LONG-TERM RESULTS OF PANCREAS TRANSPLANTATION UNDER TACROLIMUS IMMUNOSUPPRESSION

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Background. The long-term safety and efficacy of tacrolimus in pancreas transplantation has not yet been demonstrated. The observation of prolonged pancreatic graft function under tacrolimus would indicate that any potential islet toxicity is short-lived and clinically insignificant. We report herein the results of pancreas transplantation in patients receiving primary tacrolimus immunosuppression for a minimum of 2 years.

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Methods. From July 4, 1994 until April 18, 1996, 60 patients received either simultaneous pancreas-kidney transplant (n=55), pancreas transplant only (n=4), or pancreas after kidney transplantation (n=1). Baseline immunosuppression consisted of tacrolimus and steroids without antilymphocyte induction. Azathioprine was used as a third agent in 51 patients and mycophenolate mofetil in 9. Rejection episodes within the first 6 months occurred in 48 (80%) patients and were treated with high-dose corticosteroids. Antilymphocyte antibody was required in eight (13%) patients with steroid-resistant rejection.

Results. With a mean follow-up of 35.1±5.9 months (range: 24.3–45.7 months), 6-month and 1-, 2-, and 3-year graft survival is 88%, 82%, 80%, and 80% (pancreas) and 98%, 96%, 93%, and 91% (kidney), respectively. Six-month and 1-, 2-, and 3-year patient survival is 100%, 98%, 98%, and 96.5%. Mean fasting glucose is 91.6±13.8 mg/dl, and mean glycylated hemoglobin is 5.1±0.7% (normal range: 4.3–6.1%). Mean tacrolimus dose is 6.5±2.6 mg/day and mean prednisone dose 2.0±2.9 mg/day at follow-up. Complete steroid with-
drawal was possible in 31 (65%) of the 48 patients with functioning pancreases.

Conclusions. These data show for the first time that tacrolimus is a safe and effective long-term primary agent in pancreas transplantation and provides excellent long-term islet function without evidence of toxicity while permitting steroid withdrawal in the majority of patients.

Simultaneous pancreas-kidney (SPK*) transplantation has enjoyed increasing success over the last decade and has therefore become accepted therapy for diabetic patients with end-stage renal disease. However, with both SPK, and even more so with pancreas transplantation alone (PTA) and pancreas after kidney transplantation (PAK), success is limited by rejection rates with cyclosporine (CsA)-based therapy reported as high as 60–80%, even when induction antilymphocyte therapy has been used (1–3). The introduction of tacrolimus (TAC) has ushered in a new era for immunosuppression of solid organ recipients. Its use is associated with a lower incidence of acute rejection in primary kidney transplantation compared with CsA in both U.S. and European multicenter trials (4, 5). TAC also has the ability to rescue kidney, liver, and pancreas grafts from rejection refractory to standard immunosuppressive protocols (6-8) and has the added advantage of permitting concomitant steroid tapering in both adult (9) and pediatric (10) renal transplantation, with up to 60% of patients eventually weaned from prednisone. Additional data suggest that TAC may also yield longer half-lives for kidney transplants than standard CsA-based regimens (11). These observations have encouraged several centers, (8, 12, 13) including our own (14), to evaluate the safety and efficacy of TAC as primary therapy for pancreas transplantation. Thus far, reports with relatively short-term (one year or less) follow-up have confirmed the utility of TAC, and in some cases, suggested it is superior to CsA for SPK (8, 12, 14). Because of the reported potential for diabetogenicity associated with TAC (4–6, 9, 15), there has been reluctance by some centers to adopt this drug for primary pancreas transplantation, even though the reputed diabetogenicity has been shown to be short-lived and reversible in the majority of cases (4–6, 9, 10, 15). Nevertheless, we felt it important to examine in more detail the outcome of pancreas transplantation under TAC, especially in the long term, paying particular attention to the long-term diabetogenic potential, which has utmost relevance in the pancreas transplant recipient. We, therefore, report herein our experience in the first 60 pancreas recipients transplanted at our institution under TAC immunosuppression, all of whom have been followed for a minimum of 2 years. The results support the use of TAC as a safe long-term agent for pancreas transplantation without an increased risk of posttransplant diabetes compared with traditional CsA-based regimens.

PATIENTS AND METHODS

Donor and recipient demographics. Between July 4, 1994 and April 18, 1996, 60 patients (29 men, 31 women) with a mean age of 36.8 ± 6.3 years (range: 25.8–52.6 years) received TAC-based immunosuppression as primary therapy for cadaver pancreas transplantation. Fifty-five (92%) patients underwent simultaneous pancreas-kidney (SPK) transplantation, 4 (6.5%) a pancreas transplant alone (PTA), and 1 (1.5%) a pancreas after a previous kidney transplant (PAK). Of the 55 SPK patients, 49 (90%) were primary kidney transplant recipients and 6 (11%) were undergoing repeat transplantation (5 second, 1 third). All patients were undergoing primary pancreas transplantation. The mean number of HLA matches and mismatches was 1.4±1.1 and 4.3±1.2, respectively (Table 1). The mean donor age was 26.2±12.9 years (range: 6–54 years). Eight donors were ≤45 years old, and 14 were ≥15 years old. The mean cold ischemia time (CIT) for the kidney transplant was 14.9±5.2 hr (range: 6–25 hr) and for the pancreas transplants 16.8±4.9 hr (range: 7–28 hr). Seventeen of the pancreas transplants were drained into the bladder, and 43 were drained enterically.

Immunosuppression. All patients received primary TAC-based immunosuppression with a steroid tapering regimen, as described previously (14). Antilymphocyte antibody induction was not used. In addition to TAC and steroids, 51 (85%) patients received azathioprine (AZA) at 2 mg/kg/day and 9 (15%) received mycophenolate mofetil (MMF) (CellCept®) at 1 g twice daily. AZA and MMF doses were titered to maintain a white blood cell count >5000/mm³ and according to gastrointestinal side effects in the case of MMF. Patients received intravenous TAC at 0.05 mg/kg/day for 5 days postoperatively, followed by an initial oral dose of 0.15 mg/kg twice daily. The TAC dose was adjusted to achieve target whole blood trough levels of 20–25 ng/ml in the first 2 weeks after transplant, 15–20 ng/ml by 1 month, 10–15 ng/ml by 2 months, 7–12 ng/ml by 6 months, and 5–10 ng/ml thereafter. In the presence of stable graft function steroids were tapered by 2.5–5 mg every 2 weeks with the aim of complete steroid weaning by 12–18 months. All patients received prophylaxis for Pneumocystis carinii pneumonia with trimethoprim-sulfamethoxazole. Cytomegalovirus (CMV)-seronegative recipients of CMV-seropositive organ donors (n=14) had biweekly testing for CMV antigenemia (pp65) and were treated with a 14-day course of intravenous ganciclovir if CMV antigenemia was positive. Routine prophylaxis for CMV was not given.

Rejection. The diagnosis of acute rejection was suspected in patients with a >10% increase in baseline serum creatinine (SCr) or a rising or sustained increase in serum lipase (15), or both. The presence of rejection was confirmed either by fine needle aspiration biopsy of the kidney or pancreas or core needle biopsy of the kidney, or both. Biopsy-confirmed rejection was treated with either intravenous somatrembol boluses (generally 500 mg daily for 3 days) or by a tapering steroid recycle (200 mg to 20 mg over 6 days). Steroid-resistant rejection episodes were treated with antilymphocyte antibody (OKT3 or ATGAM) for 7–14 days.

Statistical analysis. Patient survival rate was calculated from the date of transplantation until death, and the graft (kidney or pancreas) survival rate from the date of transplantation until graft failure or patient death. Survival curves were generated using the Kaplan-Meier (product limit) method. Data were analyzed for statistical significance by analysis of variance where appropriate.

<table>
<thead>
<tr>
<th>Table 1. HLA matches and mismatches</th>
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<tbody>
<tr>
<td>No. of HLA matches</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>0</td>
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<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
</tr>
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<td>4</td>
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<tr>
<td>5</td>
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<td>6</td>
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</tbody>
</table>
RESULTS

Patient and graft survival. The mean follow-up was 35.1±5.9 months (range: 24.3–45.7 months). Overall 6-month and 1-, 2-, and 3-year actuarial patient survival was 100%, 98%, 98%, and 96.5% (Fig. 1). Of 60 recipients, 57 (95%) are currently alive. One PTA patient died of a brain stem infarct 10 months after transplant; this patient had lost her graft at 3 months to recurrent rejection. The two other deaths occurred in SPK patients. One patient died of multiple system organ failure and inanition 25 months after transplant. A second SPK patient died 39 months after transplant of unknown causes on dialysis; the lymphocytotoxic crossmatch had become positive on the third day after transplant.

After 100% pancreaticojejunostomy, the transplant was retransplanted to the right iliac fossa because of severe pancreatitis 13 days after transplant. Four pancreases were lost to rejection, three to thrombosis, two to infection (one splenic artery anastomotic pseudoaneurysm with abscess), two as a result of severe pancreatitis, and one to duodenal ischemia with fistula. High-risk donor factors contributing to the eight nonimmunologic graft losses could be identified in five cases and included prolonged CIT (23 hr) and pressor support in one, a ligated inferior pancreaticoduodenal artery that was unrecognized at the time of organ recovery in one, donor obesity (weight 127 kg) in one, donor hypernatremia (Na=170 mEq/L) in one, and donor pneumococcal sepsis with a hemorrhagic capillary leak syndrome in one. Renal graft losses were caused by rejection in six cases and patient death in one case.

Rejection. Biopsy-proven rejection episodes within the first 6 months after transplantation occurred in 48 of 60 (80%) patients, including 43 of 55 SPK (78%), 4 of 4 PTA (100%), and the 1 PAK patient. Rejection episodes were classified as mild (Banff grade I) in 33 (69%) patients, moderate (Banff grade II) in 13 (27%), and severe (Banff grade III) in 2 (4%). Acute rejection was treated with high-dose corticosteroids and optimization of TAC levels initially in all cases, with reversal in 40 of 48 (83%). Of the 48 patients with rejection, 8 (17%) did not respond to high-dose steroids and were treated with a 7–14-day course of antilymphocyte antibody (OKT3 in 6, ATGAM in 2) with reversal of rejection in 7 (88%). In 2 of the 60 patients, the rejection episodes were irreversible and progressed to kidney graft loss at 12 and 32 days and pancreas graft loss at 21 and 14 days after transplant, respectively. One of these patients had developed a positive lymphocytotoxic cross-match after transplant, as described above.

Long-term immunosuppression and outcome. All patients received TAC for primary immunosuppression. Two patients (one SPK, on PTA) were converted to Neoral at 6 and 19 months after transplant, respectively, in unsuccessful attempts to reverse ongoing rejection; both patients lost their pancreas grafts, at 8.5 months and 20 months after transplant, respectively, to chronic rejection. The SPK patient continues to have a functioning renal transplant (SCR=1.8 mg/dl) at 34 months after transplant. An additional patient who had two rejection episodes was switched to Neoral 12 months after transplant for persistent hyperglycemia (glucose>180 mg/dl) but continues to have elevated glucose levels.

Of the nine patients originally on TAC-MMF, two (one PTA, one SPK) have lost their grafts (pancreas and kidney, respectively) to rejection. Four of the nine TAC-MMF patients were taken off MMF; three were switched to AZA...
because of gastrointestinal side effects resistant to MMF dose reduction, and one PTA patient was switched to Cytoxan and Neoral in an unsuccessful attempt to reverse ongoing rejection. Of the 51 patients originally receiving TAC-azathioprine (TAC-AZA), eight were converted to TAC-MMF because of rejection; of these, one SPK patient lost her kidney transplant to chronic rejection at 35.7 months but continues to have pancreas graft function, and one lost his pancreas to rejection at 14 months. Overall, of the 51 patients originally on TAC-AZA, pancreas graft loss occurred in 11 patients and kidney graft loss in 6. Of the 48 patients with functioning pancreases, 31 (65%) have been weaned off prednisone at a mean of 17.0±9.9 months (range: 8–39 months) after transplant; 2 are taking 10 mg/day; 3 are taking 7.5 mg/day, 10 are on 5 mg/day; 1 is taking 5 mg and 2.5 mg on alternate days, and 1 is on 2.5 mg/day. One SPK patient had initially been weaned off prednisone 11 months after transplantation but experienced a late mild rejection episode at 14 months, treated successfully with high-dose steroids. This patient currently has good renal and pancreatic graft function (SCr = 1.8 mg/dl, fasting glucose = 81 mg/dl) and is on 10 mg of prednisone daily, in addition to 8 mg of TAC and 500 mg of MMF daily. No other patients weaned off steroids has subsequently had a rejection episode or has been restarted on steroids. Of the 49 patients with functioning kidneys (48 SPK, 1 PAK), the mean prednisone dose is 2.2±2.3 mg/day; 32 (65%) are currently off prednisone and 3 are taking 10 mg/day, 3 7.5 mg/day, 10 5 mg/day, and 1 is taking 5 and 2.5 mg on alternate days.

**Graft function and TAC.** Of the 48 patients with a functioning pancreas (45 SPK, 2 PTA, 1 PAK), 47 remain on TAC and 1 has been switched to Neoral because of persistent hyperglycemia (fasting glucose > 180 mg/dl); this latter patient currently has a fasting glucose ranging from 130 to 170 mg/dl on Neoral at 150 mg twice daily, 5 mg of prednisone, and at MMF 500 mg twice daily. In the other 47 patients, the mean TAC dose is 6.3±1.8 mg/day and the mean TAC level is 8.0±2.2 ng/ml. Corresponding mean fasting glucose levels in these 47 patients are 91.6±13.8 mg/dl and mean glycosylated hemoglobin (HbA1c) is 5.1±0.7% (normal range: 4.3–6.1%). Fasting glucose, SCr, TAC dose, and TAC levels at corresponding time points after transplantation in the 45 SPK patients with functioning grafts are shown in Table 3. In the two patients with functioning grafts after PTA, mean fasting glucose is 99.5±21.9 mg/dl with a mean TAC level of 11.5 ng/ml (TAC dose of 6.0±2.8 mg/day) at a mean of 31.1 months' follow-up; in the PAK patient, fasting glucose is 69.

### Table 2. Causes of graft loss

<table>
<thead>
<tr>
<th>Graft type</th>
<th>Patient</th>
<th>Date of transplant</th>
<th>Cause of graft loss (time after transplant)</th>
</tr>
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<tbody>
<tr>
<td>SPK</td>
<td>RC</td>
<td>9/19/94</td>
<td>Antibody-mediated rejection (21 days)</td>
</tr>
<tr>
<td>SPK</td>
<td>DB</td>
<td>9/28/94</td>
<td>Thrombosis (1 day)</td>
</tr>
<tr>
<td>SPK</td>
<td>TS</td>
<td>11/7/94</td>
<td>Ischemia of duodenum with fistula**</td>
</tr>
<tr>
<td>SPK</td>
<td>AB</td>
<td>11/26/94</td>
<td>Candida infection (14 days)</td>
</tr>
<tr>
<td>SPK</td>
<td>TM</td>
<td>12/7/94</td>
<td>Low-flow necrosis (10 days)</td>
</tr>
<tr>
<td>SPK</td>
<td>JM</td>
<td>1/18/95</td>
<td>Thrombosis (1 day)</td>
</tr>
<tr>
<td>SPK</td>
<td>DP</td>
<td>1/21/95</td>
<td>Normal islet function (39 months)</td>
</tr>
<tr>
<td>SPK</td>
<td>JG</td>
<td>5/27/95</td>
<td>Recurrent rejection (20 months)</td>
</tr>
<tr>
<td>SPK</td>
<td>CM</td>
<td>7/10/95</td>
<td>Splenic artery anastomotic pseudoaneurysm,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>abcess (22 days)</td>
</tr>
<tr>
<td>SPK</td>
<td>TM</td>
<td>8/19/95</td>
<td>Necrotizing pancreatitis (1 day)</td>
</tr>
<tr>
<td>SPK</td>
<td>KS</td>
<td>10/21/95</td>
<td>Thrombosis (1 day)</td>
</tr>
<tr>
<td>SPK</td>
<td>JO</td>
<td>2/16/96</td>
<td>Normal islet function (26 months)</td>
</tr>
<tr>
<td>PTA</td>
<td>DY</td>
<td>7/27/95</td>
<td>Rejection (2.5 months)</td>
</tr>
<tr>
<td>PTA</td>
<td>DB</td>
<td>9/17/95</td>
<td>Rejection (8.8 months)</td>
</tr>
</tbody>
</table>

* Ligated inferior pancreaticoduodenal artery.
** Immunosuppression stopped at 14 days.
\* NA, not applicable.

### Table 3. Graft function and metabolic parameters in pancreas-kidney patients receiving TAC**

<table>
<thead>
<tr>
<th>Time after transplant (mo)</th>
<th>SCr (mg/dl)</th>
<th>Fasting glucose (mg/dl)</th>
<th>TAC trough level (ng/ml)</th>
<th>TAC dose (mg/day)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1.8±1.5</td>
<td>90.8±15.0</td>
<td>15.4±6.1</td>
<td>19.5±7.7</td>
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<tr>
<td>3</td>
<td>1.4±0.5</td>
<td>96.7±20.0</td>
<td>12.8±4.9</td>
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<tr>
<td>6</td>
<td>1.4±0.6</td>
<td>89.8±14.8</td>
<td>10.1±3.1</td>
<td>9.5±3.8</td>
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<tr>
<td>12</td>
<td>1.4±0.6</td>
<td>93.9±20.4</td>
<td>10.0±2.9</td>
<td>7.4±2.6</td>
</tr>
<tr>
<td>24</td>
<td>1.4±0.8</td>
<td>93.7±18.1</td>
<td>8.4±2.7</td>
<td>6.3±2.1</td>
</tr>
<tr>
<td>At follow-up**</td>
<td>1.5±0.9</td>
<td>92.0±20.7</td>
<td>8.0±2.0</td>
<td>6.2±1.8</td>
</tr>
</tbody>
</table>

* SPK patients with functioning grafts.
** Mean follow-up: 32.5±6.3 mo.
\* Analysis of variance with repeated measures.
ng/ml on a trough TAC level of 6.5 mg/dl and SCr is 1.2 mg/dl with a trough TAC level of 6.5 mg/ml on a TAC dose on 5 mg of TAC/day at 30 months' follow-up.

Transient hyperglycemic episodes. Transient hyperglycemic episodes (defined as a rise in blood glucose over 180 mg/dl) occurred in a total of 26 patients at a mean of 45.2±118 days after transplant (median: 23 days). These episodes were associated with treatment of rejection in 16 (62%) of 26 cases and TAC toxicity in 1 (4%). Nine patients in whom the cause of hyperglycemia was unknown were evaluated to search for possible donor-related causes that could account for delayed graft function. The mean donor age for these patients was 29±14.8 years (median: 35 years). The mean CIT was 17.5±4.9 hr (median: 18 hr). Seven of nine (78%) of these donors were on pressors before organ retrieval (four were on >2 pressors). In the other two cases, no obvious cause for the transient hyperglycemic episode could be discovered. During transient hyperglycemic episodes, mean blood glucose level was 218±52 mg/dl (median: 200 mg/dl). The mean TAC level during episodes of hyperglycemia was 19.2±9.1 ng/ml (median: 17.6 ng/ml) with a concomitant mean oral TAC dose of 18.5±6.7 mg/day (median: 18 mg/day). In the 16 cases where hyperglycemia was associated with treatment of rejection, intravenous TAC was used to optimize trough TAC levels in 3 patients at a mean dose of 1.5±0.76 mg/day. Bolus therapy with solumedrol was given in all 16 patients to treat rejection. Mean SCr during hyperglycemic episodes was 2.0±1.2 mg/dl. In none of these patients did the transient hyperglycemic episode result in graft loss or diminished long-term pancreatic function, and all have normal glucose metabolism beyond 2 years.

DISCUSSION
Tacrolimus has gained widespread acceptance as an effective immunosuppressive agent in solid organ transplantation as both a primary (4, 5, 7–10) and rescue agent (6, 7, 8, 17). In randomized trials of TAC and CsA for renal transplantation, short-term outcomes have shown that TAC is superior to CsA in reducing rejection incidence (4, 5), and possible long-term advantages for renal allograft half-life have also been described (11). An additional advantage of this drug, demonstrated in our own institution, is its steroid-sparing effects, with complete steroid withdrawal possible in up to 60% of renal allograft recipients (9, 10). Accompanying these favorable observations have been concerns over the diabetogenicity of TAC, which has been reported in the short term with an incidence ranging from 6% to 28% of renal transplant patients (4, 5, 9, 10, 16). However, the final incidence of posttransplant diabetes mellitus (PTDM) in these studies ranges from 1.4% to 12.6%, which is no different than that in CsA-based regimens, and is reversible in 37–83% (4, 5, 9, 10, 16). In our experience, this reversibility can be maximized with judicious early (over 2–3 months) TAC dose reduction, along with steroid tapering.

Potential reasons for impaired glucose metabolism and transient hyperglycemia in the early postoperative period after pancreas transplantation include impaired early insulin secretion by the recovering ischemic graft, reduced β-cell responsiveness, impaired nonoxidative glucose metabolism, and impaired early inhibition of glucagon secretion (18). The diabetogenic effects of TAC in rats have been shown to involve transcriptional inhibition of insulin mRNA caused by the binding of TAC to FKBP-12, which is present in high concentration in pancreatic B cells, with subsequent inhibition of calcineurin activity in these cells (19). However, when TAC administration (which was given at a higher than therapeutic dose of 10 mg/kg/day in this study) was stopped, insulin mRNA transcription and insulin production normalized (19). Other experimental studies have confirmed that TAC's effects on in vitro inhibition of insulin gene transcription are reversible and are time- and dose-dependent (20). In fact, one study even showed that TAC protects mouse pancreatic islets from streptozocin-induced injury (21). Furthermore, in a randomized trial comparing CsA and TAC in liver transplant recipients, Steinmuller and colleagues (22) found no differences in the incidence of impaired glucose tolerance or clinically significant PTDM. Strumpf reported that the oral glucose tolerance test and HgbA1C levels were unchanged in seven nondiabetic autoimmune subjects after 10 weeks of FK 506 therapy (23). These experimental and clinical observations recapitulate observations made by ourselves (9, 10) and others (4, 5) demonstrating the reversibility of TAC-induced PTDM.

Despite these observations, justifiable concern has been expressed over the use of a potentially (albeit reversible) diabetogenic agent such as TAC for pancreas transplantation. The short-term safety and efficacy of TAC in pancreas transplantation has been reported in both single-center and multicenter trials for both primary and rescue therapy (8, 12–14). Gruessner has recently shown in a follow-up multicenter analysis of TAC immunosuppression for pancreas allograft recipients statistically significant improvements in 1-year graft survival of SPK patients when compared to a matched pair group receiving CsA (12). In his study, only 4% of recipients were converted from TAC to CsA for diabetogenicity by 1 year. However, no details on TAC dosing and levels or steroid dose were provided for these patients (12). Of note, 86% of the recipients in the retrospective multicenter analysis by Gruessner had received anti-T-cell induction therapy along with TAC, steroids, and either azathioprine (94%) or MMF (5%), and steroid tapering was not mentioned. Other studies (13, 24–26) have also reported the use of TAC for pancreas transplantation in small numbers of patients with short-term follow-up, but its safety and efficacy in the long term, particularly with respect to the potential for sustained graft function without clinical evidence of islet toxicity, has not been reported. Therefore, we thought it prudent to analyze our experience with TAC for primary pancreas transplantation in patients with a minimum of 2 years' follow-up.

In the current study, 60 patients receiving pancreas transplants between July 4, 1994 and April 18, 1996 have been followed for a mean of 35.1 months. The majority (85%) received TAC-AZA with prednisone. During the latter part of this early experience with TAC-based immunosuppression, MMF was used instead of AZA as a third drug in nine patients. Although our rejection incidence of 80% is somewhat higher than that reported in other recent studies with TAC-based therapy for pancreas transplantation (12), the majority (69%) of these rejections were classified as mild and none of these patients had received anti-T-cell induction therapy. Furthermore, only eight patients (17%) required OKT3 for steroid-resistant rejection. Steroid withdrawal was
accomplished in 65% of the patients at a mean of 17.0±9.9 months after transplantation. Prednisone was reinstituted after its discontinuation in only one patient who experienced a late mild rejection episode 1 year after transplantation. The number of patients receiving MMF was too small to draw any meaningful conclusions regarding its potential benefits as a third agent with TAC-prednisone, although in a larger patient group with shorter follow-up at our institution, MMF appears to confer an immunologic benefit with a lower incidence of rejection (27). MMF has been subsequently incorporated as part of our routine immunosuppressive regimen for pancreas transplantation.

The efficacy of TAC-based immunosuppression without the use of induction antilymphocyte antibody, in both kidney (9, 10), and now pancreas transplantation (14), is perhaps best reflected by the current series, in which long-term graft function without evidence of islet toxicity, reflected by mean fasting glucose levels of 90.4±17.6 mg/dl (range: 43–135) and HgbA1C of 5.1±0.7% (range: 3.2–6.5%), was observed at a mean follow-up of 35.1±5.9 months. In the group of patients exhibiting transient hyperglycemia, the mean TAC level of 19.2±9.1 and the mean oral TAC dose of 18.5±6.7 mg/day were quite high. Dose reduction resulted in resolution of hyperglycemia in all cases, confirming that the hyperglycemia in these patients was TAC dose-dependent. Furthermore, the glucose remained normal beyond 2 years.

Our center has now performed 147 pancreas transplants under TAC-based immunosuppression. In the initial group of 60 patients reported herein, long-term pancreatic graft function without evidence of islet toxicity along with the ability to taper steroids in 65% of patients, accompanied by a very low incidence (13%) of steroid-resistant rejection requiring antilymphocyte antibody treatment, have reassured us that TAC is both safe and effective for long-term outcome in cadaver pancreas transplantation.

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REFERENCES


CHRONIC VIRAL HEPATITIS IN RENAL TRANSPLANT RECIPIENTS WITH ALLOGRAFTS FUNCTIONING FOR MORE THAN 20 YEARS\textsuperscript{1,2}

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Background. The impact of infection with hepatotropic viruses (hepatitis B virus [HBV] and hepatitis C virus [HCV]) on morbidity and mortality, and allograft function in renal transplant recipients with allografts functioning for >20 years is not known.

Methods and Results. Seventy-nine of 511 renal transplants performed at the Cleveland Clinic Foundation from January 1963 to January 1978 are known to have functioned for at least 20 years (level 5A). Fifty-four of these patients had hepatitis testing updated after their 19th year of transplantation. Fifteen patients had evidence of ongoing viral infection: persistent hepatitis B surface antigen in three (6%), HCV antibody (enzyme-linked immunosorbent assay II supplemented by recombinant immunoblot assay) in 11 (20%), and both viruses in one (2%). Of the 10 surviving patients, 8 were tested further for viral replication. HCV RNA (polymerase chain reaction; Amplicore) was positive in 6/7 (86%), and HBV DNA (hybridization) was positive in 1/2 (50%). An elevated alanine aminotransferase (>35 U/L) was present in all hepatitis patients, α-fetoprotein >10 ng/ml in 2/8 (25%), and cryoglobulins >50 μg/ml in 3/6 (50%) infected with HCV. No hepatocellular carcinoma was detected by hepatic ultrasound. In patients with chronic viral hepatitis, probable cirrhosis developed in 20% (3/15) compared to one patient in the group without hepatitis, but there was no mortality from liver failure in either group. Diabetes mellitus was significantly more common in those with than without hepatitis (11/15 vs. 10/39; \(P=0.002\)), but severe infection was not different (9/15 vs. 15/39). Five hepatitis patients (33%) have died of non-hepatic causes (one from meningitis, one from unknown cause, and three from coronary heart disease [CHD] vs. only two individuals without hepatitis [5%]; \(P=0.014\)). Although the more frequent occurrence of CHD among those with hepatitis was not significant (7/15 vs. 8/39; \(P=0.09\)), CHD as a cause of death in those with HCV was significantly increased (\(P=0.03\)).

Conclusions. Twenty-year renal transplant recipients infected with hepatotropic viruses (HBV and HCV) have a high rate of active viral replication (88%), a greater frequency of diabetes (\(P=0.01\)), and a higher overall mortality (\(P=0.014\)).

Chronic infection with hepatitis B and C viruses (HBV* and HCV) are relatively common in patients receiving hemodialysis and in recipients of renal transplants. Chronic hepatitis B (hepatitis B surface antigen positivity) affects 3–10% of patients receiving chronic hemodialysis (1). Positive anti-HCV serology (second-generation enzyme-linked immunosorbent assay assay) can be detected in 8.1% (range: 0–51%) of patients in selected hemodialysis units in the United States, but its prevalence varies considerably in different regions of the world (2, 3). Anti-HCV positivity has been reported in 10–26% of renal transplant recipients, the majority of whom have detectable HCV RNA, as measured by the polymerase chain reaction method (2, 3).

\* Abbreviations: CHD, coronary heart disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

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