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RESULTS OF PANCREAS TRANSPLANTATION AFTER STEROID WITHDRAWAL UNDER TACROLIMUS IMMUNOSUPPRESSION[1]

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Purpose. **The results of steroid withdrawal in pancreas transplant recipients under tacrolimus immunosuppression were analyzed.**

Methods. **From July 4, 1994 until April 30, 1998, 147 pancreas transplantations were performed in 141 patients, including 126 simultaneous pancreas-kidney transplantations, 13 pancreas after kidney transplantation, and 8 pancreas transplantations alone. Baseline immunosuppression consisted of tacrolimus and steroids without antilymphocyte induction. Twenty-three patients were excluded from analysis because of early graft loss in 17 cases, retransplantation in 5 cases, and simultaneous pancreas-kidney transplantation after heart transplantation in 1 patient.**

Results. **With a mean follow-up of 2.8±1.1 years (range 1.0 to 4.8 years), complete steroid withdrawal was achieved in 58 (47%) patients with a mean time to steroid withdrawal of 15.2±8 months (range 4 to 40 months after transplantation). Of the entire cohort of 141 patients, overall 1-, 2-, and 4-year patient survival rates were 98%, 95.5%, and 86%, respectively. Overall 1-, 2-, and 4-year graft survival rates were 83%, 80%, and 71% (pancreas) and 95%, 91%, and 84% (kidney), respectively. Of the 124 patients analyzed for steroid withdrawal, 1-, 2-, and 4-year patient survival rates were 98%, 97%, and 92%, respectively. Overall 1-, 2-, and 4-year graft survival rates were 98%, 91.5%, 83% (pancreas) and 97%, 95%, and 91% (kidney). Patient, pancreas, and kidney survival rates at 1 year were 100%, 100%, and 98% (off steroids) versus 97%, 91%, and 96% (on steroids, all NS) and at 4 years were 100%, 94%, and 95% (off steroids) versus 78%, 68%, and 85% (on steroids, P=0.01, 0.002, and NS, respectively). The cumulative risk of rejection at the time of follow-up was 76% for patients on steroids versus 74% for patients off steroids (P=NS). Seven patients originally tapered off steroids were treated for subsequent rejection episodes, which were all steroid sensitive, and two of these seven patients are currently off steroids. Thirteen patients received antilymphocyte therapy for steroid-resistant rejection, five of whom are now off steroids. Tacrolimus trough levels were 9.3±2.4 ng/ml (off steroids) and 9.7±4.3 (on steroids, P=NS). Mean fasting glucose levels were 98±34 mg/dl (off steroids) and 110±41 mg/dl (on steroids, P=NS). Mean glycosylated hemoglobin levels were 5.2±0.9% (off steroids) and 6.2±2.1% (on steroids, P=0.02), and mean serum creatinine levels were 1.4±0.8 mg/dl (off steroids) and 1.7±1.0 mg/dl (on steroids, P=0.02).**

Conclusion. **These data show for the first time that steroid withdrawal can be safely accomplished in pancreas transplant recipients maintained on tacrolimus-based immunosuppression. Steroid withdrawal is associated with excellent patient and graft survival with no increase in the cumulative risk of rejection.**

The results of pancreas transplantation have improved dramatically over the last decade with 1-year patient survival rates greater than 90%, and pancreas graft survival rates in simultaneous pancreas-kidney transplantations (SPK*) greater than 80% in most centers (*1–3*). These results have continued to improve in large part due to the introduction of novel immunosuppressive agents, including tacrolimus (TAC) and mycophenolate mofetil (MMF). A recent review by Stratta (*4*) indicated that the majority of pancreas transplantations are still performed using antibody induction therapy with cyclosporine (CsA) based immunosuppression, but that there is an increasing trend to adopt new drug combinations including TAC and MMF with or without antibody induction therapy. We have previously reported our initial long-term experience with TAC as baseline immunosuppressive therapy for pancreas transplantation without antibody induction (*3*), which was associated with excellent graft survival and function. In a more recent analysis of pancreas transplantation under TAC, in which adjuvant bone marrow administration was studied, we reported 1- and 3-year SPK graft survival rates of 86% and 80%, respectively (*5*). One of the early concerns associated with the use of TAC was its reported potential for diabetogenicity (*6, 7*), although this is reversible in the majority of cases (*8, 9*). As a consequence, the use of TAC for pancreas transplantation has only recently been adopted in some centers (*3, 5, 10–12*). One potential advantage of TAC that would be especially well suited for pancreas transplant recipients is its now well-reported association with safe steroid withdrawal in approximately 60% of other solid organ recipients (*13–15*). Safe steroid withdrawal under Neoral or CsA in the pancreas transplant population has not been systematically attempted and hence not reported except for preliminary experiences in a small number of patients (*16*). In our center, we have attempted to withdraw steroids as a part of our standard

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* Abbreviations: AZA, azathioprine; CMV, cytomegalovirus; CyA, cyclosporine; Hbg_{A1C}, glycosylated hemoglobin; MMF, mycophenolate mofetil; PTDM, posttransplantation diabetes mellitus; SCR, serum creatinine; SPK, simultaneous pancreas-kidney transplantations; TAC, tacrolimus.

immunosuppressive protocol in pancreas transplant recipients since 1994. We now report our overall experience from July 4, 1994 to April 30, 1998 with steroid withdrawal in pancreas transplant recipients receiving tacrolimus-based therapy. The results indicate that steroid withdrawal is safe and associated with excellent short- and long-term patient survival and graft function with no increased risk of delayed rejection episodes or toxicity compared with those patients who remain on steroids.

MATERIALS AND METHODS

Donor and recipient demographics. Between July 4, 1994 and April 30, 1998, 147 pancreas transplantations were performed in 141 patients with a mean recipient age of 40.5±6.8 years (range 27.6 to 59.3 years). TAC-based immunosuppression was used as primary therapy in all patients. There were 126 SPK, 13 pancreas after previous kidney transplantations (PAK), and 8 pancreas transplantations alone (PTA). The mean donor age was 30.0±13.6 years (range 6.8 to 62.7 years). The mean cold ischemia time for the kidney transplants was 16.6±4.3 hours and for the pancreas transplants 17.7±1.2 hours. The mean number of HLA matches was 1.3±1.1 and mismatches 4.3±1.2.

For a meaningful analysis of the results of steroid withdrawal, only patients undergoing primary pancreas transplantation with graft function beyond 3 months of transplantation were analyzed. There were 17 pancreas losses within 3 months of transplantation, 5 retransplantations, and one SPK after heart transplantation. These 23 cases were excluded, leaving 124 pancreas transplantations for analysis. Of these 124 cases, there were 109 SPK, 9 pancreas after previous kidney transplantations, and 6 pancreas transplantations alone.

Immunosuppression. All patients received primary TAC-based immunosuppression with a steroid-tapering regimen, as described previously (*3*). Antilymphocyte antibody induction was not used. Of the 124 patients analyzed, 72 (59%) received initial therapy with TAC, prednisone, and MMF (CellCept) 1 g b.i.d. TAC, prednisone, and azathioprine (AZA) at 2 mg/kg/day was the initial therapy in the remaining 52 (41%) patients. AZA and MMF doses were titered to maintain a white blood count >5000/mm^3 and dosage according to gastrointestinal side effects in the case of MMF. Patients received intravenous TAC at 0.03 to 0.05 mg/kg/day for 4 to 6 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 transplantation, 15–20 ng/ml by 1 month, 10–15 ng/ml by 3 months, 7–12 ng/ml by 6 months, and 5–10 ng/ml thereafter. All patients received prophylaxis for pneumocystitis carinii pneumonia with trimethaprim-sulfamethoxazole. Cytomegalovirus (CMV)-seronegative recipients of CMV-positive organ donors had biweekly testing for CMV antigen (pp65) and were treated with a 14-day course of intravenous ganciclovir if CMV antigenemia was positive. Routine prophylaxis for CMV was not given.

Steroid withdrawal. Steroids were initiated as 0.5–1 g of intravenous methylprednisolone intraoperatively followed by a tapering steroid regimen over the first 5 postoperative days to 20 mg per day of prednisone by postoperative day 6. In the presence of subsequent stable graft function, prednisone was tapered by 2.5–5 mg every 2 weeks with the aim of complete steroid withdrawal with concomitant careful monitoring of pancreas and renal graft function. Steroid tapering was generally ceased if a rejection episode supervened within the first 3 months after transplantation. Some patients continued to be weaned off steroids after successful treatment of early rejection episodes with high-dose corticosteroids, although steroid withdrawal generally proceeded more slowly in this scenario. Of the 124 patients analyzed, 58 (47%) achieved complete steroid withdrawal with a mean time to complete steroid withdrawal of 15.2±8 months (range 4 to 40 months).

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, or both, as described previously (*17*). 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 methylprednisolone boluses (generally 500 mg daily × 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 and donor demographic information was summarized using descriptive statistics. For continuous variables, groups were compared using the standard independent sample *t* test. For categorical variables, the chi-square test was applied. Patient survival rate was calculated from the date of transplantation until death, and allograft survival rate from date of transplantation until graft failure or patient death. Survival (event-free) rates were calculated using the Kaplan-Meier method. Time-to-event analysis (time to rejection, graft failure, or death) was based on the log-rank test. Statistical significance was considered at $P<0.05$.

RESULTS

Patient and graft survival. The mean follow-up was 2.8±1.1 years (range 1.0 to 4.8 years). The overall 6-month and 1-, 2-, 3-, and 4-year actuarial patient survival rates for all 141 patients were 99%, 98%, 95.5%, 93%, and 86% (Fig. 1). Overall 6-month and 1-, 2-, 3-, and 4-year actuarial kidney graft survival rates were 95%, 95%, 91%, 87%, and 84% (Fig. 1). Overall pancreas graft survival rates for all 147 cases at 6 months, 1, 2, 3, and 4 years were 85.6%, 83%, 80%, 77%, and 71%, respectively (Fig. 1). Of the 141 patients who underwent transplantation, 131 (93%) are currently alive. There were four deaths from cardiac events at 2, 2.5, 3.2, and 3.7 years after transplantation; two patients died of sepsis at 0.5 and 1.8 years after transplantation; one patient died of a cerebral vascular accident at 0.9 years after transplant; one patient died of posttransplant lymphoproliferative disease at 0.3 years after transplant; and two patients died with unknown etiology at 1.4 and 3.9 years after transplantation. Of those 124 patients analyzed after steroid withdrawal, 1-, 2-, and 4-year patient survival rates were 98%, 97%, and 92% (Fig. 2). In this group, kidney and pancreas graft survival rates at 1, 2, and 4 years were 97% and 98%, 95% and 91%, and 91% and 83%, respectively (Fig. 2). Of the 10 patients who died, 3

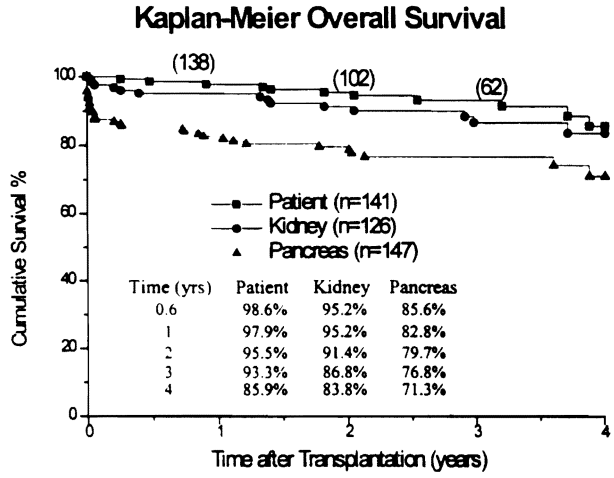

FIGURE 1. Overall patient, kidney, and pancreas allograft survival rates for 147 pancreas transplants.

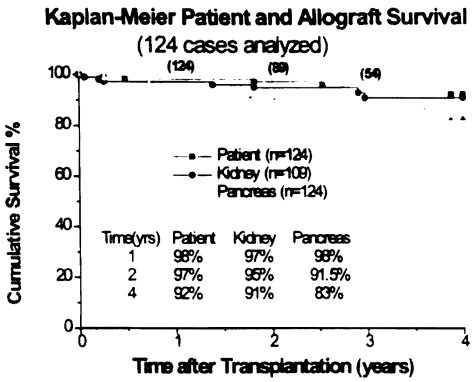

FIGURE 2. Patient, kidney, and pancreas allograft survival rates excluding retransplants and graft losses within the first 3 months after transplantation.

had been tapered off steroids (all cardiac deaths) and 7 remained on steroids at the time of death.

Early graft loss. There were a total of 17 pancreases and 4 kidneys that were lost within the first 3 months after transplantation. Of the 17 pancreases lost, 7 were due to pancreatitis at 4, 8, 8, 8, 8, 12, and 76 days after transplantation; 6 were lost to allograft thrombosis at 1, 1, 1, 1, 4, and 4 days after transplantation; 2 were lost to sepsis at 21 and 22 days after transplantation; and 1 was lost due to humoral rejection at 22 days after transplantation. There were four kidneys lost within 3 months of transplantation. Two kidneys were lost due to sepsis at 14 and 72 days after transplantation; one was lost due to thrombosis at 16 days after transplantation; and one was lost to humoral rejection at 12 days after transplantation. All patients with graft loss within 3 months of transplantation were excluded from subsequent analysis, because none of these patients had the opportunity to be tapered off steroids before graft loss.

Results of steroid withdrawal. Of the 124 patients analyzed, 58 (47%) were tapered off steroids completely and 66 (53%) remained on steroids at the time of this analysis, which was completed as of April 30, 1998, providing a minimum of 1-year follow-up for all patients. The 1- and 4-year patient survival rates of the patients off steroids were 100% and 100% and those still on steroids 97% and 78% respectively (P=0.01; Fig. 3). Actuarial pancreas graft survival rates off steroids at 1, 2, and 4 years were 100%, 100%, and 94%, respectively, and the rates of those still on steroids were 91%, 83.5%, and 67.5%, respectively (P=0.002; Fig. 4). There were 109 patients with simultaneous kidney transplants who were analyzed for steroid withdrawal; 55 (50%) were tapered off steroids and 54 remain on steroids. The actuarial 1-, 2-, and 4-year graft survival rates of those kidney transplant recipients off steroids were 98%, 98%, and 95%, respectively, and the rates of those remaining on steroids were 96%, 91%, and 85%, respectively (P=NS; Fig. 5). Of those patients still on steroids, prednisone dose is 6.2±3.7 mg per day (range 2.5 to 20 mg, median 5 mg per day). A total of seven patients who were initially completely weaned off prednisone were restarted on prednisone at a mean of 12 months (range 7 to 20 months) after transplantation. Of these seven patients, six had biopsies performed for rising SCR and were treated for rejection with high-dose corticosteroids. The seventh patient was empirically treated for rejection for a decreasing urinary amylase. All seven patients responded to steroid therapy for treatment of rejection, which was biopsy-proven in six cases. Of these six, four had mild rejection (Banff grade IA or IB) and two had only borderline rejection. Of the seven patients, two have now again been weaned completely off steroids.

Late allograft loss (>3 months after transplantation). Of the 124 patients analyzed for steroid withdrawal, 14 had late pancreas loss (Table 1) and 10 late renal allograft loss (Table 2) beyond 3 months after transplantation. Of the 14 pancreas allografts that were lost, 2 patients had been weaned off steroids and 12 patients continue on steroids. Nine of the 14 late pancreas losses were due to rejection at 0.7, 0.7, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 2, and 2.1 years after transplantation. Three pancreas grafts were lost due to death at 0.3, 1.8, and 3.9 years after transplantation. One graft was lost due to sepsis at 0.3 years after transplantation and one due to vascular occlusion at 3.6 years after transplantation. Of the 9 pancreas allograft losses due to rejection >3 months after transplantation, only one patient had been tapered completely off steroids. This patient had been weaned off steroids at 4 months after transplantation and now has graft survival of 26 months. Eight of the 9 late pancreas allograft losses (89%) occurred in patients who remained on steroids. Of the 10 late renal allograft losses, 3 patients had been tapered off steroids and 7 patients remain on steroids. Five renal allograft losses were due to rejection at 1.3, 1.4, 2.9, 3, and 3.7 years after transplantation; 4 were due to patient death at 0.3, 1.4, 1.8, and 2 years after transplantation; 1 was due to sepsis at 0.4

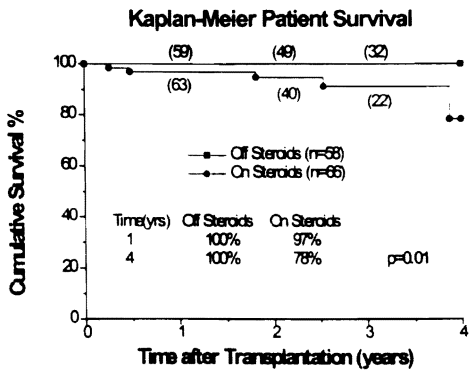

FIGURE 3. Patient survival rates comparing those off steroids with those on steroids.

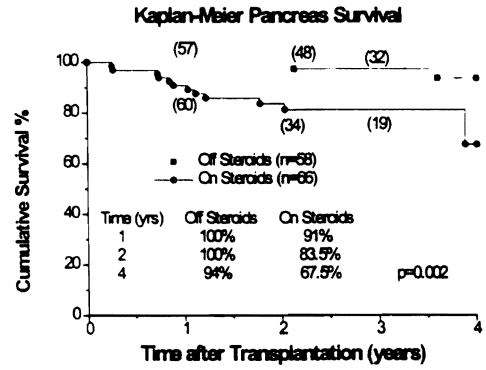

FIGURE 4. Pancreas allograft survival rates comparing those off steroids with those on steroids.

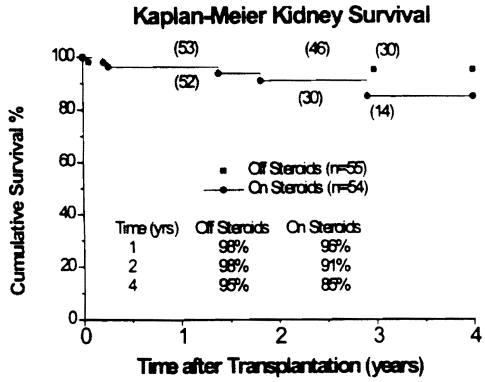

FIGURE 5. Kidney allograft survival rates comparing those off steroids with those on steroids.

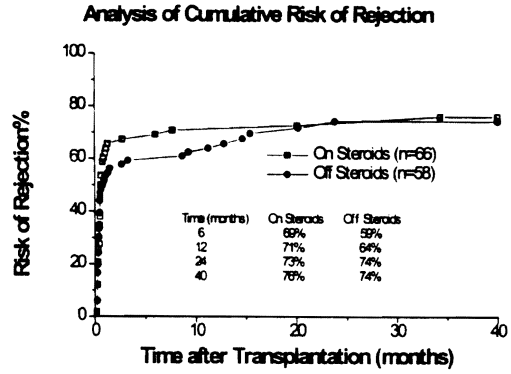

FIGURE 6. Cumulative risk of rejection in pancreas transplant recipients comparing those off steroids with those on steroids.

TABLE 1. Causes of pancreas allograft loss (>3 mo)[a]

Cause	Number	Time after transplantation (yr)	Off steroids	On steroids
Rejection	9	0.7, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 2, 2.1	1	8
Death	3	0.3, 1.8, 3.9	0	3
Sepsis	1	0.3	0	1
Vascular occlusion	1	3.6	1	0
Total	14		2	12

[a] n=14.

TABLE 2. Causes of renal allograft loss (>3 mo)[a]

Cause	Number	Time after transplantation (yr)	Off steroids	On steroids
Rejection	5	1.3, 1.4, 2.9, 3, 3.7	2	3
Death	4	0.3, 1.4, 1.8, 2	1	3
Sepsis	1	0.4	0	1
Total	10		3	7

[a] n=10.

years after transplantation. Of the five renal allograft recipients who experienced late graft loss due to rejection, two had been weaned off steroids at 8 and 30 months after transplantation, respectively, and these grafts survived to 36 and 44 months after transplantation, respectively. The remaining three renal allograft losses were in patients who remained on steroids.

Rejection. There was no significant difference in the cumulative risk of rejection for patients on or off steroids (Fig. 6). The rejection-free survival rate in patients off steroids was 28% and the rate in those on steroids was 27% at the time of follow-up. There was a significant difference in the total number of episodes of acute rejection per patient, which was 1.0±0.84 in the patients off steroids versus 1.56±1.45 in those patients still on steroids (P=0.006). Of those patients who had been completely weaned off steroids, the number of rejection episodes before weaning was 0.2±0.79 per patient and after weaning was 0.08±0.17 per patient. Of those patients who were off steroids by the time of this analysis, only three have had late rejection episodes, which were reversed by steroid treatment in all patients. In the patients remaining on steroids, four patients have had late rejection at 8–39 months after transplantation. Three of these four patients underwent allograft biopsy because of rising SCR. The fourth patient was treated for rejection because of a rising serum lipase. Of the three patients who underwent biopsy, one had moderate rejection (Banff grade II), one had mild to moderate rejection (Banff grade IB), one had mild rejection (Banff grade IA), and one had minimal to borderline rejection. Three of the four patients responded to a steroid recycle. The patient with moderate rejection required antilymphocyte therapy with OKT3. Overall, 13 patients received antilymphocyte therapy (OKT3 in 11, ATGAM in 2) for steroid-resistant rejection at some point after transplantation. Of these 13 patients, 5 have been tapered off steroids with good graft function. Of the remaining eight patients who were not tapered off steroids after antilymphocyte therapy, six are alive, four with functioning grafts (three kidney only, one kidney and pancreas) and two experienced graft loss due to recalcitrant rejection.

Graft function and steroid withdrawal. The serum amylase, lipase, glycosylated hemoglobin (Hbg_{A1C}), SCR, fasting glucose, and tacrolimus trough levels in those patients with functioning grafts are shown in Table 3. There was no significant difference in serum amylase, lipase, fasting glucose, or TAC trough levels off or on steroids. There was a statistically significant difference in Hbg_{A1C} values in those patients tapered off steroids (5.2±0.9%) compared with those still on steroids (6.2±2.1%, P=0.02). SCR was also statistically better in those patients tapered off steroids (1.4±0.8 mg/dl) compared with those still on steroids (1.7±1.0 mg/dl, P=0.02).

DISCUSSION

The ultimate goal of pancreas transplantation as a treatment option for type I diabetes is freedom from exogenous

TABLE 3. Laboratory values of functioning allografts

	Off steroids (n=58) mean±SD	On steroids (n=66) mean±SD	P value
Amylase (mg/dl)	75±56	75±57	NS
Lipase (mg/dl)	150±238	111±129	NS
FK trough levels (ng/ml)	9.3±2.4	9.7±4.3	NS
HbA_{1C} (%)	5.2±0.9	6.2±2.1	0.02
SCR (mg/dl)	1.4±0.8	1.7±1.0	0.02
Glucose (mg/dl)	98±34	110±41	NS

insulin administration with improvement or disappearance of diabetic secondary complications and improved quality of life (*18–23*). That pancreas transplantation has achieved widespread acceptance as a safe and effective treatment for type I diabetes is reflected in the much improved results reported over the last several years, which has been facilitated in our center by the use of TAC as a primary therapy for immunosuppression without antilymphocyte induction therapy (*3, 5, 24*). We have previously reported both the short-term (*24, 25*) and long-term (*3*) results of pancreas transplantation under TAC immunosuppression and more recently the results of pancreas transplantation with adjuvant bone marrow infusion with the intent to procure reduced immunological responsiveness (*5*). Concurrent with this experience, others have reported the safe and effective use of TAC for pancreas transplantation (*10–12*).

One of the important side effects of calcineurin agent-based immunosuppression (including both TAC and CsA) is diabetogenicity. In early reports using TAC in primary renal transplantation, the risk of insulin-dependent diabetes after transplantation (PTDM) was a justifiable concern (*6, 7, 9*), however, with concomitant dose reduction greater than 80% of patients experiencing PTDM experience complete reversal of this complication (*8, 13*). However, these early observations may have led many centers to hesitate in using TAC for pancreas transplantation. We have previously reported that excellent long-term pancreatic graft function can be achieved under TAC immunosuppression without evidence of islet toxicity, which has obviated any concern in our center for the potential long-term diabetogenicity of this agent in pancreas transplantation. Another advantage of TAC that had been originally reported in the kidney and liver transplant literature was the concomitant ability to taper and withdraw steroids in up to 60% of patients with no adverse impact on long-term patient or graft survival (*13–15, 26*). This also has been observed with the use of TAC for rescue of refractory rejection in renal allograft recipients (*27*). The potential for steroid withdrawal with TAC seemed to us to render this agent ideally suited for use in pancreas transplantation, where the overall goal is to eliminate the need for insulin dependence and avoid the long-term risk of steroid-induced complications, which may exacerbate the pre-existing complications of peripheral vascular disease and other target organ damage. Therefore, one of our earliest goals was to achieve complete steroid withdrawal in the pancreas transplant population. A review of the literature fails to reveal any concerted attempt to achieve steroid withdrawal in pancreas transplant recipients with conventional CsA immunosuppression. The purpose of this study was therefore to analyze the safety and efficacy of steroid withdrawal in a large cohort of patients undergoing pancreas transplantation under TAC.

In the current study, a total of 124 pancreas transplant recipients were analyzed. Patients who had lost their grafts within 3 months of transplant were excluded from this analysis because they would not have been candidates for complete steroid withdrawal. The results should be interpreted bearing this in mind, because they represent the outcome after successful engraftment after the first 3 months. Complete steroid withdrawal was achieved in 58 of 124 patients (47%) with a mean time to steroid withdrawal of 15.2±8 months. Patient and pancreas survival were statistically higher in the group of patients who had been tapered completely off steroids, and this is reflective of the fact that these patients were selected on the basis of the absence of significant early complications as well as the absence of significant rejection episodes before attempted steroid tapering. Significantly, however, most patients had experienced at least one rejection episode before weaning but once weaning was achieved, further episodes of rejection were rare. Only seven patients who were originally tapered off steroids required re-treatment for subsequent rejection, and of these seven, two have been tapered off steroids once again. Biochemical parameters were identical in both those patients off and on steroids except for Hbg_{A1C} and SCR, which were statistically better in the patients off steroids. This is probably reflective of the better overall outcome in those patients, which in turn facilitated steroid withdrawal in this group.

Attempts at steroid withdrawal in solid organ transplantation have heretofore been confined to patients undergoing kidney, heart, or liver transplantation. The earliest report of withdrawal of prednisone in cadaver kidney transplantation was published in 1977 by Thaysen and Lokkegaard (*28*), before the CsA era. Steroid withdrawal in the CsA era has been reported largely in the European literature but more recently has become an area of intense interest in the North American literature. In 1988, Stratta et al. (*29*) reported successful steroid weaning in 89% of 25 diabetic recipients of living-related renal transplants. Half of these patients subsequently required reinstitution of steroid therapy, but eventually 64% of these patients again were rendered steroid free. In 1990, Schulak et al. (*30*) reported the results of a prospective, randomized trial using CsA maintenance immunosuppression with or without maintenance prednisone therapy in both cadaver and living-related transplant recipients. Rejection episodes were more frequent in the nonprednisone group as was rejection severity. In a series of papers by Hricik et al. (*31,32*), steroid withdrawal in CsA-treated renal transplant recipients was analyzed both for the potential salutary effects on PTDM (*31*) and lipid metabolism (*16*). In a small series of seven renal transplant recipients with PTDM and one recipient of a SPK who exhibited evidence of PTDM, seven patients discontinued insulin or oral hypoglycemic agents within 4 months of discontinuing steroids (*31*). In this study, mean Hbg_{A1C} declined from 10.6±3.6% before steroid withdrawal to 6.0±1.3% within 1 month of steroid cessation with concomitant unchanged mean CsA trough levels. In a subsequent article designed to predict the outcome of steroid withdrawal, Hricik et al. (*32*) observed that steroid withdrawal was successful in only 41% of renal transplant recipients in whom prednisone was discontinued in <6 months after transplantation, but in 79% of patients in whom prednisone was discontinued >6 months after transplantation. In addition to studies of the potential beneficial effect of steroid withdrawal on lipoprotein profiles of CsA-treated adult kidney recipients (*16*), Ingulli et al. reported beneficial effects of steroid withdrawal on blood pressure and lipid profile in the pediatric population (*33*). Subsequent studies have also confirmed the beneficial effect of steroid withdrawal on lipid metabolism, PTDM, and in the case of children, growth and development in renal transplant recipients (*34, 35*). Steroid withdrawal has also been reported in the liver transplant population by Mazariegos et al. (*15*), as part of an attempt of total weaning of immunosuppression in a select group of liver transplant recipients.

Early reports of steroid withdrawal in renal transplant recipients receiving CsA concluded that weaning should only be attempted at least 6 months after successful transplantation because of the potential risk for rejection and CsA toxicity (*32*, *34*). More recent reports of steroid withdrawal in the TAC era have focused on early steroid withdrawal in kidney recipients with maintenance of a steroid-free state in the long-term in approximately 60% of patients (*13*, *14*, *35*, *36*). We have previously reported in an initial study of 60 pancreas transplantations performed under TAC immunosuppression that steroid withdrawal was accomplished in 65% of those with functioning grafts (*3*). We have also recently reported the results of adjuvant bone marrow administration to 53 SPK recipients under TAC immunosuppression, in whom 67% were steroid free at 3 years (*5*). Our expanded experience with steroid withdrawal reported herein has indicated that this approach is safe and associated with very little risk of late graft loss to rejection. Whether MMF provides an added advantage over AZA in terms of the ability to wean patients off steroids in this population will require further study. Of 52 patients on AZA in the current study, 32 (61%) were weaned off steroids versus 26 (42%) of those on MMF (P=NS). Because the mean time to steroid withdrawal in the AZA group was 20 months versus 12 months in the MMF group (P=0.001), the lower incidence of steroid withdrawal in the MMF group likely reflects the shorter term follow-up in this more recently transplanted group.

To identify which pancreas transplant recipients are most likely to benefit while at the same time achieve safe steroid withdrawal will require prospective randomized trials under a strict set of selection criteria. In the current study, patients were not randomly assigned to steroid withdrawal and hence were a selected group, which may account for the observed improved patient and graft survival rates and reduced frequency of rejection episodes per patient in those who were withdrawn from steroids compared with those who remained on steroids. Nevertheless, this is the first report demonstrating that steroid withdrawal is safe and can be accomplished in approximately 50% of pancreas transplant recipient patients with acceptable patient and graft survival rates in the short- and medium-term. We believe that the steroid sparing effects of TAC previously documented in other solid organ transplant recipients are also applicable to the pancreas transplant population. Whether this steroid-free state will further improve the reversal of type I diabetes-induced complications after successful pancreas transplantation will require further study.

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REFERENCES

1. Gruessner A, Sutherland DER. Analysis of United States (US) and non-US pancreas transplants as reported to the International Pancreas Transplant Registry (IPTR) and to the United Network of Organ Sharing (UNOS). In: Cecka JM, Terasaki PI, eds. Clinical transplants 1998. Los Angeles, CA: UCLA Tissue Typing Laboratory, 1999: 53.
2. Sollinger HW, Odorico JS, Knechtle SJ, et al. Experience with 500 simultaneous pancreas-kidney transplants. Ann Surg 1998; 228(3): 284.
3. Jordan ML, Shapiro R, Gritsch HA, et al. Long term results of pancreas transplantation under tacrolimus immunosuppression. Transplantation 1999; 67: 266.
4. Stratta RJ. Immunosuppression in pancreas transplantation: progress, problems, and perspective. Transpl Immunol 1998; 6: 69.
5. Corry RJ, Chakrabarti PK, Shapiro R, et al. Simultaneous administration of adjuvant donor bone marrow in pancreas transplant recipients. Ann Surg 1999; 230: 372.
6. Scantlebury V, Shapiro R, Fung JJ, et al. New onset of diabetes in FK506 vs. cyclosporine treated kidney transplant recipients. Transplant Proc 1991; 23: 3169.
7. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation: FK506 Kidney Transplant Study Group. Transplantation 1997; 63: 977.
8. Shapiro R, Scantlebury V, Jordan ML, et al. Reversibility of tacrolimus induced post-transplant diabetes: an illustrative case and review of the literature. Transplant Proc 1997; 29: 2737.
9. Mayer AD, Dmitrewski J, Squifflet JP, et al. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. Transplantation 1997; 64: 436.
10. Gruessner RWG for the Tacrolimus Pancreas Transplant Study Group. Tacrolimus in pancreas transplantation: a multicenter analysis. Clin Transplant 1997; 11: 299.
11. Kaufman DB, Leventhal JR, Stuart J, Abecassis MM, Fryer JP, Stuart FP. Mycophenalate mofetil and tacrolimus as primary maintenance immunosuppression in simultaneous pancreas-kidney transplantation: initial experience in 50 consecutive cases. Transplantation 1999; 67: 586.
12. Burke GW, Ciancio G, Alejandro R, et al. Use of tacrolimus and mycophenolate mofetil for pancreas-kidney transplantation with or without OKT3 induction. Transplant Proc 1998; 30: 1544.
13. Shapiro R, Jordan ML, Scantlebury VP, et al. A prospective, randomized trial of FK506-based immunosuppression after renal transplantation. Transplantation 1995; 59: 485.
14. Shapiro R, Jordan ML, Scantlebury V, et al. Outcome after steroid withdrawal in renal transplant patients receiving tacrolimus-based immunosuppression. Transplant Proc 1998; 30: 1375.
15. Mazariegos GV, Reyes J, Marino IR, et al. Weaning of immunosuppression in liver transplant recipients. Transplantation 1997; 63: 243.
16. Hricik De, Bartucci MR, Mayes JT, Schulak JA. The effects of steroid withdrawal on the lipoprotein profiles of cyclosporine-treated kidney and kidney-pancreas transplant recipients. Transplantation 1992; 54: 868.
17. Sugitani A, Egidi MF, Gritsch HA, Corry RJ. Serum lipase as a marker for pancreatic allograft rejection. Transplant Proc 1998; 30: 645.
18. Fioretto P, Steffes NW, Sutherland DER, et al. Reversal of lesions of diabetic nephropathy after pancreas transplantation. New Engl J Med 1998; 339: 69.
19. Tyden G, Bolinder J, Solders G, Brattstrom C, Tibell A, Groth CG. Improved survival in patients with insulin-dependent diabetes mellitus and end-stage diabetic nephropathy 10 years after combined pancreas and kidney transplantation. Transplantation 1999; 67: 645.
20. Solders G, Tyden G, Persson A, Groth CG. Improvement of nerve conduction in diabetic neuropathy: a follow up study 4 years after combined pancreas and renal transplantation. Diabetes 1992; 41: 946.
21. Foger B, Königsrainer A, Palos G, et al. Effect of pancreas

transplantation on lipoprotein lipase, postprandial lipemia and HDL cholesterol. Transplantation 1994; 58: 899.
22. Landgraf R. Impact of pancreas transplantation on diabetic secondary complications and quality of life. Diabetologia 1996; 39: 1415.
23. Corry RJ, Zehr P. Quality of life in diabetic recipients of kidney transplants is better with the addition of the pancreas. Clin Transplant 1990; 4: 238.
24. Corry RJ, Egidi M, Shapiro R, et al. Pancreas transplantation with enteric drainage under tacrolimus induction therapy. Transplant Proc 1997; 29: 642.
25. Gritsch HA, Egidi M, Sugitani M, et al. Comparison of azathioprine and mycophenolate mofetil in pancreas transplantation. Transplant Proc 1998; 30: 526.
26. McKee M, Mattei P, Schwarz K, Wise B, Columbani P. Steroid withdrawal in tacrolimus (FK506)-treated pediatric liver transplant recipients. J Pediatr Surg 1997; 32: 973.
27. Jordan ML, Naraghi R, Shapiro R, et al. Tacrolimus rescue therapy for renal allograft rejection: five-year experience. Transplantation 1997; 63: 223.
28. Thaysen JH, Lokkegaard H. Permanent withdrawal of prednisone in nekro-kidney transplantation. Scand J Urol Nephrol Suppl 1977; 42: 198.
29. Stratta RJ, Armbrust MJ, Oh CS, et al. Withdrawal of steroid immunosuppression in renal transplant recipients. Transplantation 1988; 45: 323.
30. Schulak JA, Mayes JT, Moritz CE, Hricik DE. A prospective randomized trial of prednisone versus no prednisone maintenance therapy in cyclosporine-treated and azathioprine-treated renal transplant patients. Transplantation 1990; 49: 327.
31. Hricik DE, Bartucci MR, Moir EJ, Mayes JT, Schulak JA. Effects of steroid withdrawal on post-transplant diabetes mellitus in cyclosporine-treated renal transplant recipients. Transplantation 1991; 51: 374.
32. Hricik De, Whalen CC, Lautman J, et al. Withdrawal of steroids after renal transplantation: clinical predictors of outcome. Transplantation 1992; 53: 41.
33. Ingulli E, Tejani A, Markell M. The beneficial effects of steroid withdrawal on blood pressure and lipid profile in children posttransplantation in the cyclosporine era. Transplantation 1993; 55: 1029.
34. Schulak JA, Hricik De. Steroid withdrawal after renal transplantation. Clin Transplant 1994; 8: 211.
35. Shapiro R, Scantlebury VP, Jordan ML, et al. Pediatric renal transplantation under tacrolimus-based immunosuppression. Transplantation 1999; 67: 299.
36. Grewal HL, Thistlewaite JB Jr, Loss GE, et al. Corticosteroid cessation 1 week following renal transplantation using tacrolimus/mycophenolate mofetil based immunosuppression. Transplant Proc 1998; 30: 1378.

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