American Journal of Transplantation 2003; 3: 855–864
Blackwell Munksgaard

ISSN 1600-6135

Prospective, Randomized, Multi-Center Trial of Antibody Induction Therapy in Simultaneous Pancreas-Kidney Transplantation

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A randomized, multicenter, prospective study was conducted at 18 pancreas transplant centers in the United States to determine the role of induction therapy in simultaneous pancreas-kidney (SPK) transplantation. One hundred and 74 recipients were enrolled: 87 recipients each in the induction and noninduction treatment arms. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and corticosteroids. There were no statistically significant differences between treatment groups for patient, kidney, and pancreas graft survival at 1-year. The 1-year cumulative incidence of any treated biopsy-confirmed or presumptive rejection episodes (kidney or pancreas) in the induction and noninduction treatment arms was 24.6% and 31.2% (p = 0.28), respectively. The 1-year cumulative incidence of biopsy-confirmed, treated, acute kidney allograft rejection in the induction and noninduction treatment arms was 13.1% and 23.0% (p = 0.08), respectively. Biopsy-confirmed kidney allograft rejection occurred later post-transplant and appeared to be less severe among recipients that received induction therapy. The highest rate of Cytomegalovirus (CMV) viremia/syndrome was observed in the subgroup of recipients who received T-cell depleting antibody induction and received organs from CMV serologically positive donors. Decisions regarding the routine use of induction therapy in SPK transplantation must take into consideration its differential effects on risk of rejection and infection.

Key words: Immunosuppression, induction therapy, pancreas transplantation

Received 31 January 2003,revised 27 February 2003 and accepted for publication 12 March 2003

Introduction

Use of contemporary maintenance immunosuppressive regimens in simultaneous pancreas-kidney (SPK) transplantation has played a key role in improving patient and graft survival rates and decreasing the risk of acute rejection. Independent uses of either mycophenolate mofetil (MMF) or tacrolimus show advantages over the complementary agents azathioprine and cyclosporine (CsA), respectively. Single-center, retrospective reports (1,2), and a recent multicenter, randomized, prospective trial (3) demonstrate that the risk of acute rejection in SPK transplant recipients is reduced using MMF instead of azathioprine. A multicenter, prospective, randomized study of tacrolimus vs. CsA microemulsion in SPK transplant recipients receiving MMF, steroids, and induction therapy demonstrates improved pancreas allograft functional survival and lower rates of rejection for recipients receiving tacrolimus (4). Combining MMF and tacrolimus has gained widespread acceptance as the preferred modality of maintenance immunotherapy in SPK transplantation (5–9). National data from the Scientific Registry of Transplant Recipients (SRTR) demonstrates that MMF and tacrolimus are used in greater than 80% and 75% of SPK recipients, respectively (10).

'Induction' therapy is a complementary form of immunosuppression involving antilymphocyte antibody pharmacologics that are parenterally administered for a short course

immediate post-transplant. The origin of the use of the term 'induction' is difficult to trace (it may relate to similar practices applied in the field of oncology); other words such as 'priming' and 'conditioning' have also been used. The rationale for using induction therapy pertains to the agents' potent anti-T-cell immunosuppressive properties. In this context, induction therapy is used in conjunction with maintenance agents for the purpose of minimizing the risks of early rejection episodes. It is also included when calcineurin inhibitor therapy is minimized during a course of delayed renal allograft function.

Induction therapy is almost routinely included in immunosuppressive protocols for SPK transplant recipients. According to the SRTR, induction therapy is used with greater frequency in pancreas transplant recipients than for any other solid-organ recipients. The proportion of pancreas transplant recipients who received induction therapy in 2001 exceeded 70% (10). In contrast to evidence-based decisions regarding maintenance immunosuppression, the use of induction therapy has been largely guided by practical experience rather than by results of formal, randomized, prospective, multicenter trials. The rationale is often based on the view that the relatively higher immunological risk of graft loss or rejection observed for SPK transplantation, compared with kidney transplantation alone, can be better managed by the addition of induction therapy.

The contrary viewpoint is that the combination of MMF and tacrolimus is sufficiently potent that the inclusion of induction therapy will not favorably impact outcomes but could impose a greater risk of infectious complications at an added cost. Several studies have reported that SPK transplant recipients maintained on tacrolimus, MMF, and corticosteroids without antibody induction therapy have patient and graft survival rates similar to recipients in whom induction therapy was used (11–14).

The aim of this study was to more accurately quantify the potential benefits and risks of induction therapy in SPK transplantation. The study was designed as a prospective, randomized, multicenter trial to evaluate the efficacy and safety of antibody induction therapy in SPK transplant recipients receiving a consistent maintenance protocol of tacrolimus, MMF, and corticosteroids. The primary efficacy endpoint was incidence of biopsy-confirmed acute kidney rejection. Patient and graft survival were secondary efficacy endpoints. Quality of pancreas and kidney allograft function was also compared, as well as safety assessments including incidence of opportunistic infections.

Patients and Methods

Overview

This was a randomized, open label, multicenter, prospective, parallel group study conducted at 18 centers in the United States. Approximately 119 recipients were attempted to be enrolled into each treatment arm. This was based on a power analysis with the following expectations and assumptions. With a sample size of 238 patients (119/group) there would be an 80% power to detect an absolute difference of 15% between treatment groups. This assumed that the acute rejection rate would be 25% in recipients receiving induction therapy and 40% in recipients not receiving induction (alpha = 0.05, one tailed).

The institutional review board at each center approved the protocol and written informed consent of potential recipients was obtained before enrollment. Simultaneous pancreas-kidney transplant recipients were randomized before transplantation in a 1 : 1 fashion to either receive or not receive induction therapy. Transplants were performed from February 1998 to June 1999. All recipients were followed for a minimum of 12 months. The study was designed for primary analysis of all endpoints at 6 months with extended follow-up to assess primary endpoints at 12 months.

Inclusion/exclusion criteria

Males and females, 12 years of age or older, at least 40 kg in body weight, with Type I or Type II diabetes who received a primary SPK transplant from a cadaveric donor were eligible for enrollment. Female recipients of childbearing potential had a negative pregnancy test before enrollment and had agreed to practice effective birth control during the study and for 6 weeks after the discontinuation of MMF.

Exclusion criteria were: (1) current panel reactive antibody (PRA) levels >20%; (2) recipient of pediatric en-bloc kidneys; (3) previous organ transplant; (4) recipient of another organ in addition to the pancreas and kidney allografts; (5) recipient of a living donor kidney transplant; (6) recipient of organs from a nonheart beating donor; (7) ABO incompatible blood type with donor; (8) bone marrow or stem cell infusions in conjunction with the transplant; (9) known hypersensitivity to tacrolimus, MMF, Cremophor, and/or HCO-60; (10) recipient of investigational immunosuppressants; (11) pregnancy or lactation; (12) a known carrier of any of the human immunodeficiency viruses. Recipients with delayed graft function were also excluded from the study after randomization upon determination post-transplant that the serum creatinine had failed to decrease by 20% within the first 24 h.

Treatment plan

Each transplant center randomized recipients using a centralized telephone system. Recipients were randomized to either the induction or noninduction treatment arms before the surgical procedure. The choice of induction agent was based on the institutional standard at each center and remained consistent throughout the study. Any commercially available agent could be used. This resulted in the inclusion of IL-2 receptor antibody induction agents (daclizumab and basiliximab) as well as T-cell depleting antibody induction agents [muromonab-CD3, antithymocyte globulin (equine), and antithymocyte globulin (rabbit)]. Anti-thymocyte globulin (rabbit) was not approved for marketing by the FDA until 12/30/98, consequently, relatively few recipients were randomized to receive that agent. Recipients who received muromonab-CD3, antithymocyte globulin (equine) and antithymocyte globulin (rabbit) were given a minimum of 7 and maximum of 10 days of treatment. Recipients receiving daclizumab or basiliximab were dosed per approved labeling for kidney transplantation.

All recipients received tacrolimus, MMF, and corticosteroids as primary maintenance immunosuppression. Tacrolimus was administered at a starting dose of 0.10 mg/kg per day in two divided doses based on actual body weight. Tacrolimus therapeutic drug monitoring was performed with target 12-h whole blood trough concentrations of 12–25 ng/mL for days 1–14 post-transplant, 12–20 ng/mL for days 15–90, and 10–15 ng/mL after day

90. Mycophenolate mofetil and corticosteroids were administered in the same dosing regimen in both treatment arms. Mycophenolate mofetil was administered at a dose of 2 g daily in divided doses beginning on day 1 post-transplant. Recipients received methylprednisolone (500 mg) intraoperatively, and on postoperative days 1 and 2. Subsequently, corticosteroid dosing was tapered with oral prednisone (or its equivalent) administered at 30 mg/day on postoperative days 14–29, 20 mg/day on postoperative days 30–59, 15 mg/day on postoperative days 60–89, and 5–10 mg/day after postoperative day 90.

Cytomegalovirus prophylaxis

Cytomegalovirus prophylaxis was administered to all recipients with serologic evidence of previous exposure to CMV and to recipients receiving organs from a donor with a positive CMV serologic status. Ganciclovir was administered parenterally for 7 days post-transplant followed by an oral agent (ganciclovir, high dose acyclovir, or valacyclovir) for a period of 3 months postoperatively.

Survival rates and rejection

Kidney graft failure was defined as removal, loss of function requiring return to dialysis, or death with a functioning graft. Pancreas graft failure was defined as removal of the graft, loss of endocrine function requiring return to exogenous insulin therapy for a minimum of 30 days, or death with a functioning graft. Renal function was monitored by serial measurement of serum creatinine. All episodes of renal dysfunction, defined by an increase in serum creatinine of ≥ 0.5 mg/dL or a doubling of serum creatinine from baseline or nadir, whichever was less, were evaluated for the possible occurrence of rejection. All recipients treated for rejection were to have biopsy-confirmation of kidney allograft rejection either before or within 24 h of initiating antirejection therapy. Biopsies were evaluated by the pathologist at the clinical site using the Banff criteria and were blinded to the treatment group. Banff grades for severity of kidney rejection were only recorded during the first 6 months post-transplant. After the 6-month post-transplant period, rejection was classified as acute and/or chronic without detail pertaining to severity. Pancreas graft rejection was assessed and diagnosed per standard institutional practice. This included the use of signs and symptoms consistent with rejection, measurements of serum or urinary amylase, and biopsy of the pancreas. Rejection episodes were treated per institutional practice with corticosteroids or any commercially available antilymphocyte antibody preparation. Rejection was defined according to the strength of the clinical/histological correlation of the diagnosis. Recipients were classified as having experienced an 'ever treated' rejection episode (liberal definition) if corticosteroids or antilymphocyte therapy were administered for rejection regardless of whether or not a biopsy was performed. Among this group, if a kidney biopsy demonstrated histological changes consistent with acute rejection of Banff grade 1 A or greater, they were classified as having experienced biopsy-confirmed, treated, acute kidney rejection (stringent definition).

CMV infection

CMV viremia/syndrome was defined as isolation or identification of CMV from any site (blood, urine, sputum, or stool) or positive seroconversion (presence of CMV IgM or fourfold increase in CMV IgG titers). CMV tissue invasive disease was defined as invasive or symptomatic CMV infection with histological evidence of viral cytopathic effect or a positive CMV culture from a deep tissue specimen in the setting of suggestive clinical manifestations. Specimens used for diagnosis of CMV tissue invasive disease included liver or lung biopsy, endoscopic mucosal biopsy or brushing, bronchoscopic mucosal biopsy or brushing, bronchoaveolar lavage, and cerebrospinal fluid. The presence of positive blood culture or seroconversion in the setting of symptomatic infection was also considered sufficient to establish the diagnosis of CMV disease.

Statistical analysis

The measures of efficacy were: (1) patient survival; (2) kidney and pancreas allograft survival; (3) incidence of any treated rejection (biopsy-proven or presumptive) of the kidney or pancreas allograft; (4) incidence of any biopsy-confirmed, treated, acute kidney allograft rejection; and (5) quality of renal function. Recipients were followed for 12 months post-transplant or until death. Comparison of nominal and ordinal-scaled outcomes was made using the Pearson Chi-square test. Laboratory data with repeated measures over time were analyzed using generalized estimating equations for normally distributed data to account for the correlation over time for each patient (for example, serum creatinine measured at 1, 3, and 6 months). Laboratory data were summarized using means for normally distributed data and medians for data non-normally distributed. Time-to-event data were analyzed using the Kaplan-Meier product limit estimator, with comparison of the survival curves using the log-rank test. Cumulative incidence refers to the Kaplan-Meier probability of the event at the end of 1 year, whereas the actual rate refers to the total number of events through 1 year divided by the total number of recipients. Logistic regression models were used to jointly assess the risk of a binary outcome (e.g. acute rejection) for various factors (e.g. race, treatment group). Continuous data were presented as mean $\pm$ standard deviation unless otherwise noted. All statistical tests were two-tailed and $p < 0.05$ was considered significant. All analyses were based on actual treatment received, with five recipients who did not receive their randomized treatment (two randomized to induction, three to noninduction) analyzed according to the treatment they received.

Results

There were 228 potential SPK transplant recipients randomized in the study: 114 to each treatment group. Thirty-nine recipients (21 induction, 18 noninduction) developed delayed renal allograft function and were excluded from the study as per the study protocol. Thirteen potential recipients (five induction, eight noninduction) were randomized and subsequently not transplanted: one noninduction recipient withdrew from the study; and one induction recipient did not have follow-up information available. A total of 174 recipients were enrolled in the study and received either induction ($n = 87$) or noninduction ($n = 87$) treatment. Recipient and donor demographics in the treatment arms were similar (Tables 1 and 2).

All recipients were followed for a minimum of 1 year. Approximately 66% of recipients in both groups remained on the combination of tacrolimus, MMF, and corticosteroids over the 12-month follow-up period. The primary reason for discontinuation of either tacrolimus or MMF was adverse events. Of the 87 recipients who received antibody induction, IL-2 receptor antibodies were used in 51 (59%) and anti-T-cell depleting antibodies were used in 36 (41%) (Table 3).

Figures 1A–C illustrate the median tacrolimus concentration (+75th percentile), mean MMF dose (+SD), and mean prednisone dose (+SD), respectively, among recipients in the two treatment arms. There were no differences in tacrolimus exposure between the induction and noninduction treatment arms. At week 2, the mean dose in both groups was 0.12 mg/kg/day. At month 6, the mean dose in both groups was 0.13 mg/kg/day. At 1 year, the mean

Table 1: Demographic characteristics of simultaneous pancreas-kidney transplant recipients

	Induction (n = 87) Value or percentage	Noninduction (n = 87) Value or percentage
Age (years)	39.1 ± 7.5	38.1 ± 7.0
Gender		
Females	36 (41%)	38 (44%)
Males	51 (59%)	49 (56%)
Race		
Caucasian	75 (86%)	71 (82%)
African-American	7 (8%)	10 (11%)
Oriental	1 (1%)	0
Hispanic	4 (5%)	6 (7%)
Body weight (kg)	70.2 ± 12.7	69.6 ± 14.8
Pancreas exocrine drainage		
Bladder	29 (33%)	24 (28%)
Enteric	58 (67%)	62 (71%)
Missing	0	1 (1%)
CMV		
Donor + /recipient +	18 (21%)	18 (20.5%)
Donor + /recipient –	35 (40%)	38 (44%)
Donor –/recipient +	8 (9%)	13 (15%)
Donor –/recipient –	26 (30%)	18 (20.5%)
HLA 0 mismatch	8 (9%)	8 (9%)
Panel reactive antibody level (%)	0.7 ± 2.1	1.3 ± 3.6

Table 2: Demographic characteristics of cadaver organ donors

Characteristic	Induction (n = 87) Value or percentage	Noninduction (n = 87) Value or percentage
Age (years)	27.1 ± 10.7	28.7 ± 12.1
Gender		
Male	58 (66.7%)	60 (69.0%)
Female	29 (33.3%)	27 (31.0%)
Race		
Caucasian	60 (69.0%)	58 (66.7%)
African American	13 (14.9%)	13 (14.9%)
Hispanic	11 (12.6%)	15 (17.2%)
American Indian	2 (2.3%)	0
Other	1 (1.2%)	1 (1.2%)
Cold ischemia time of kidney (h)	11.8 ± 5.6	12.2 ± 5.3
Cold ischemia time of pancreas (h)	13.1 ± 5.6	13.9 ± 5.2

dose was 0.12 mg/kg/day in the induction group and 0.11 mg/kg/day in the noninduction group. The corresponding median 12-h trough tacrolimus whole blood concentrations at week 2, month 6, and 1 year were 12.4, 10.9, and 10.2 ng/mL in the induction arm and 13.2, 11.1, and 10.9 ng/mL in the noninduction arm. The mean MMF doses were similar in the two treatment arms. At week 2, month 6, and 1 year, the mean MMF doses were 1875, 1597, and 1544 mg/day in the induction group, and 1952, 1638, and 1472 mg/day in the noninduction group.

Table 3: Antibody induction therapy (n = 87)

IL-2 receptor antibodies	
Daclizumab	39 (45%)
Basiliximab	12 (14%)
Anti-T-cell depleting antibodies	
Anti-thymocyte globulin (equine)*	17 (20%)
Muromonab-CD3	17 (20%)
Anti-thymocyte globulin (rabbit)	2 (2%)

*Two recipients also received daclizumab though antithymocyte globulin (equine) was the induction agent used at the center.

Patient and graft survival

There were no statistically significant differences in 1-year patient, kidney, or pancreas graft survival among the cohorts of recipients in the two treatment arms. Patient and graft survival (calculated using Kaplan-Meier) is illustrated in Figure 2. One-year actual patient, kidney, and pancreas graft survival rates in the induction treatment arm were 96.6%, 96.6%, and 83.9%, respectively (Table 4). One-year actual patient, kidney, and pancreas

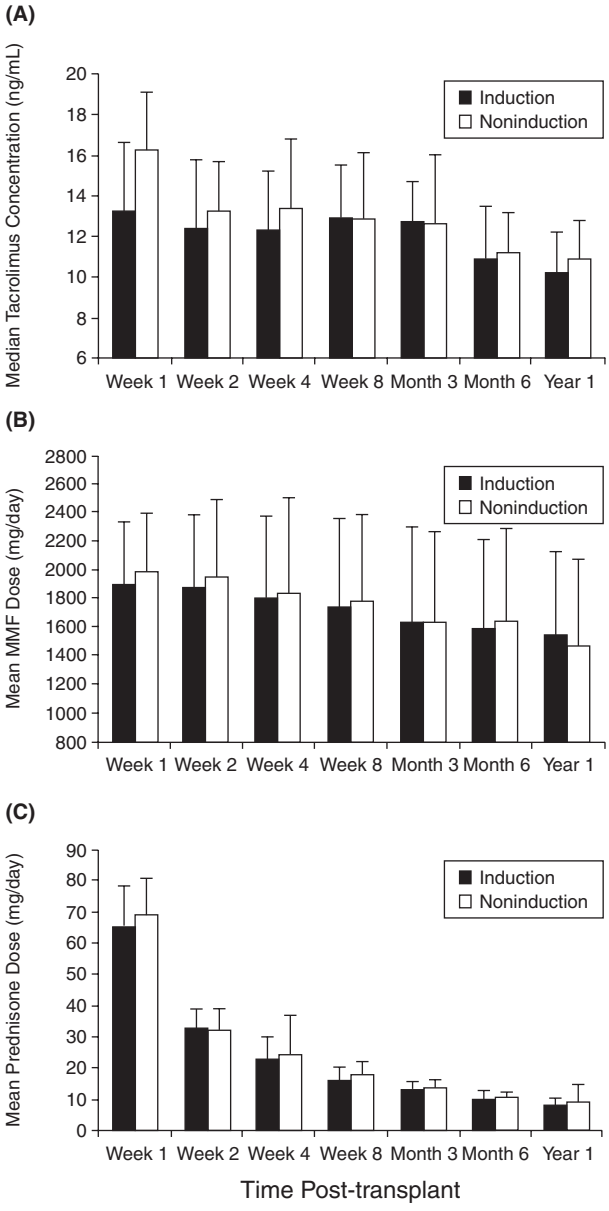

Figure 1: Comparative immunosuppression showing (A) median 12-h trough concentrations of tacrolimus (+75th percentile), (B) mean dosing of mycophenolate mofetil (+SD), and (C) mean dosing of prednisone (+SD) in simultaneous pancreas-kidney transplant recipients according to use of induction immunotherapy.

graft survival rates in the noninduction treatment arm were 94.3%, 92.0%, and 85.1%, respectively. The etiology of patient death or graft loss is shown in Table 4.

Rejection

Rejection rates were analyzed according to the strength of the clinical/histological correlations of the diagnosis. The

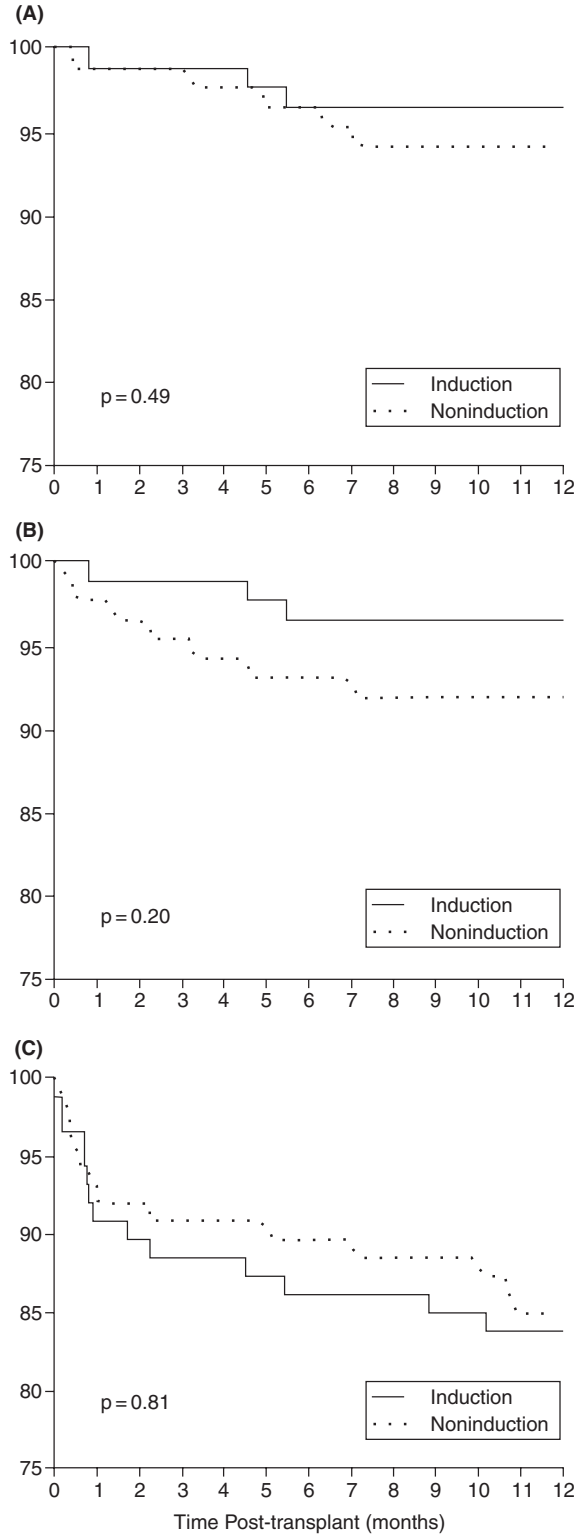

Figure 2: One-year patient (A), kidney (B), and pancreas (C) survival in simultaneous pancreas-kidney transplant recipients according to use of induction immunotherapy (Kaplan-Meier estimates shown).

Table 4: One-year actual patient and graft survival

Survival	Induction n = 87	Noninduction n = 87
Patient survival (n)	96.6% (84)	94.3% (82)
Deaths*	3	5
Bacterial infection	0	2
Fungal infection	1	2
Stroke	0	1
Hemorrhage (non GI)	1	0
Cardiac arrest	1	0
Kidney graft survival (n)	96.6% (84)	92.0% (80)
Kidney losses	3	7
Death	3	3
Rejection	0	2
Ruptured kidney	0	1
Infection	0	1
Pancreas graft survival (n)	83.9% (73)	85.1% (74)
Pancreas losses	14	13
Death	3	2
Rejection	2	3
Vascular thrombosis	2	5
Technical	2	1
Insulin use >30 days	2	0
Infection	1	1
Other	2	1

*Two noninduction recipients died after graft loss of both the kidney and pancreas. One noninduction recipient died after pancreas graft loss only.

one-year cumulative incidence of *any treated* biopsy-confirmed or presumed kidney or pancreas allograft rejection episode (liberal definition) in the induction and noninduction treatment arms was 24.6% and 31.2% (p = 0.28), respectively (Figure 3).

The 1-year cumulative incidence of biopsy-confirmed, treated, acute kidney allograft rejection (stringent definition) in the induction and noninduction treatment arms was 13.1% and 23.0% (p = 0.08), respectively (Figure 4). Not included were three recipients (two induction and one noninduction) whose kidney biopsy was classified as 'borderline changes' according to Banff criteria but whose renal function improved with antirejection therapy. Table 5 shows detail regarding timing, severity, and recurrence of biopsy-confirmed, treated, acute kidney rejection episodes. Renal allograft rejection occurred later in the induction group (median time: 98.0 days post-transplant) than in the noninduction group (median time: 19.0 days post-transplant) (p = 0.01). There were fewer cases of Banff Class 2B and 3 rejection in the induction group (one case out of 10) vs. the noninduction group (seven cases out of 18) (p = 0.19). Recurrent rejection, defined as experiencing multiple rejection episodes at least 30 days apart, was observed in one recipient in the induction group and three recipients in the noninduction group.

The effect of patient race on the risk of rejection was also assessed. Table 6 summarizes biopsy-confirmed, treated, acute kidney rejection in African-American vs. non-African-American recipients. The risk of biopsy-confirmed, treated, acute kidney rejection was more than fivefold greater in African-American recipients when compared with non-African-American recipients even when controlling for induction vs. noninduction using a logistic regression model (p = 0.002).

Laboratory values and safety assessments

Analyses of renal allograft function (BUN, Cr), pancreas allograft function (glucose, HgbA1C), bone marrow

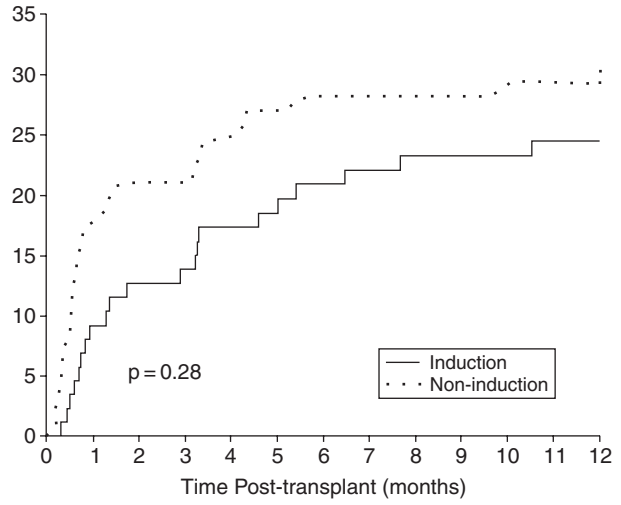

Figure 3: Cumulative incidence of ever treated (biopsy-confirmed or presumed) rejection episodes of the kidney or pancreas allograft in simultaneous pancreas-kidney transplant recipients according to use of induction immunotherapy.

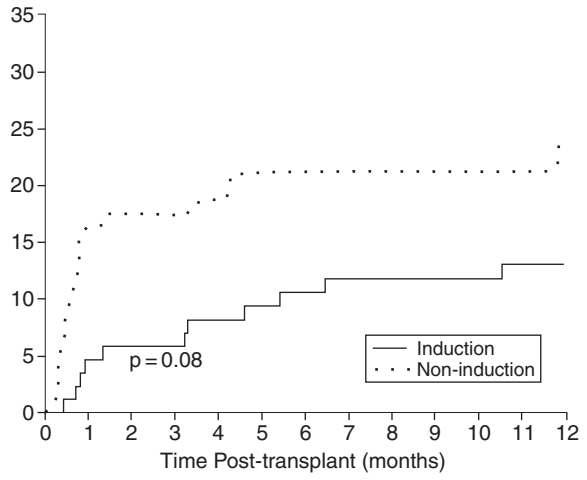

Figure 4: Cumulative incidence of biopsy-confirmed, treated, acute kidney allograft rejection episodes in simultaneous pancreas-kidney transplant recipients according to use of induction immunotherapy.

Table 5: One-year actual biopsy-confirmed, treated, acute kidney rejection

	Induction n = 87	Noninduction n = 87
Actual biopsy-confirmed, treated, acute kidney rejection (n)*	12.6% (11)	21.8% (19)
Median time to onset (days post-transplant)	98.0	19.0
Banff classification of most severe rejection episode		
1 A	3	3
1B	0	2
2 A	6	6
2B	1	4
3	0	3
Not available	1	1
Number of recipients with recurrent rejection	1	3

*p = 0.11, Chi-square test.

Table 6: One-year biopsy-confirmed, treated, acute kidney rejection by recipient race

Group	Induction†	Noninduction†
African-American*	3/7 (43%)	5/10 (50%)
Non-African-American*	8/80 (10%)	14/77 (18%)

*Odds ratio (African-American to non-African-American) 5.30 (p = 0.002).
†Odds ratio (non-induction to induction) 1.86 (p = 0.15).

function (Hgb, plts, WBC), liver function tests, and total cholesterol levels showed no statistically significant differences between the treatment arms (data not shown). The mean serum creatinine at different follow-up time points is depicted in Figure 5. In the induction group, mean serum creatinine values at week 2, month 6, and month 12 post-transplant were 1.32 mg/dL, 1.32 mg/dL, and 1.33 mg/dL, respectively. In the noninduction group, mean serum creatinine values at week 2, month 6, and month 12 were 1.47 mg/dL, 1.39 mg/dL, and 1.38 mg/dL, respectively. Although there was no statistically significant difference between groups in mean serum creatinine, there was a trend toward lower serum creatinine over time in the induction arm (p = 0.06). With respect to elevated serum creatinine values, the proportion of recipients who ever had a serum creatinine greater than 2 mg/dL at any time through post-transplant year 1 was statistically significantly higher in the noninduction group (40%) vs. the induction group (21%) (p = 0.007).

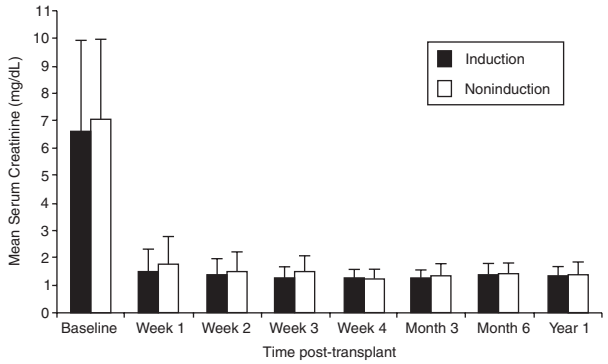

Figure 5: Mean (+SD) serum creatinine values post-transplant in simultaneous pancreas-kidney transplant recipients according to use of induction immunotherapy.

The occurrence of CMV tissue invasive disease and CMV viremia/syndrome was also assessed. The incidence of CMV tissue invasive disease was 3.5% (3/87 recipients) in both the induction and noninduction treatment arms and was not affected by the type of induction therapy given (Table 7). However, a greater proportion of recipients in the induction group developed CMV viremia/syndrome (14.9%) when compared with the noninduction group (6.9%) (p = 0.09). In recipients at high risk to acquire CMV (donor CMV seropositive), 20.8% of recipients that received induction developed CMV viremia/syndrome compared with 7.1% in the noninduction group (p = 0.04). When the high-risk cohort was stratified according to the induction agent received, there was a statistically significant difference in the incidence of CMV viremia/syndrome among recipients who received anti-T-cell antibody induction agents (45.8%) vs. IL-2 receptor antibodies (0.0%) or no induction (7.1%) (p < 0.0001, Table 7).

Discussion

Several single-center publications have challenged the common practice of routinely using induction therapy for SPK transplantation. Corry et al. (12) reported 1-year patient, kidney, and pancreas survival rates of 98%, 95%, and 83%, respectively, in more than 100 SPK recipients using tacrolimus, steroids, and either azathioprine or MMF without induction therapy. An extension of this experience examined long-term outcomes (13). At a mean follow-up of 3 years, patient, kidney, and pancreas survival rates were 96.5%, 91%, and 80%, respectively. Reddy et al. (14) reported 1-year actual patient, kidney, and

Table 7: CMV infection

	Anti-T cell Antibody induction	Anti-IL-2R Antibody induction	Non-induction
CMV tissue invasive disease			3.5% (3/87)
All recipients	5.6% (2/36)	2.0% (1/51)	3.5% (3/87)
Recipients at high risk*	8.3% (2/24)	3.5% (1/29)	5.4% (3/56)
CMV viremia/syndrome			
All recipients†	33.3% (12/36)	2.0% (1/51)	6.9% (6/87)
Recipients at high risk*†	45.8% (11/24)	0.0% (0/29)	7.1% (4/56)

*CMV seropositive organ donor.
†$p < 0.0001$, Chi-square test.

pancreas survival rates of 93%, 93%, and 90%, respectively, in a single-center retrospective analysis of 30 SPK recipients also using tacrolimus, MMF, and steroids without induction therapy. The incidence of primary and recurrent acute rejection was 30%, and 10%, respectively. The rate of CMV infection was 13% (0% tissue-invasive).

The prospective, randomized approach of the current study had many advantages, including consistent use of a maintenance regimen that is still used in the majority of transplant centers engaged in SPK transplantation. However, there were some notable limitations. The study had an enrollment not sufficiently powered to generate statistical significance of endpoints with relatively rare occurrence (i.e. mortality and graft loss). This was primarily because of the unexpected low rate of rejection in both treatment groups. To have 80% power to detect a difference in biopsy-confirmed, treated, acute kidney rejection of 9.2% with a rate of 12.6% in the induction group and 21.8% in the noninduction group would have required 229 patients in each group for a total sample size of 458 patients. The exclusion criteria also precluded analysis of recipients with delayed renal allograft function. This accounted for 39 recipients (approximately 17% of the total enrollment). The rationale was that it was common medical practice to minimize calcineurin inhibitor exposure during the time of renal recovery by temporary substitution with an antilymphocyte agent. Another limitation was that relatively few recipients received antithymocyte globulin (rabbit). This occurred as a result of the fact that enrollment began months before marketing approval of the agent.

One-year patient and graft survival rates in both treatment arms were nearly identical. This was not an unexpected observation. Historically, virtually all studies that have examined the influence of induction therapy on patient and graft survival rates have generated the same conclusion. An exception to that generalization comes from a recent analysis of data by the International Pancreas Transplant Registry (IPTR) on outcome of US cases of SPK transplantation. Recipients with systemic venous/enteric exocrine drainage of the pancreas that received tacrolimus-MMF immunosuppression demonstrated a statistically significant improvement in pancreas allograft survival with the addition of induction therapy (15). The current study was not designed to examine the relationship of surgical methods on outcome, though it may be an important consideration in future studies.

In general, the pertinent endpoints of studies examining the role of induction therapy relate to the incidence, timing, severity, and recurrence rates of rejection. In this study, the method by which rejection was defined had bearing on the relative efficacy of induction therapy. Using a liberal definition based on presumptive assessment of rejection did not indicate that induction therapy altered outcome. However, when a more stringent definition was used, which was based on a clinical/histological correlation that required biopsy-confirmation of acute kidney allograft rejection, there was a notable difference in the incidence, timing, and severity of acute rejection: all favoring the inclusion of induction therapy.

With respect to infectious complications, the rate of CMV viremia/syndrome was higher in recipients that received T-cell-depleting induction agents, particularly in recipients receiving cadaveric organs from donors previously exposed to CMV according to serologic evaluation. This is a potentially important observation, as acquisition of CMV infection has been associated with decreased patient survival in SPK transplantation (16). Longer-term follow up will be required to determine its consequences in these study cohorts, and whether it will become an endpoint useful in distinguishing among the different classes of induction agents. It is important to note that the T-cell-depleting antibodies employed in this study overwhelmingly included muromonab-CD3 and equine antithymocyte globulin (collective use 34/36 cases) with only two cases of rabbit antithymocyte globulin use. Furthermore, the study was designed to examine the concept of induction therapy in general terms, rather than assess the risks and benefits according to a particular class of agents.

A recently published complementary study has examined the utility of a specific induction agent in SPK transplantation (17). The study was designed as a multicenter, prospective, randomized study comparing two dosing regimens of daclizumab (1 mg/kg for five doses and

2 mg/kg for two doses) vs. no antibody induction therapy in SPK recipients on tacrolimus, MMF, and prednisone. The primary endpoint was a composite of rejection (kidney or pancreas), graft loss, or death within the first 6 months post-transplant. This composite endpoint was reached by 34% of recipients that received the standard 5-dose regimen, 20% of recipients that received the short 2-dose schedule, and 50% of recipients in the noninduction treatment arm. With respect to patient and graft survival rates, there were no significant differences among the three study groups. The incidence of acute kidney rejection (presumptive or biopsy-proven) was 18% in the standard 5-dose treatment group, 8% in the short course two-dose treatment arm, and 36% in the noninduction group. The incidence of major bacterial, fungal, or viral infections requiring hospitalization was 6–9% in all three groups. No serious adverse drug events associated with daclizumab were reported.

Finally, concerns regarding the relatively high cost of induction therapy have led many centers to carefully consider its routine use. Excessive costs for pharmacologics significantly affect the financial margin on the initial hospitalization for the transplant procedure. From this perspective, hospital expenses cannot be neglected when determining the utility of induction therapy. However, decision-making must also take into consideration how upstream fiscal enactments may impact downstream medical quality issues. For example, regarding the risk of acute rejection, if a course of induction therapy reduces the incidence of early re-hospitalization for antibody treatment of rejection, then the cost/benefit analysis might favor its use. Conversely, if the incidence of infectious complications is associated with inclusion of induction therapy, then quality medical issues may disfavor its routine use. As many transplant contract obligations require the provider to indemnify transplant-related complications for a given time post-transplant, the *timing* of rejection and/or infectious complications also becomes an important consideration.

In conclusion, for SPK transplant recipients without delayed renal graft function, the addition of antibody induction therapy to a maintenance regimen consisting of tacrolimus, MMF, and corticosteroids did not significantly affect patient and graft survival rates throughout 1 year of post-transplant follow up. Induction therapy was associated with a clinical advantage in the incidence, timing, and severity of biopsy-confirmed, treated, acute kidney rejection episodes. Recipients that received induction therapy also benefited from fewer elevations in serum creatinine levels. Offsetting these benefits was a trend toward more CMV viremia/syndrome. Anti-T-cell depleting induction agents, in particular, were associated with a statistically significantly higher rate of CMV viremia/syndrome, especially in the subgroup of recipients who received organs from CMV serologically positive donors. Given the complexities of defining medical benefit and the intricacies of related fiscal issues, each transplant center must determine whether the use of induction therapy in general, and application of a specific agent, in particular, is appropriate based on these diverse perspectives.

Acknowledgments

This study was presented at Transplant 2000: the Joint Congress of the ASTP and ASTS, May 2000, in Chicago, IL. It was supported by a grant from Fujisawa Healthcare, Inc., Deerfield, IL.

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