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Induction in Pancreas Transplantation: T-cell Depletion Versus IL-2 Receptor Blockade

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Background. There is limited data exist on relative outcomes with T-depletion versus IL-2 receptor (IL2R) blockade induction in pancreas transplantation. **Methods.** We analyzed all patients who underwent simultaneous pancreas-kidney or pancreas transplant alone at our institution between January 1, 2011, and December 31, 2019. **Results.** Of 417 pancreas transplant recipients, 291 received induction with a T-depleting agent and 126 received induction with an IL2R blocker. No difference was detected in pancreas allograft death-censored ($P=0.7$) or uncensored ($P=0.5$) survival. Although pancreas rejection was more common overall ($P=0.03$), this difference was no longer present in recipients at low immunologic risk ($P=0.08$). Cytomegalovirus and bacterial infections were significantly more common in the patients who received T-cell depleting agents for induction (21% versus 11%, $P=0.03$; 34% versus 23%, $P=0.04$, respectively). On multivariate analysis, history of pancreas rejection (Hazard ratio (HR) = 4.7, $P=0.0001$; 95% Confidence interval (CI), 2.16-10.12) and higher calculated panel reactive antibodies (HR = 1.01, $P=0.04$; 95% CI, 1.0002-1.02) were associated with increased risk of pancreas allograft failure, but choice of induction was not (HR = 0.64, $P=0.3$; 95% CI, 0.27-1.51). Further, on multivariate analysis, Cytomegalovirus infection was associated with increased risk of pancreas allograft rejection (HR = 1.78, $P=0.01$; 95% CI, 1.11-2.87), but choice of induction was not (HR = 0.84, $P=0.46$; 95% CI, 0.54-1.32). Similarly, bacterial infection was associated with increased risk of patient death (HR = 2.94, $P=0.04$; 95% CI, 1.03-8.32). **Conclusion.** Our data suggest that IL-2 receptor blockade may be a reasonable choice of induction for pancreas transplant recipients at low immunologic risk.

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INTRODUCTION

Pancreas transplantation in patients with insulin-dependent diabetes mellitus reduces many complications associated with prolonged hyperglycemia, improves quality of life,[1-3] and prolongs life.[4,5] However, alloimmunity continues to contribute to chronic pancreas allograft dysfunction and limits its long-term success.[6,7] Acute and chronic pancreas allograft rejection are important factors for long-term pancreas allograft failure.[8,9] To prevent acute rejection and reduce the need for maintenance immunosuppression, the use of biologic agents for induction at time of transplant has become standard of care for pancreas transplantation. T-cell depleting agents, such as rabbit antithymocyte globulin (rATG) or alemtuzumab (ALEM), as well as the IL-2 receptor (IL2R) blocking agent (basiliximab), are used as induction agents for pancreas transplantation. According to registry data, rATG and ALEM are the 2 most commonly used induction agents for simultaneous pancreas and kidney (SPK) transplants. However, high-quality studies comparing outcomes between induction with T-cell depletion and IL2R blockade in pancreas transplantation are lacking.

We analyzed our experience comparing these 2 induction approaches in terms of patient and pancreas allograft survival, rejections, and infectious complications.

MATERIALS AND METHODS

Study Population

This was a single-center retrospective study. The study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin. We included all patients who underwent SPK or pancreas transplant alone (PTA) at our institution between January 1, 2011, and December 31, 2019. None of our patients had pancreas after kidney transplants.

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We found no statistically significant differences between antithymocyte globulin and ALEM recipients in patient survival, graft survival, rejections, or infections, so the 2 groups were combined for analysis in this article. In addition, there were no significant differences between SPK and PTA recipients in the impact of T-depletion versus IL2R blockade on outcomes, so the 2 groups were combined for further analysis.

Donor and recipient characteristics were collected from the University of Wisconsin Allograft Recipient Database. Information on donors included donation after circulatory death, age, gender, race, body mass index, hypertension, terminal serum creatinine, death due to cerebrovascular accident, Kidney Donor Profile Index, and cold ischemic time of the kidney and the pancreas. Information on recipients included age, race, gender, body mass index, length of time on dialysis in months, and duration of diabetes in years. Immunologic factors included average human leukocyte antigens mismatch (of 6), panel reactive antibody (PRA) < or ≥10%, and type of induction therapy. Pancreas factors included enteric or bladder drainage of exocrine secretions.

Pancreas Transplant Procedure

All pancreas allograft transplants were accomplished using enteric drainage, a side-to-side duodeno-jejunostomy to the proximal jejunum without a Roux-en-Y, and systemic venous drainage to the proximal right common iliac vein or distal inferior vena cava. In patients with SPK transplant, the kidney transplant was placed contralaterally to the left iliac vessels. Patients did not routinely receive a nasogastric tube and did not go to the intensive care unit postoperatively. No intravenous anticoagulation was used routinely.

Induction and Maintenance Immunosuppression

Immunosuppression was accomplished with induction therapy and triple maintenance therapy, which was adjusted to patients based on immunologic risk. The final decision of induction therapy was made by the primary transplant surgeon at the time of transplant surgery.

Induction was with either ALEM (30 mg × 1), antithymocyte globulin (rATG, 1.5 mg/kg × 4), or basiliximab (20 mg × 2). Maintenance therapy for all patients included oral tacrolimus (initial target levels 8–10 ng/mL in the first year and 6–8 ng/mL thereafter) and oral mycophenolic acid (720 mg BID). Steroids were administered as 100 mg IV dexamethasone intraoperatively and tapered thereafter. In patients receiving ALEM, early steroid withdrawal was performed in rare, selected patients.

Infection Prophylaxis

Standard prophylaxis included antibacterial, antifungal, and antiviral therapies that are protocolized and risk stratified. In patients at high risk (donor positive/recipient negative) or intermediate (recipient positive) risk for cytomegalovirus (CMV) infection, prophylaxis with valganciclovir was used for 6 mo. In those at low risk for CMV infection (donor negative/recipient negative), acyclovir was given for 3 mo for prophylaxis of herpes infection.

All patients also received clotrimazole or nystatin for 1 mo and sulfamethoxazole-trimethoprim for 1 y as antifungal and antipneumocystis prophylaxis, respectively.

Pancreas Allograft Rejections and Death-censored Pancreas Allograft Loss

Most pancreas rejections were diagnosed by biopsy, but we included those that were diagnosed by clinical judgement based on serum pancreas enzyme levels. The most common indication for pancreas graft biopsy was an unexplained rise in pancreatic enzymes. The practice patterns for the indication of pancreas biopsy have been consistent, except recently we have been performing protocol biopsy guided by the detection of de novo Donor-specific antibodies even with stable pancreatic enzymes.

Death-censored pancreas graft failure was defined as pancreatectomy, retransplantation, or return to insulin for >3 mo. The patients who had pancreas allograft loss within 30 d of surgery from mechanical complications of the surgery were not included in the analysis.

Statistical Analysis

Continuous data were compared using Student's *t*-test, whereas categorical data were analyzed using the chi-square test, when appropriate. Univariate and multivariate Cox regression analyses were performed to determine the risk factors associated with death-censored kidney allograft failure. *P* values <0.05 were considered statistically significant. The only time we used a cutoff of $P < 0.1$ was in choosing which variables from the univariable analysis would be included in the multivariable analysis. All analyses were performed using the MedCalc Statistical Software, version 16.4.3 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2016). Data are reported as mean ± SD or percentages.

Stratification of patients into the low immunologic risk group was based on not having a prior transplant and having a calculated panel reactive antibodies (cPRA) <10.

RESULTS

Baseline Characteristics

A total of 417 pancreas transplants were performed during the study period; 291 (70%) received induction with a T-depleting agent (183 with antithymocyte globulin and 108 with ALEM), whereas 126 (30%) received induction with an IL2R blocker (basiliximab) (Table 1).

Baseline characteristics are shown in Table 1. Considering the baseline demographics between the 2 groups, there were significant differences in (1) SPK transplants, with more SPK transplants in the IL2R blocker group than the T-cell depleting group (84% versus 59%, $P = 0.001$); (2) PTA transplants, with fewer PTA transplants in the IL-2R blocker group as compared to the T-cell depleting group (16% versus 41%, $P = 0.001$); (3) cPRA, with lower cPRA in the IL2R blocker group than the T-cell depleting group (9.4 ± 22 versus 14 ± 28, $P = 0.03$); and (4) the posttransplant mean follow-up, for which the mean posttransplant follow-up was longer in the IL2R blocker group than the T-cell depleting group (6 ± 2.5 y versus 4.6 ± 2.3 y, $P = 0.001$). The mean cold ischemia time for pancreas allografts was 13 ± 4 h in the IL2R blocker group, whereas in the T-cell depleting group, it was 14 ± 10 h, a difference which was not statistically significant ($P = 0.06$). A history of previously failed pancreas allograft was not different between the IL2R blockade group and the T-cell depleting group (10% versus 10%, $P = 1$). Similarly, human leukocyte antigens-mismatches in the IL2R blocker group and the T-cell depleting group were not significantly different (4.3 ± 1.1 versus 4.4 ± 1.2, $P = 1$).

TABLE 1.

Baseline characteristics

Characteristics	T-depleting induction group (n = 291)	IL2R blockade induction group (n = 126)	*P*
Mean age at time of transplant (y)	46 ± 10	46.5 ± 10	0.2
Caucasian (%)	247 (85%)	110 (87.3%)	0.5
Male (%)	164 (56.3%)	80 (63.5%)	0.2
DCD transplants (%)	58 (20%)	18 (14%)	0.1
Enteric drainage (%)	291 (100%)	126 (100%)	
Cold ischemic time (h)	14 ± 10	13 ± 4	0.06
History of previously failed pancreas transplant (%)	28 (10%)	13 (10%)	1
SPK transplant (%)	**171 (59%)**	**106 (84%)**	**0.001**
PTA (%)	**120 (41%)**	**20 (16%)**	**0.001**
HLA mismatch	4.4 ± 1.2	4.3 ± 1.1	1
cPRA	**14 ± 28**	**9.4 ± 22**	**0.03**
Low immunologic group (cPRA <10, no previous transplant)	209 (72%)	94 (74%)	0.6
Mean follow-up posttransplant (y)	**4.6 ± 2.3**	**6 ± 2.5**	**0.001**

cPRA, calculated panel reactive antibodies; DCD, donor after circulatory death; IL2R, IL-2 receptor; PTA, pancreas transplant alone; SPK, simultaneous pancreas and kidney transplant.

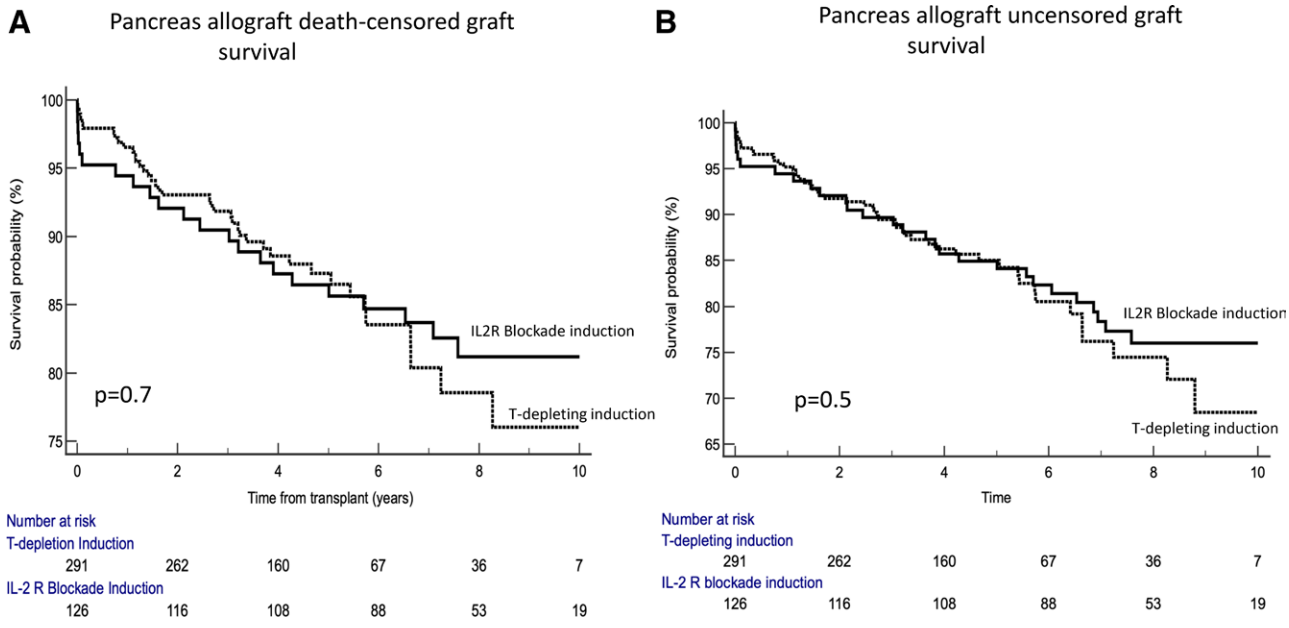

FIGURE 1. Pancreas allograft outcomes. A, Pancreas allograft death-censored graft survival. B, Pancreas allograft uncensored graft survival. IL2R, IL-2 receptor.

Patient and Graft Survival

There was a total of 16 (4%) patient deaths, 10 (3%) in the T-depleting group and 6 (5%) in the IL2R blocker group ($P = 0.3$) (Figures 1A,B and 2A,B; Tables 2 and 3). There was a total of 62 patients with death-censored pancreas allograft failure, 40 (14%) with death-censored pancreas graft failure in the T-depleting group and 22 (17.4%) with the IL2R blocker ($P = 0.4$). No difference was detected in pancreas death-censored ($P = 0.7$) and uncensored ($P = 0.5$) graft survival between the T-depleting and IL2R blocker groups (Figure 1A,B).

On multivariate analysis, history of pancreas rejection (hazard ratio (HR) = 4.7, $P = 0.0001$; 95% confidence hinterval (CI), 2.16-10.12) and higher cPRA (HR = 1.01, $P = 0.04$; 95% CI, 1.0002-1.02) were associated with increased risk of death-censored pancreas allograft failure, but choice of induction was not (HR = 0.64 $P = 0.3$; 95% CI, 0.27-1.51) (Table 2).

In subgroup analysis of patients with low immunologic risk (n = 303), no difference was detected in pancreas death-censored ($P = 0.9$) and uncensored ($P = 0.6$) graft survival between the T-depleting and IL2R blocker groups (Figure 2A,B).

In the SPK group (n = 277), no difference was detected in pancreas death-censored graft survival ($P = 0.4$) between T-depleting induction and IL2R blockade induction (Figure 3A). Similarly, in the PTA group (n = 140), no difference was detected in pancreas death-censored graft survival ($P = 0.4$) (Figure 3B).

On multivariate analysis, bacterial infection within the first year after transplant was associated with increased risk of patient death (HR = 2.94, $P = 0.04$; 95% CI, 1.03-8.32), but the choice of induction was not (HR = 0.94; $P = 0.91$, 95% CI, 0.32-2.71) (Table 3).

Pancreas Allograft Rejection

There was a total of 110 (26%) patients with acute rejection of their pancreas allograft, 67 (23%) in the T-depleting group and 43 (34%) in IL2R blocker group ($P = 0.02$) (Figure 4A,B; Table 4). On unadjusted Kaplan-Meier analysis, there were

TABLE 2.

Variables associated with death-censored pancreas allograft survival

Variables	Univariate analysis			Multivariate analysis		
	HR	*P*	95% CI	HR	*P*	95% CI
Age at time of transplant	0.98	0.15	0.95-1.00			
White	0.67	0.23	0.35-1.29			
Male	0.84	0.51	0.51-1.39			
Donor type (DCD vs Others)	0.82	0.59	0.40-1.67			
Type of transplant (SPK vs PTA)	0.72	0.22	0.43-1.21			
Induction (T-depleting vs IL2R blockade)	0.91	0.73	0.53-1.55	0.64	0.3	0.27-1.51
HLA matching per additional match	0.96	0.69	0.78-1.17			
Cold Ischemia time per hour	0.68	0.99	0.96-1.02			
Pancreas rejection	**3.89**	**<0.0001**	**2.35-6.45**	**4.7**	**0.0001**	**2.16-10.12**
CMV infection in first year posttransplantation	0.27	0.64	0.29-1.41			
Fungal infection posttransplantation	0.73	0.76	0.10-5.30			
Bacterial infection posttransplantation	0.99	0.99	0.58-1.70			
History of previous failed pancreas	**2.48**	**0.005**	**1.32-4.66**	0.3	0.2	0.03-2.34
cPRA >10	**1.01**	**0.03**	**1.00-1.02**	**1.01**	**0.04**	**1.0002-1.02**

CI, confidence interval; CMV, cytomegalovirus; cPRA, calculated panel reactive antibodies; DCD, donor after circulatory death; HR, hazard ratio; IL2R, IL-2 receptor; PTA, pancreas transplant alone; SPK, simultaneous pancreas and kidney transplant.

TABLE 3.

Variables associated with patient death

Variables	Univariate analysis			Multivariate analysis		
	HR	*P*	95% CI	HR	*P*	95% CI
Age at time of transplant	1.03	0.13	0.98-1.09			
White	0.40	0.11	0.12-1.25			
Male	0.41	0.09	0.15-1.14	0.49	0.18	0.17-1.39
Donor type (DCD vs Others)	2.20	0.14	0.76-6.34			
Type of transplant (SPK vs PTA)	3.40	0.10	0.77-14.97			
Induction (T-depleting vs IL2R blockade)	0.77	0.63	0.27-2.21	0.94	0.91	0.32-2.71
HLA matching per additional match	0.93	0.75	0.63-1.39			
Cold Ischemia time per hour	1.01	0.21	0.99-1.04			
CMV infection in first year posttransplantation	1.93	0.25	0.61-6.05			
Bacterial infection posttransplantation	**3.34**	**0.02**	**1.21-9.21**	**2.94**	**0.04**	**1.03-8.32**
More than 1 pancreas transplant	0.71	0.74	0.09-5.41			
cPRA >10	1.01	0.26	0.99-1.03			
Pancreas allograft rejection	0.64	0.48	0.18-2.24			

CI, confidence interval; CMV, cytomegalovirus; cPRA, calculated panel reactive antibodies; DCD, donor after circulatory death; HR, hazard ratio; IL2R, IL-2 receptor; PTA, pancreas transplant alone; SPK, simultaneous pancreas and kidney transplant.

significantly more rejections in the IL2R blockade group than the T-depleting group ($P = 0.03$) (Figure 4A). However, when limiting the analysis to low immunologic risk patients, no difference was detected in pancreas allograft rejection between the T-depleting and IL-2R blockade group ($P = 0.08$) (Figure 4B).

On multivariate analysis, CMV infection after transplant (HR = 1.78, $P = 0.01$; 95% CI, 1.11-2.87) was associated with increased risk of pancreas rejection, but choice of induction was not (HR = 0.84, $P = 0.46$; 95% CI, 0.54-1.32). Being White (HR = 0.4, $P = 0.0006$; 95% CI, 0.25-0.68) and having an SPK transplant (HR = 0.62, $P = 0.03$; 95% CI, 0.40-0.95) were protective for pancreas allograft rejection (Table 4).

Incidence of CMV and Bacterial Infections After the Pancreas Transplant

The incidence of infections was analyzed after the pancreas allograft transplant to look for adverse effects that may be attributable to T-depleting induction (Figure 5A,B). There was a total of 74 (18%) patients with posttransplant CMV infection, 60 (21%) in the T-depleting induction group and 14 (11%) in the IL2R blocker induction group ($P = 0.03$) (Figure 5A). There was a total of 128 (31%) patients with bacterial infections such as urinary tract infections, pyelonephritis, or pneumonia, 99 (34%) in the T-depleting group and 29 (23%) in IL2R blocker group ($P = 0.04$) (Figure 5B).

DISCUSSION

There are limited data comparing outcomes with different induction agents in pancreas transplantation. T-depleting agents (rATG or ALEM) and IL2R blockers (basiliximab) have all been used as induction therapy.[10-12] In this large series of >400 pancreas transplants, 291 patients received induction with a T-depleting agent, and 126 patients received induction with a IL2R blocker agent. We compared the pancreas allograft outcomes, patient death, and infections in these 2 groups. With the understanding that higher immunologic risk

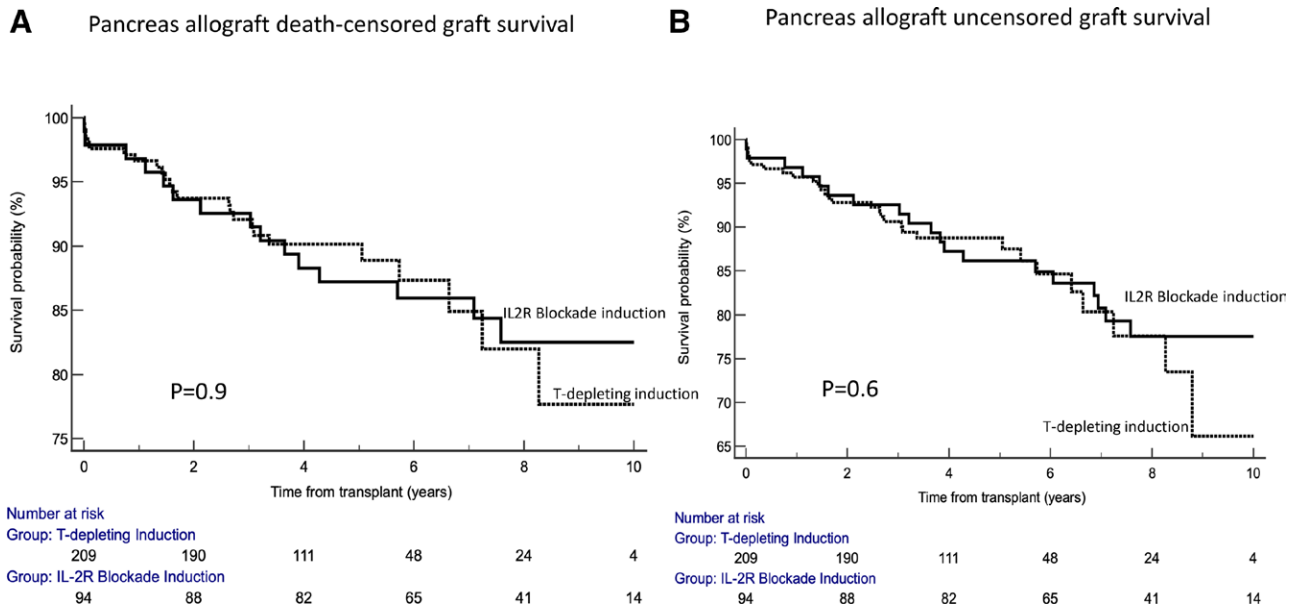

FIGURE 2. Pancreas allograft outcomes in patients with low immunologic risk. A, Pancreas allograft death-censored graft survival. B, Pancreas allograft uncensored graft survival. IL2R, IL-2 receptor.

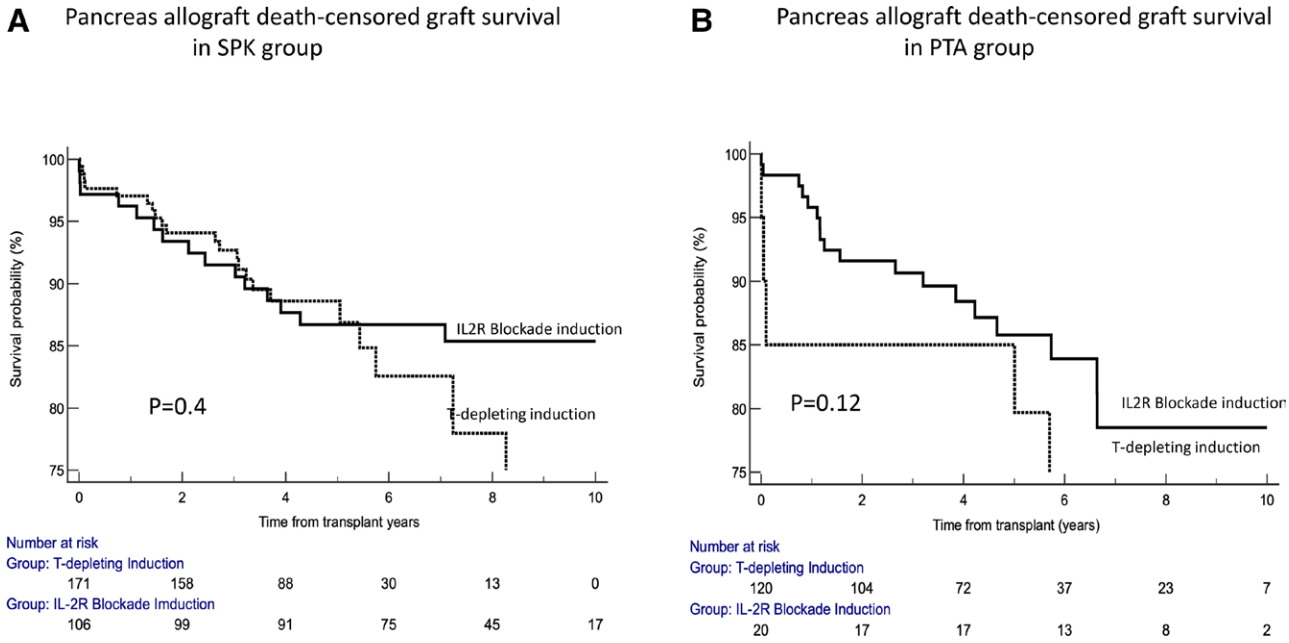

FIGURE 3. Pancreas allograft outcomes in SPK and PTA groups. A, Pancreas allograft death-censored graft survival in SPK group. B, Pancreas allograft death-censored graft survival in PTA group. IL2R, IL-2 receptor; PTA, pancreas transplant alone; SPK, simultaneous pancreas and kidney transplant.

patients were more likely to have received T-depleting induction, patient and pancreas allograft survival were not different in multivariable analyses of those who received the IL2R blockade for induction. In addition, the overall difference in rejection rates between T-depletion and IL2R blockade was not seen in low immunologic risk patients, and on multivariable analysis, we did not find any significant difference in the incidence of pancreas allograft rejection between the 2 induction groups. In our study, the patients were placed into the low immunologic risk group based on not having a prior transplant and having a cPRA <10. Additional factors that would likely suggest lower immunologic risk include SPK (versus PTA) transplant and history of good adherence with medical care. We do not have donor-specific antibodies data for most of our cohort, but the presence of donor-specific antibodies in the current era would clearly put transplant recipients in a higher immunologic risk category. We found a significantly higher risk of CMV and bacterial infections in the patients who received induction with a T-depleting agent than the IL2R blockade.

There are a few studies that have compared the 2 T-depleting induction agents rATG versus ALEM in pancreas transplantation. These studies did not find any significant difference between these 2 agents in terms of patient and pancreas allograft survival.[13,14] Mogliocca et al compared ALEM induction with basiliximab induction in an earlier era of SPK transplantation before 2005.[15] They did not find statistically significant differences in patient survival (99% versus 95%), kidney allograft survival (93% versus

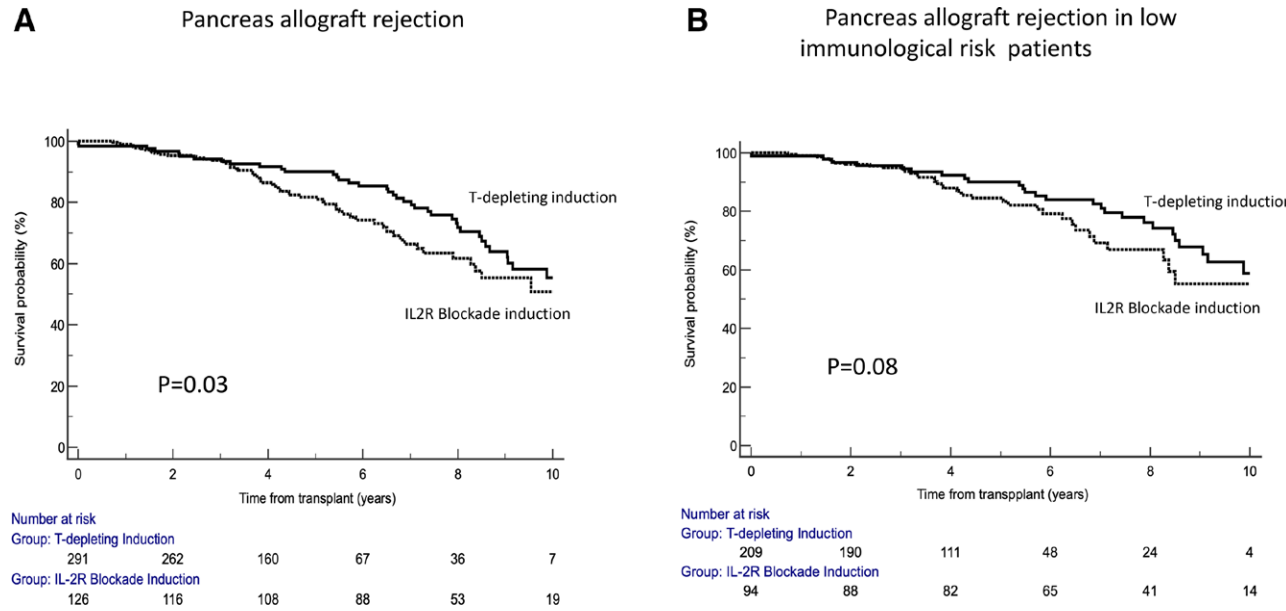

FIGURE 4. Pancreas allograft rejection. A, Pancreas allograft rejection. B, Pancreas allograft rejection in low immunologic risk patients. IL2R, IL-2 receptor.

TABLE 4.

Variables associated with pancreas allograft rejection

Variables	Univariate analysis			Multivariate analysis		
	HR	*P*	95% CI	HR	*P*	95% CI
Age at transplant	**0.98**	**0.04**	**0.961-0.99**	0.98	0.08	0.96-1.00
White	**0.46**	**0.002**	**0.28-0.75**	**0.41**	**0.0006**	**0.25-0.68**
Male	0.98	0.92	0.67-1.43			
Donor type (DCD vs Others)	0.86	0.59	0.50-1.46			
Type of transplant (SPK vs PTA)	**0.66**	**0.03**	**0.45-0.96**	**0.62**	**0.03**	**0.40-0.95**
Induction (T-depleting vs IL2R blockade)	**0.65**	**0.03**	**0.43-0.97**	0.84	0.46	0.54–1.32
HLA matching per additional match	1.12	0.15	0.95-1.32			
Cold Ischemia time per hour	0.98	0.30	0.95-1.01			
CMV infection in first year posttransplantation	**1.72**	**0.02**	**1.07-2.75**	**1.78**	**0.01**	**1.11-2.87**
Fungal infection posttransplantation	0.59	0.47	0.14-2.47			
Bacterial infection posttransplantation	0.86	0.49	0.57-1.30			
More than 1 pancreas transplant	0.70	0.24	0.39-1.26			
cPRA >10	1.003	0.26	0.99-1.009			

CI, confidence interval; CMV, cytomegalovirus; cPRA, calculated panel reactive antibodies; DCD, donor after circulatory death; HR, hazard ratio; IL2R, IL-2 receptor; PTA, pancreas transplant alone; SPK, simultaneous pancreas and kidney transplant.

90%), or pancreas allograft survival (92% versus 85%) between the 2 groups. In another study, Bazerbachi et al compared rATG and basiliximab induction. Long-term graft function and survival were not affected by induction regimen.[16] That study included fewer than half as many patients as ours, but the results are consistent with our findings, in which we did not detect any significant differences in terms of patient and graft survival between T-depleting induction and IL2R blockade induction. Notably, our study included PTA in addition to SPK, with the same results.

There are some contradictory reports regarding pancreas allograft rejection and the use of induction agent. Several studies did not find significant differences in the rate of pancreas rejection based on induction.[13,14] In contrast, Bazerbachi et al found a higher incidence of rejection with basiliximab induction. These differences in results are likely due to the fact that none of the studies were randomized, and they differed in their approach to selecting patients to receive basiliximab—some programs were likely more aggressive in limiting recipients of basiliximab to those felt to be at lower immunologic risk. Our study did not find a significant difference in pancreas allograft rejection between T-depleting induction and IL2R blockade induction, likely because IL2R blockade tended to be used in recipients of first transplants with lower cPRA, those receiving SPK rather than PTA, and those whose historical adherence to medical regimens was felt to be better.

Multiple studies have reported higher rates of CMV viremia with rATG and ALEM induction in SPK recipients. CMV viremia is reported to range from 16% to 46% with T-depleting induction and around 7% with IL2R blockade induction.[12,14,15] Our study also found higher incidence of CMV viremia with T-depleting induction than the IL2R blockade (21.5% versus 11%). We also found a higher incidence of bacterial infections in patients with T-depletion than the IL2R blockade.

This study has all the limitations of being an observational series from a single center. Decisions to use IL2R blockade

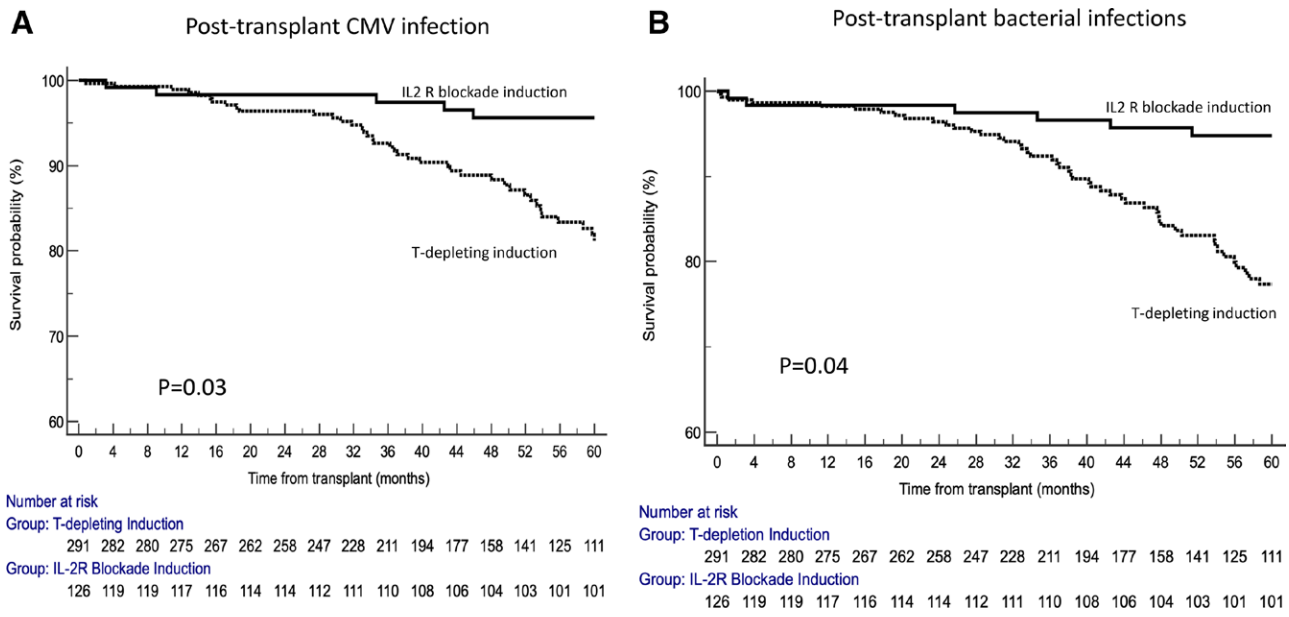

FIGURE 5. Infections after transplant. A, Posttransplant CMV infection. B, Posttransplant bacterial infections. CMV, cytomegalovirus; IL2R, IL-2 receptor.

were not based on randomization but on surgeon preference and subjective assessment of patients being at lower immunologic risk at the time of transplant. However, data on all transplant recipients are collected prospectively, and our database is one of the few in the country large enough to provide these results. Additionally, although our single-center design is a limitation, to the best of our knowledge, this is the largest modern series describing the issues related to T-depleting induction versus IL2R blocker induction in pancreas allograft recipients including both SPK and PTA recipients. With this, we were able to provide more granular data, and it reflects a homogeneous approach to induction, maintenance immunosuppression protocols, and the use of CMV and bacterial prophylaxis. Our findings suggest that, in appropriately selected patients, IL2R blockade induction for pancreas transplantation provides equivalent patient and pancreas survival when compared with T-depleting induction. However, bacterial and CMV infection rates were higher in patients who received the T-cell depleting agent for induction. Based on these findings, we suggest that IL2R blockade may be a reasonable choice of induction for pancreas transplant recipients at low immunologic risk. These observations highlight the need to randomize clinical trials to better define appropriate induction agent use in pancreas transplant recipients.

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