Alemtuzumab Induction and Tacrolimus Monotherapy in Pancreas Transplantation: One- and Two-Year Outcomes

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Background. Alemtuzumab (Campath-1H) induction with tacrolimus monotherapy has been shown to provide effective immunosuppression for kidney, liver, lung, and small bowel transplantation. This drug combination was evaluated in pancreas transplant recipients.

Methods. Sixty consecutive pancreas transplants (30 simultaneous pancreas-kidney, 20 pancreas after kidney, and 10 pancreas alone) were carried out under this protocol between July 2003 to January 2005. The mean follow-up was 22 months (range 17–33).

Results. One-year patient, pancreas, and kidney allograft survival were 95%, 93%, and 90%, respectively. With 22 months follow-up, patient, pancreas, and kidney survival were 94%, 89%, and 87%, respectively. The rejection rate was 30% (18/60), with four patients (7%) experiencing steroid-resistant rejection. Major infection occurred in three (5%) patients resulting in two (3.3%) deaths from disseminated histoplasmosis and a herpes virus infection. One patient with cryptococcal meningitis was successfully treated. Seven (11.7%) patients experienced cytomegalovirus infection, all of whom responded to treatment with ganciclovir. One (1.7%) case of polymorphic posttransplant lymphoproliferative disease was seen, which regressed with a temporary discontinuation of tacrolimus and high-dose ganciclovir. The mean serum creatinine of the 30 simultaneous pancreas-kidney transplants at one year posttransplant was 1.37±0.33 mg/ml. The preexisting creatinine in pancreas after kidney transplants was not adversely affected by this immunosuppressive protocol.

Conclusion. A single dose of perioperative alemtuzumab followed by daily tacrolimus monotherapy provides effective immunosuppression for pancreas transplantation, but the optimal use of this drug combination is not yet clear.

Keywords: Pancreas transplantation, Immunosuppressive, Steroid-avoidance, Campath.

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Since mid 2001, T cell depletion combined with low-dose tacrolimus monotherapy has been used as a standard protocol for organ transplantation at our center (*1*). Lymphoid depletion with antithymocyte globulin (ATG, Thymoglobulin) in 2001–2002 gave way to alemtuzumab depletion from 2003 onward after it was demonstrated that alemtuzumab (Campath-1H) is a more potent agent with fewer acute side effects (*2–6*). However, the strategy with both antibody preparations was based on the same two therapeutic principles: first, reduction of global immune reactivity prior to arrival of the allograft, and second, the minimalistic use of posttransplant immunosuppression. The immunologic rationale behind the principles has been reviewed elsewhere (*7, 8*).

The co-application of these principles with the combination of alemtuzumab and tacrolimus monotherapy has been demonstrated in our center for liver (*9*), kidney (*10, 11*), lung (*12*), and small bowel (*13*) transplantation. It has been possible in many of these patients to increase the interval between doses of maintenance tacrolimus monotherapy to every two days or even to as long one dose per week. Since both the calcineurin inhibitor drugs and prednisone are diabetogenic, the potential attractiveness is obvious of a regimen that includes both steroid avoidance and minimum exposure to tacrolimus. However, in our previous experience with ATG-tacrolimus, the risk of rejection of pancreas grafts with the institution of space weaning was thought to be greater than that to other kinds of organ allografts (*1*). Consequently, in our early experience with pancreas transplantation reported here under alemtuzumab-tacrolimus, efforts were not made to space wean beyond a one dose per day for at least one year. Moreover, weaning after one year was not systematically attempted.

PATIENTS AND METHODS

Immunosuppressive Protocol

From July 2003 to January 2005, 60 consecutive primary pancreas transplants were performed under the alemtuzumab/tacrolimus monotherapy regimen (30 simultaneous pancreas-kidney [SPKs], 20 pancreas after kidney [PAKs], 10 pancreas alone [PTA]). Follow-up in this group of adults was to June 1, 2006 with a range of 17–33 months (mean 22).

The 30 mg alemtuzumab was given perioperatively over two hours. Two grams of methylprednisolone were given, one gram as premedication for the alemtuzumab infusion to prevent a cytokine syndrome and the second gram at the time of pancreas allograft reperfusion. Twice-daily tacrolimus was started orally at day one posttransplant with a

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12-hr trough target of 10–12 ng/ml. At one year posttransplant, an attempt was made in a few of the stable patients to convert to once-a-day tacrolimus with a 24-hr trough target of 7–9 ng/ml. Any further reduction of tacrolimus doses was guided by clinical status (e.g. infection, posttransplant lymphoproliferative disease).

Antibiotic prophylaxis included routine trimethoprim/sulfamethoxasole (life-long) and nystatin (three months). Valganciclovir prophylaxis (450 mg PO daily) was maintained for three months postoperatively for cytomegalovirus (CMV), except in the CMV seropositive donor to seronegative patients, where it was continued for 12 months. CMV antigenemia was performed weekly for the first three months, and monthly thereafter.

Rejection was monitored by routine postoperative amylase and lipase levels. Elevation of these pancreatic enzymes, usually twice the baseline, would prompt an ultrasound-guided biopsy to confirm or refute allograft rejection histologically. Rejection scored as moderate or severe was treated with antibody therapy (usually 30 mg Campath 1H). Minimal or mild acute rejection was treated with steroid boluses. No maintenance prednisone was ever added. Steroid resistance, as defined as no reduction in lipase levels after two grams of intravenous (IV) methylprednisolone for biopsy-confirmed rejection, was treated with anti-T cell antibody. In a small number of patients, mycophenolate mofetil (MMF; 500 mg twice per day) was added temporarily until amylase and lipase levels returned to baseline. However, an increase in maintenance tacrolimus to achieve a 12-hr trough above 10 ng/ml usually was adequate treatment.

RESULTS

Mortality, graft function, and other data are given separately for SPK, PAK, and PTA in Table 1, and then grouped for the following overall analysis of all 60 cases.

TABLE 1. Breakdown of outcomes in pancreas transplant categories

	SPK (n=30)		PAK (n=20)		PTA (n=10)	
	1 year	2 year	1 year	2 year	1 year	2 year
Deaths	1	2	0	1	1	0
Patient survival (%)	97	93	100	95	90	90
Pancreas loss	3	4	0	1	1	2
Pancreas survival (%)	90	87	100	95	90	80
Kidney loss	3	4	0	1	—	—
Kidney survival (%)	90	87	100	95	—	—
Rejection	9 (30%)		6 (30%)		3 (30%)	
Infection						
Cytomegalovirus	4 (13%)		1 (5%)		2 (20%)	
Cryptococcal meningitis	0		1 (5%)		0	
Human herpesvirus 6	0		1 (5%)		0	
Histoplasmosis	0		0		1 (10%)	
Posttransplant lymphoproliferative disease	1 (3%)		0		0	

Patient and Graft Survival

One-year patient survival was 95%, pancreas graft survival was 93%, and renal allograft was 90%. With a mean follow-up of 22±9 months (range 17–33 months), patient survival was 94%, pancreas graft survival was 89%, and kidney allograft survival was 87%.

Causes of Patient Death and Graft Loss

The four patient deaths were due (one each) to disseminated histoplasmosis (PTA, 3 months), stroke (SPK, 13 months), autoimmune hemolytic anemia (SPK, 10 months), and sepsis (PAK, 13 months). All four had functioning pancreas grafts at the time of death. The three graft losses that occurred without patient death were caused (one each) by arterial thrombosis, rejection, and a pseudoaneurysm of an extension graft that required pancreatectomy.

Rejection

The overall rejection rate in this cohort over the entire follow-up period was 30%, with rejection episodes occurring between 3–18 months posttransplantation. Four patients experienced pancreas allograft rejection more than one year posttransplantation. Of the 18 patients with rejection, 11 were successfully treated with boluses of methylprednisolone. The remaining seven patients with severe or moderate rejection (n=3) or steroid-resistant rejection (n=4) were treated with a second lymphoid depletion (usually another dose of Campath-1H). Pancreatic rejection was highly correlated with persistently low trough tacrolimus levels, consistent with our previous report that early posttransplant pancreas rejection is rare if the 12-hr tacrolimus trough is ≥10 ng/ml (*14*) Beyond one year, rejection was uncommon if the tacrolimus trough level was above 7 ng/ml.

Infection and Posttransplant Lymphoproliferative Disease (PTLD)

Severe infection was seen in three (5%) patients, resulting in two (3.3%) deaths, one from histoplasmosis and the other from a combined CMV/herpes virus (HHV6) infection. The third patient had cryptococcal meningitis and was successfully treated with antifungal therapy. All seven (11.7%) of 60 patients in whom cytomegalovirus infection was detected by CMV antigenemia were successfully treated with either IV gancyclovir or high dose valganciclovir (900 mg orally BID).

One patient developed Epstein-Barr virus (EBV)-associated polymorphic PTLD 15 months posttransplant, manifested by a small bowel bleed requiring exploration and resection. The patient responded to a temporary cessation of tacrolimus and high-dose valganciclovir. The patient is now two years posttransplantation and doing well with functioning allografts on once daily tacrolimus.

Creatinine

SPK

The mean serum creatinine level in the SPK group was 1.44±0.32 mg/dl one year posttransplantation and 1.37±0.33 mg/dl at 18 months.

PAK

In the PAK group, the serum creatinine provided by the prior renal allografts in 20 recipients was 1.41±0.27 mg/dl at

TABLE 2. Serum creatinine from the time of pancreas transplantation (day 0) in PAK patients

	Day 0	3 months	6 months	9 months	12 months	>18 months
N	20	20	20	20	20	19
Mean	1.41	1.43	1.50	1.51	1.48	1.45
SD	0.27	0.36	0.48	0.44	0.40	0.38
P value vs. day 0[a]		0.67	0.13	0.60	0.38	0.13

[a] Paired two-tailed Student's *t*-test.

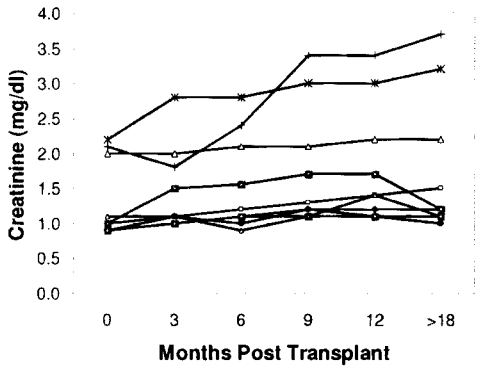

FIGURE 1. Months posttransplant.

the time of pancreas transplantation. With all but one of the 20 patients and grafts surviving for 18 subsequent months, there was no significant increase in the serum creatinine (Table 2).

PTA

In the PTA group, the patient who died after three months from histoplasmosis was excluded. The serum creatinines of the other nine patients are shown individually in Figure 1. The slight upward trend in most of these patients was ascribed to tacrolimus nephrotoxicity. As expected, the nephrotoxicity was most obvious in those with preexisting renal dysfunction.

DISCUSSION

This experience demonstrated that a single dose of alemtuzumab, followed by tacrolimus monotherapy, provides effective immunosuppression for pancreas transplantation. The results were consistent with the studies of alemtuzumab reported from other centers (*15–22*) and by us (*9–12*) in which alemtuzumab was combined with various baseline immunosuppressants for different other kinds of organ transplantation. In addition to the one and two year patient and graft survival, the profile of infectious and other complications (including the risk of PTLD) in our pancreas recipients was similar to that usually reported under conventional multiple drug immunosuppression. Despite relatively high 12 and 24 hr drug trough levels, tacrolimus monotherapy used in our protocol was relatively free of nephrotoxicity. However, the optimal timing and dosage of alemtuzumab and tacrolimus remain to be determined.

The management policy employed for the 60 recipients reported here was strongly influenced by our prior experience between July and December 2001 with 14 pancreas recipients (10 SPK, 4 PTA) in whom the lymphoid depletion was done with a single dose of 5 mg/kg ATG (Thymoglobulin) rather than with alemtuzumab (*1*). In these patients, tacrolimus doses were spaced after four or more months to one dose per day, every other day, or longer intervals. The "space weaning" was associated with a high rate of rejection of the kidney, pancreas, or both organs. The diagnosis and management of pancreas rejection proved to be particularly difficult. To avoid these problems, space weaning, even to the point of one dose per day, was avoided throughout the first year in the current series.

With the policy of continuous twice daily tacrolimus for the first year, the alemtuzumab-depleted patients reported here had a zero incidence of rejection during the first three months. From this time onward, however, 30% of the recipients experienced rejection. Efforts to reduce either the doses or the dose frequencies of tacrolimus, or to withdraw MMF after MMF had been introduced to treat breakthrough rejection, were not well tolerated. It appeared that the requisite maintenance immunosuppression for these patients was fixed at whatever level had been arbitrarily decided upon at the outset. Of interest, the late dependence on immunosuppression may be more pronounced than that observed in the 14 ATG-depleted patients of 2001 (*23*).

The differences between the two series do not constitute a comparison between ATG and alemtuzumab. It has been increasingly recognized that alloengraftment/tolerance mechanisms can be subverted by the timing and quantity of posttransplant immunosuppression thereby contributing to the amount of treatment needed chronically (*8, 24, 25*). With this insight, better strategies for the more efficient combined use of alemtuzumab and tacrolimus should be possible (*25*).

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