 7% of these patients required anti-T cell therapy for the treatment of acute rejection. Burke *et al* compared consecutive cohorts of SKPT patients receiving TAC, MMF and steroids with or without OKT3 induction [3] The addition of OKT3 induction did not confer any benefits in terms of patient- and graft survival rates or the incidence of rejection.

In our study, the patient-, kidney-, and pancreas graft survival rates were 100%, 100%, and 88% in the no-induction group, and 88%, 88%, and 76% in the IL-2R antagonist induction group. After censoring for death with functioning grafts, kidney and pancreas graft survival rates were 100% and 88% respectively, in both groups. The incidences of acute renal or pancreas allograft rejection in our study were similar to those reported in other clinical trials evaluating TAC, MMF, and steroid-based regimens with or without anti-T cell antibody induction. However, we noted that the incidence of biopsy-proven pancreas rejection (24–35%) was higher than the incidence of kidney rejection (12%). This rejection pattern is in contrast to previous studies in which kidney- and pancreas rejection following SKPT have been reported as synchronous or separate events in both animal models and in humans [7, 9, 23]. However, most of these studies reported a higher incidence of kidney rejection than pancreas rejection because of the reliability of serum creatinine as a marker for the early diagnosis of rejection coupled with the relative ease and safety of kidney biopsy [23]. The higher incidence of biopsy-proven acute pancreas rejection observed in our study may be related to our low threshold for performing pancreas biopsies in the clinical setting of unexplained fever, leukocytosis, abdominal pain, or elevations in the serum amylase, lipase or glucose [16].

In a subgroup analysis of 8 African-American SKPT patients (3 patients in the IL-2R antagonist induction and 5 patients in the no-induction group), the incidence of either pancreas or kidney rejection was 4/8 (50%), which is higher than expected in SKPT patients receiving TAC, MMF and steroids. The impact of ethnicity on the rates of kidney or pancreas rejection after SKPT remains to be determined.

Achieving a therapeutic TAC level early after transplantation may be an important factor in improving clinical outcomes in SKPT. In our study, there was a trend towards higher TAC levels at 1 week post-transplant in the no-induction than in the IL-2R antagonist induction group ($P = 0.08$), but no added adverse events were noted in the no-induction group, despite the higher TAC levels. Achieving an early therapeutic TAC level may minimize the benefits of antibody induction [4].

Activated T-lymphocytes play a central role in the development of acute rejection following organ transplantation. Currently, none of the available immunosuppressive agents target activated T-lymphocytes which are characterized by the expression of the α-chain of the IL-2R [26]. Monoclonal antibodies directed against the α-chain of the IL-2R have been developed with the goal to reduce acute rejection without the added toxicities seen with polyclonal or monoclonal antibodies directed against all T lymphocytes. Due to the unique mechanism of action of IL-2R antagonists and their safety profile, the addition of these agents to the standard regimen in organ transplant recipients seems logical [1, 12, 15, 24, 25].

Initial clinical experience with two of these IL-2R antagonists, basiliximab and daclizumab, have been promising in renal and cardiac transplantation, [1, 12, 15, 24, 25]. Basiliximab is a chimeric anti-IL-2R α monoclonal antibody with a half-life of 7 days, and daclizumab is a

humanized monoclonal antibody with a half-life of 20 days. The dosing strategies of these two agents are different owing to their differences in pharmacology and pharmacokinetics. Basiliximab and daclizumab in combination with cyclosporine, azathioprine or MMF, and steroids have been shown in four multi-center, randomized, controlled clinical trials to reduce the incidence of acute renal allograft rejection by about 30–40% at 6 months [12, 15, 24, 25]. In a randomized, comparative study, heart transplant recipients receiving daclizumab ($n = 28$) in combination with cyclosporine, MMF and steroids had a lower incidence of acute rejection than controls ($n = 27$), 18% vs. 63%, respectively [1].

In a recent survey of five pancreas transplant centers in the United States, daclizumab in combination with TAC, MMF and steroids was found to be safe in a cohort of 71 SKPT recipients [19]. Patient-, kidney-, and pancreas graft survival rates and acute rejection rates at 6 months were comparable to those reported in patients receiving TAC, MMF, and steroids, with or without anti-T lymphocyte antibody induction [2, 6, 13, 14, 17, 20, 22].

The theoretical benefits of IL-2R antagonists in SKPT and the benefits of IL-2R antagonists seen in other organ transplants were not observed in our study and may be related to various factors. Firstly, the sample size in our study was small and was not powered to detect a difference or equivalence. Based on the low event rates observed in the no-induction arm, to detect a significant difference in the incidence of rejection between the two treatment arms would require at least 80–100 patients in each arm. Secondly, we used two different IL-2R antagonists. Basiliximab and daclizumab have not been compared in any head-to-head clinical studies. In an attempt to study this issue, we did not find any differences in any of the endpoints between the two IL-2R antagonist subgroups. It is beyond the scope of this preliminary report to discuss any potential differences between these two agents, since our study was not powered to detect any differences between these two agents. Third, different dosing regimens of IL-2R antagonists were used in this study. If drug exposure and the degree of IL-2R blockade are necessary for optimal immunosuppressive effects, then perhaps monitoring of serum levels or IL-2R blockade may be indicated.

The clinical benefits of basiliximab and daclizumab have been observed in patients receiving cyclosporine, azathioprine or MMF, and steroids. The negative findings of our study may be related to the potent immunosuppressive state achieved with the combination of TAC, MMF and steroids, which overshadow any potential benefits of IL-2R antagonists. None of our patients had delayed graft function; therefore, high therapeutic TAC levels were achieved early post-transplant. However, antibody induction may play a role in patients with delayed graft function in which achieving high therapeutic TAC levels early after transplantation is not desirable. Antibody induction may also play a role in patients who are highly sensitized or in other high-risk immunologic settings after SKPT. The results from two multi-center, randomized, comparative studies in the SKPT population will provide important information on the use of IL-2R antagonists in SKPT, including the optimal agent, the optimal dosing strategies, and the target group that derives the most benefit.

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