Steroid Withdrawal in Simultaneous Pancreas-Kidney Transplantation: A 7-Year Report

J. Malheiro, L. Martins, I. Fonseca, A.M. Gomes, J. Santos, L. Dias, J. Dores, F. Oliveira, R. Seca, R. Almeida, A. Henriques, A. Cabrita, and M. Teixeira

ABSTRACT

Simultaneous pancreas-kidney transplantation (SPK) is the treatment of choice for selected diabetic patients with end-stage renal disease. Maintenance steroid therapy is associated with significant morbidity and mortality among SPK transplant recipients. Steroid withdrawal regimens are becoming more common, albeit with reservations regarding its safety and efficacy. We performed a retrospective review of 77 SPK transplant recipients from May 2000 to December 2007. The subjects received induction therapy with thymoglobulin followed by maintenance immunosuppression with tacrolimus and mycophenolate mofetil. A late steroid withdrawal protocol was adopted. The rates of acute rejection, graft and patient survival, and side effects were analyzed. One-year patient, kidney, and pancreas survivals were 93%, 91%, and 86%, respectively. Eleven patients experienced acute rejection. Mean follow-up time was 1155.5 ± 776.1 days. Prednisolone withdrawal was carried out between 6 and 12 months posttransplantation in 42 patients (77.8%) with at least 1 year follow-up; no case of acute rejection occurred. At present, 72 patients have a functioning kidney graft, and 65 patients also have a functioning pancreas graft. The mean serum creatinine is 1.12 ± 0.49 mg/dL and the mean HbA1c concentration is 4.5% ± 0.4%. The patients have a low prevalence of hypertension, hyperlipidemia, and obesity. Steroid withdrawal was successful and safe in the majority of in-study patients and safe without an increase of immune events. Our patient and graft outcomes are within other international SPK transplant units standards.

SIMULTANEOUS PANCREAS-KIDNEY (SPK) transplantation has been developed for patients suffering from type 1 diabetes mellitus and end-stage renal disease. Patients are generally given conventional immunosuppressive treatment after transplantation, using steroids, calcineurin inhibitors, and antagonists of purine metabolism.[1,2] Most centers also use induction with antilymphocyte preparations.[3,4]

The use of steroids for maintenance therapy in solid organ transplant recipients is common, despite their detrimental effects on osteoporosis, bone fractures, arterial hypertension, insulin resistance, and cataracts.[5,6] These side effects among patients undergoing SPK transplantation are particularly troublesome, given their long course of type 1 diabetes and their increased cardiovascular risk. The minimization or withdrawal of steroids in these patients is, therefore, an objective. Nevertheless, late steroid withdrawal has been reported to be associated with a significant risk of acute rejection episodes and/or functional adrenal impairment.[7–9] Herein we have presented our experience with the safety and feasibility of corticosteroid withdrawal among SKP transplant recipients.

PATIENTS AND METHODS

From May 2000 to December 2007, 77 C-peptide-negative patients with type 1 insulin-dependent diabetes mellitus underwent SPK transplantation. All subjects received induction therapy with antithymocyte globulin (Fresenius) administered at 3 mg/kg for 7 to 10

From the Nephrology Unit (J.M., L.M., I.F., J.S., L.D., A.H., A.C.) and Pancreas-Kidney Transplant Unit (J.M., L.M., I.F., J.S., L.D., J.D., F.O., R.S., R.A., A.H., A.C., M.T.), Hospital Geral Santo António, Centro Hospitalar do Porto, Porto, Portugal, and Nephrology Unit (A.M.G.), Centro Hospitalar Vila Nova Gaia/Espinho, Gaia, Portugal.

Address reprint requests to Dr Jorge Malheiro, Nephrology Unit, Hospital Geral Santo António, Centro Hospitalar do Porto, Largo Prof Abel Salazar, 4099-001 Porto, Portugal. E-mail: malheirojorge@sapo.pt, jjorgemalheiro@gmail.com

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360 Park Avenue South, New York, NY 10010-1710

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doses; tacrolimus at a dose of 0.1 mg/kg twice daily; mycophenolate mofetil (MMF) 2 g/d; and intravenous methylprednisolone for 4 days (day 1: 500 mg; day 2: 250 mg; day 3: 250 mg; and day 4: 125 mg). The maintenance immunosuppression included tacrolimus (target trough level- 8–14 ng/mL), MMF adjusted according to tolerability, and oral prednisolone started (day 5) at 1 mg/kg/d and tapered to 10 mg/d by the end of the third month after transplantation. A further taper of the prednisolone dose was made after 6 months posttransplant when clinically feasible. Full steroid withdrawal was evaluated after 6-month follow-up, considering the exclusion criteria of a previous acute rejection episode, gastrointestinal intolerance to MMF, and clinical context to avoid MMF namely, previous severe infectious episodes and the presence of BK virus nephritis. It was started at 6 months with the purpose of complete steroid suspension by the end of the first year.

We performed a retrospective review of recipient demographic and clinical data, SPK transplantation details, patient and allograft outcomes, as well as serial laboratory measurements. Delayed graft function was defined as the need for dialysis during the first week after transplantation. Biopsy-proven rejection was diagnosed using the Banff criteria. No pancreatic biopsy was made.

Statistical Analysis

Descriptive statistics were expressed as mean values ± standard deviations or median (interquartile range). Differences between patients with versus without steroids were tested by the nonparametric Mann-Whitney *U* test due to the small number of patients with steroids. Categorical variables were analyzed with the chi-square or Fisher exact probability test. Patient and graft survivals were estimated using a life table statistical technique. A *P* value less than .05 was considered significant. Data were analyzed using the SPSS 15.0 statistical package.

RESULTS

We reviewed the clinical records of the 77 SPK transplants performed in our unit between May 2000 and December 2007. Average age at the time of transplantation was 33.7 ± 6.3 years. Time on dialysis was 34 ± 26 months. Four patients underwent premptive transplantation. Forty-eight patients were women. Mean diabetes mellitus duration had been 22.7 ± 5 years. Mean body mass index was 22.5 ± 2.8 kg/m^2. Nineteen patients had no HLA match with the donor. Average donor age was 22.3 ± 11.1 years.

Sixteen patients (20.8%) experienced delayed graft function. Acute rejection within the first month posttransplant occurred in 11 patients (14.3%); the diagnosis was clinically presumed or biopsy-proven; nine were corticosteroid-sensitive; one was a humoral rejection treated with plasmapheresis and human immunoglobulin; and one a late, refractory acute rejection treated with OKT3. Except for this case, no other acute rejection episode was documented after the first month. Median hospitalization time was 23 days, with 2-day stay in the intensive care unit. Early failure of pancreas and kidney grafts (<3 months) occurred in 12 and 2 patients, respectively.

Mean follow-up time is 1155.5 ± 776.1 days (range = 60–2779 days). Seventy-two patients have a functioning kidney graft, and 65 also a functioning pancreas graft. Among the 72 patients with at least one functioning graft, 27 had to change their maintenance immunosuppression from MMF to sirolimus (*n* = 23) or mycophenolic acid sodium (*n* = 4), because of digestive side effects. In four cases, both MMF and sirolimus were suspended: three patients had a severe infection event and one, thrombotic microangiopathy. These patients were maintained on tacrolimus and prednisolone.

The objective of full steroid withdrawal at 1 year was accomplished in 42/54 patients (77.8%) with more than 1-year follow-up. No acute rejection episode was registered, nor any case of adrenal failure. Hence, 12 patients maintained steroids beyond the first year posttransplant. The most common cause for failure to withdraw was a previous acute rejections episode (*n* = 6); a significant infectious event that determined the suspension of MMF or sirolimus (*n* = 4); BK-driven nephritis with the need for a low-dose or even suspension of MMF therapy (*n* = 2). Patient and graft survivals among this subset of patients at 2 and 5 years are presented in Table 1.

The patients with a functioning pancreas graft (*n* = 65) showed normal fasting glycemia and an average HgA1c of 4.5% ± 0.4%. Patients with a functioning kidney graft (*n* = 72) displayed a mean serum creatinine of 1.12 ± 0.49 mg/dL, a mean 24-hour measured creatinine clearance of 75.1 ± 25.8 mL/min, and a mean 24-hours proteinuria of 0.3 g. Only two patients have a serum creatinine higher than 2 mg/dL. No significant differences were observed concerning renal and pancreas graft function between patients with versus without steroids (Table 2).

Considering all patients in the follow-up, the average weight gain was 1.5 kg since the transplant. At the last visit, the mean total cholesterol was 166 ± 34 mg/dL; the mean triglyceride level, 97 ± 47 mg/dL, and the mean high-density lipoprotein cholesterol, 58 ± 17 mg/dL. Only 12 patients need statins and 15, some antihypertensive drug. Serum lipids compared between groups with versus without steroids showed no significant differences (Table 2). Patient and graft survivals at 1 and 5 years are shown in Table 3.

DISCUSSION

The use of steroids as a maintenance immunosuppressive drug in solid organ transplantation is still common, al-

Table 1. One-Year Follow-up Patients: Patient and Graft Survivals at 2 and 5 Years, According to Steroid Strategy

	2 Years (%)	5 Years (%)
Steroid-free (*n* = 42)		
Patient	100	98
Kidney graft	98	98
Censored kidney graft*	98	98
Pancreas graft	95	90
Steroid-based (*n* = 12)		
Patient	92	83
Kidney graft	92	83
Censored kidney graft*	100	100
Pancreas graft	83	75

*Death-censored kidney allograft survival.

Table 2. Graft Function and Metabolic Data Comparison Between Steroid-Based and Steroid-Free Groups

	Steroid-Based (n = 12), median (IQ)	Steroid-Free (n = 42), median (IQ)	P
Serum creatinine (mg/dL)	1.15 (0.83–1.60)	1.10 (0.88–1.30)	.41*
Urea (mg/dL)	54 (45–72)	49.0 (43–62)	.37*
Fasting glycemia (mg/dL)	78 (70–85)	81 (74–87)	.49*
HbA1c (%)	4,8 (3.8–4.9)	4.5 (4.2–4.8)	.92*
Total cholesterol (mg/dL)	172 (151–186)	165 (139–194)	.61*
Triglycerides (mg/dL)	82 (75–98)	81 (64–117)	.68*
HDL cholesterol (mg/dL)	61 (40–74)	54 (42–61)	.33*
Weight (kg)	59 (49–65)	58 (52–66)	.73*
BMI (kg/m^2)	23.8 (22.0–26.1)	22.6 (21.1–25.1)	.57*
Antihypertensive, n (%)	4 (33.3)	10 (23.8)	0.49†
Statin, n (%)	1 (8.3)	10 (23.8)	0.42†

HDL, high-density lipoprotein; BMI, body mass index; IQ, interquartile range.
*Mann-Whitney U test; †Fisher exact probability test.

though it is associated with significant morbidity and mortality. Death is the leading cause of failure in renal transplantation, accounting for 46% of graft failures occurring after 3 years posttransplantation.[10] The major causes are cardiovascular disease and infection, both of which may be triggered or favored by the use of steroids.

Several studies have tried to address the feasibility of steroid withdrawal in SPK transplant recipients. Two routine approaches to limit steroid-related side effects are systematic steroid withdrawal in stable allograft recipients and complete steroid avoidance or their rapid elimination. A 2004 meta-analysis of late steroid withdrawal in kidney transplantation showed an increased risk of acute rejection episodes, but no increased risk of early graft failure.[9]

However, the development of new immunosuppressive drugs has decreased the immediate immunologic risks, allowing greater emphasis on improving long-term wellness in SPK transplant recipients. The initial cyclosporine-microemulsion-based trials showed a 30% risk of acute and chronic rejection following late corticosteroid withdrawal, imposing the need to maintain virtually all renal transplant patients on low-dose steroids.[11,12] The addition of MMF to cyclosporine-microemulsion enabled prednisolone withdrawal at 6 months posttransplant without an increase in acute rejection episodes.[13] Likewise, with the association of cyclosporine-microemulsion and sirolimus, steroid tapering (initiated at a mean of 415 days posttransplant) was maintained for 3 years in 78% of kidney recipients.[14] Maintenance immunosuppression with tacrolimus and MMF showed a 94% likelihood of patients being maintained off steroids following late steroid withdrawal with good graft function.[15] A recent report showed a steroid-free regimen with thymoglobulin induction followed by tacrolimus and MMF for maintenance in SPK transplantation to be safe and effective in preventing rejection episodes, with a reduced incidence of cytomegalovirus infections and better-preserved kidney function.[3]

Recently approaches have been numerous. Several units have reported early steroid withdrawal at the end of the 1 week posttransplant with favorable short-term results in terms of graft function and recipient survival, without jeopardizing the risk of acute rejection episodes.[3,16–19] Similar results were reported by other SPK centers, although using a late schedule for the withdrawal: namely, the end of 3 months[20] or between 6 months and 1 year posttransplant.[21,22]

Cantarovich et al compared the benefits of early versus late (>3 months) steroid withdrawal.[20] Despite a small number of patients in this study, they observed that the rate of acute rejection episodes was similar in both groups, but that the serum creatinine concentration tended to be lower in the group with late steroid withdrawal. Notwithstanding, few studies have investigated the long-term effects of steroid withdrawal on graft and patient survivals. Opelz in the Collaborative Transplant Study showed that among a group of patients who received steroids for a minimum of 6 months after transplantation and who were clinically stable at the time of steroid elimination,[23] 90% of grafts functioned without steroids.

The pursuit of a steroid-free or reduced exposure among SPK transplant recipients has the purpose of controlling cardiovascular risk factors (obesity, hyperlipidemia, hypertension, and glucose intolerance) in this high-risk population. The published data about the long-term effects of steroid withdrawal to reduce vascular risk/events in this setting are scarce, although better control of these risk factors would allow us to expect such an outcome. Jaber et al published a report showing that an early steroid withdrawal protocol was associated with a reduced incidence of obesity, posttransplant diabetes, and hyperlipidemia among renal transplant recipients. No difference was acknowledged in the need for antihypertension drugs.[18] Noteworthy, hyperlipidemia is a known side effect not only of steroids but also of tacrolimus and sirolimus.[18,24]

Control of cardiovascular risk factors is possible in these patients as demonstrated by our data. Nevertheless, the comparison of the lipid profiles and the need for antihypertensive drugs did not show a significant difference between the steroid-treated and steroid-free patients. The need for statins was more frequent in the steroid-free group. The hyperlipidemic effects of sirolimus (more patients under sirolimus in this group) cannot be disregarded as a contributing factor. However, the rate of patients needing these treatments can be considered to be low, compared with results in kidney transplantation alone. We acknowledge

Table 3. All SKP Transplant Patients: Patient and Grafts Survivals

	1 Year (%)	5 Years (%)
Patient	93	90
Kidney graft	91	88
Pancreas graft	86	81

SPK, simultaneous pancreas-kidney.

the limitations of this report, as it is observational, retrospective, single center without randomization. Moreover, the criteria for selection of patients between the two groups, although clinically based, showed some degree of heterogeneity.

However, the previous studies allow us to put forward our late steroid withdrawal protocol. Hence, steroid withdrawal is usually undertaken in situations where there is a good long-term graft prognosis, evidence of steroid-induced morbidity and tolerance to the remaining maintenance drugs (MMF, tacrolimus).

Complete steroid withdrawal by the end of the first year was accomplished in 77.8% of our patients with more than 1 year follow-up ($n = 54$) and no subsequent acute rejection episodes. Our data showed good, stable graft function. No significant differences in graft function were noted between the steroid-based and steroid-free groups. The overall patient and graft survivals were similar to other SPK transplant units.[20] More precise clinical criteria are necessary for full implementation of this immunosuppressive strategy.

REFERENCES

1. Strata RJ: Review of immunosuppressive usage in pancreas transplantation. Clin Transplant 13:1, 1999

2. Danovitch GM: Immunosuppressive medications for renal transplantation: a multiple choice question. Kidney Int 59:388, 2001

3. Tanchanco V, Krishnamurthi C, Winans A, et al: Beneficial outcomes of a steroid-free regimen with thymoglobulin induction in pancreas-kidney transplantation. Transplant Proc 40:1551, 2008

4. Malaise J, Kuypers DRJ, Claes P, et al: Immunosuppressive drugs after simultaneous pancreas-kidney transplantation. Transplant Proc 37:2840, 2005

5. Grotz WH, Mundinger FA, Gugel B, et al: Bone fracture and osteodensitometry with dual energy X-ray absorptiometry in kidney transplant recipients. Transplantation 58:912, 1994

6. Veenstra DL, Best JH, Hornberger J, et al: Incidence and long-term cost of steroid-related side effects after renal transplantation. Am J Kidney Dis 33:829, 1999

7. Miozzari M, Ambuhl PM: Steroid withdrawal after long-term medication for immunosuppressive therapy in renal transplant patients: adrenal response and clinical implications. Nephrol Dial Transplant 19:2615, 2004

8. Cantarovich D, Paineau J, Karam G, et al: Definitive corticosteroid withdrawal following simultaneous pancreas and kidney transplantation. Transplant Proc 23:1583, 1991

9. Pascual J, Quereda C, Zamora J, et al: Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolate mofetil: a meta-analysis of randomized, controlled trials. Transplantation 78:1548, 2004

10. Gjertson DW, Terasaki PI, Cecka JM: Impact analysis: a method for evaluating the impact of factors in clinical renal transplantation. Clin Transplant 437, 1998

11. Hricik DE: Steroid-free immunosuppression in kidney transplantation: an editorial review. Am J Transplant 2:19, 2002

12. Ratcliffe PJ, Dudley CR, Higgins RM, et al: Randomised controlled trail of steroid withdrawal in renal transplant recipients receiving triple immunosuppression. Lancet 348:643, 1996

13. Smak Gregoor PJ, de Sevaux RG, Ligtenberg G, et al: Withdrawal of cyclosporine or predisone six months after kidney transplantation in patients on triple drug therapy: a randomized, prospective, multicenter study. J Am Soc Nephrol 13:1365, 2002

14. Mahalati K, Kahan BD: A pilot study of steroid withdrawal from kidney transplant recipients on sirolimus-cyclosporine a combination therapy. Transplant Proc 33:3232, 2001

15. Citterio F, Rigotti P, Scat MC, et al: Steroid withdrawal in renal transplant patients treated with tacrolimus. Am J Transplant 2:172, 2002

16. Aoun M, Eschewege P, Hamoudi Y, et al: Very early steroid withdrawal in simultaneous pancreas-kidney transplants. Nephrol Dial Transplant 22:899, 2007

17. Freise CE, Kang SM, Feng S, et al: Excellent short-term results with steroid-free maintenance immunosuppression in low-risk simultaneous pancreas-kidney transplantation. Arch Surg 138: 1121, 2003

18. Jaber JJ, Feustel PJ, Elbahloul O, et al: Early steroid withdrawal therapy in renal transplant recipients: a steroid-free sirolimus and cellcept-based calcineurin inhibitor-minimization protocol. Clin Transplant 21:101, 2007

19. Kaufman DB, Leventhal JR, Koffron AJ, et al: A prospective study of rapid corticosteroid elimination in simultaneous pancreas-kidney transplantation. Transplantation 73:169, 2002

20. Cantarovich D, Karam G, Hourmant M, et al: Steroid avoidance versus steroid withdrawal after simultaneous pancreas-kidney transplantation. Am J Transplantation 5:1332, 2005

21. Malaise J, Nakache R, Kahl A, et al: Corticosteroid withdrawal in simultaneous pancreas-kidney transplantation: a 3-year report. Transplant Proc 37:2853, 2005

22. Jordan ML, Chakrabarti P, Luke P, et al: Results of pancreas transplantation after steroid withdrawal under tacrolimus immunosuppression. Transplantation 69:265, 2000

23. Opelz G: Collaborative transplant study. CTS Newsletter 4:3, 2000

24. Morrisett JD, Abdel-Fattah G, Hoogeveen R, et al: Effects of sirolimus on plasma lipids, lipoprotein levels, and fatty acid metabolism in renal transplant patients. J Lipid Res 43:1170, 2002