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Advantage of Rapamycin Over Mycophenolate Mofetil When Used With Tacrolimus for Simultaneous Pancreas Kidney Transplants: Randomized, Single-Center Trial at 10 Years

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Abstract

Simultaneous pancreas kidney transplantation (SPKT) is the treatment of choice for patients with type 1 diabetes and end-stage renal disease. Rapamycin and mycophenolate mofetil (MMF) have been used for maintenance immunosuppression with tacrolimus in SPKT; however, long-term outcomes are lacking. From September 2000 through December 2009, 170 SPKT recipients were enrolled in a randomized, prospective trial receiving Rapamycin (n = 84) or MMF (n = 86). All patients received dual induction therapy with thymoglobulin and daclizumab, and low-dose maintenance tacrolimus and corticosteroids. Compared to MMF, rates of freedom from first biopsy-proven acute kidney or pancreas rejection were superior for Rapamycin at year 1 (kidney: 100% vs. 88%; P = 0.001; pancreas: 99% vs. 92%; P = 0.04) and at year 10 (kidney: 88% vs. 71%, P = 0.01; pancreas: 99% vs. 89%, P = 0.01). The higher rates of rejection were associated with withholding MMF (vs. Rapamycin, p = 0.009), generally for gastrointestinal or bone marrow toxicity. There was no significant difference in creatinine, proteinuria, c-peptide, viral infections, lymphoproliferative disorders or posttransplant diabetes. HbA1C and lipid levels were normal in both groups, although higher in the Rapamycin arm. There were no significant differences in patient or allograft survival. In this 10-year SPKT study, Rapamycin in combination with tacrolimus was better tolerated and more effective than MMF. Overall, the patient and allograft survival were equivalent.

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Disclosure

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Keywords

End-stage renal disease; rapamycin; mycophenolate mofetil; simultaneous kidney-pancreas transplant; tacrolimus; type 1 diabetes

Introduction

Simultaneous pancreas kidney transplantation (SPKT) is the therapy of choice for patients with type 1 diabetes and end-stage renal disease (ESRD) (1,2). The combination of tacrolimus, mycophenolate mofetil (MMF) and steroids is a safe and effective maintenance immunosuppression regimen for SPKT (1–4). Alternatively, the addition of Rapamycin to tacrolimus has also been demonstrated to offer good short-term results in SPKT recipients (5,6). However, several studies in recipients of kidney transplants alone (7–9) as well as SPKT recipients (10) reported worse outcomes in kidney allograft survival associated with synergistic nephrotoxicity with the combination of Rapamycin and tacrolimus (11,12) that was not apparent when MMF was used with tacrolimus. Furthermore, Rapamycin is associated with proteinuria and metabolic derangements, including insulin resistance and dyslipidemia in kidney transplant recipients that could adversely impact long-term patient or allograft survival (13). Since there have been no head to head trials in this area, this study was designed to examine the long-term effect of Rapamycin versus MMF in SPKT.

In our first reported analysis (6), the rate of biopsy-proven acute rejection for kidney and pancreas transplants in a smaller data set ($n = 42$) was better for Rapamycin than MMF. The current study extends our initial findings and demonstrates the significant impact of SPKT recipients' ability to tolerate MMF from a gastrointestinal and bone marrow toxicity standpoint, and the impact of Rapamycin on the incidence of acute rejection, renal function and patient and allograft survival when combined with tacrolimus over a 10-year period.

Methods

Study design

This single center, prospective, open label, randomized trial was designed to compare the safety and efficacy of Rapamycin versus MMF in SPKT recipients. From September 1, 2000 through December 15, 2009, 170 consecutive patients with type 1 diabetes and ESRD were randomized to receive either Rapamycin ($n = 84$) or MMF ($n = 86$) (Figure 1), immediately prior to SPKT. A randomized block design was implemented for the randomization scheme using Proc Plan in SAS (Statistical Analysis Systems). Under this design, patients were randomly assigned (using an allocation ratio of 1:1) to the two treatment arms in blocks of 4 and 6 patients (block sizes were also chosen randomly), ensuring a balance of patients across treatment arms after each block of patients had been randomized. Posttransplant clinical follow-up of patients continued through January 15, 2011.

Type 1 diabetes was determined by history, and all patients underwent a confirmatory Sustacal challenge test pretransplantation (stimulated c-peptide less than 0.1 ng/mL). Patients with type 2 diabetes were excluded. All SPKT were bladder drained, with systemic venous anastomosis. All donor kidneys underwent pulsatile perfusion preservation (14). All

patients received intraoperative induction therapy with 500 mg of methylprednisolone intravenously followed by daclizumab 1 mg/kg, and thymoglobulin 1 mg/kg (over 4–6 h). Thymoglobulin was started prior to reperfusion. A total of five doses of thymoglobulin were given per patient; a second dose of daclizumab was given between days 7 and 14 (15). Rapamycin (4 mg per day) or MMF (1 gm twice a day) was planned to start postoperatively on day 1, with target Rapamycin levels of 5–7 ng/mL and target MMF dosing of 1 gm twice a day. Tacrolimus was started when the serum creatinine fell below 4 mg/dL with target levels of 5–7 ng/mL. Steroids were decreased progressively to reach 0.05 mg/kg/day by 3 months.

Acute rejection of the kidney was defined as a rise of 0.3 mg/dL or greater from the baseline creatinine accompanied by a confirmatory transplant kidney biopsy within 24 h of initiation of antirejection therapy. Acute rejection of the pancreas transplant was identified as a fall in urine amylase greater than 50% from baseline value or a rise in serum amylase or lipase accompanied by a biopsy of the pancreas within 24 h of initiation of antirejection therapy. In those instances where acute rejection of both kidney and pancreas was suspected, the kidney was biopsied preferentially. When empiric antirejection therapy was administered but allograft biopsies (kidney or pancreas) were not performed for safety or technical reasons at the discretion of the caring physician, this was considered a clinically suspected rejection episode. Banff criteria were used to determine the severity of rejection on allograft biopsy (16). Initial rejection episodes were treated with intravenous methylprednisolone (500 mg/day for 3 days with subsequent weaning). Antilymphocyte antibody (thymoglobulin 1 mg/kg/day for 5–10 days) treatment was used for patients with histologically proven moderate or severe rejection or steroid-resistant rejection. Kidney allograft loss was defined as time of reestablishment of long-term dialysis, kidney transplant removal, or death with a functioning allograft. Pancreas allograft loss was defined as return to insulin therapy due to allograft removal, lack of c-peptide production or death with a functioning allograft. Withholding of immunosuppressive medication (Rapamycin or MMF) was defined as the patient having had the drug withheld for at least 2 weeks. Discontinuation of immunosuppressive medication was defined as the drug being withheld for at least 1 year.

The primary endpoints were kidney- and pancreas-specific biopsy-proven acute rejection rates during the first 12 months posttransplant. Secondary endpoints included biopsy-proven or clinically treated acute rejection throughout the follow-up period, allograft loss (kidney- and pancreas-specific, both death-censored and uncensored), infection, other adverse events and death. The study was approved by the University of Miami Institutional Review Board (UM-IRB 2000-176; registration number NCT 00533442 at www.clinicaltrials.gov), and all patients provided written informed consent.

Statistical analysis

All analyses were performed as intent-to-treat (i.e. patients were grouped according to the treatment arm in which they were randomized). Assuming 12-month biopsy-proven acute rejection rates of 5–7% in one arm and 20–22% in the other arm, we estimated that 62–86 patients per treatment arm would be needed to achieve statistical power of at least 0.80 with a type I error of 0.05. For the two primary endpoints, the statistical plan was to perform a

log-rank test of the two biopsy-proven acute rejection rates, one for kidney and one for pancreas, through 12 months posttransplant (thus, greater statistical power achieved in comparison with using a simple test of two proportions when the hazard ratio consistently favors one group over time), censoring all patients beyond 12 months posttransplant (plus, censoring any deaths or graft losses that occurred in the absence of rejection). *T*-tests and Pearson (uncorrected) chi-squared tests were used to compare means and proportions between treatment arms. Arithmetic means $\pm$ standard deviations (S.D.) were calculated except for variables that were highly skewed toward larger values, in which geometric means and corresponding standard deviations were reported, with comparisons based on log-transformed values. The primary and secondary analyses utilized Kaplan–Meier curves with log-rank tests of the time-to-failure outcomes (organ-specific biopsy-proven acute rejection; organ-specific clinically suspected or biopsy-proven acute rejection; organ-specific death-censored and death-uncensored allograft failure; and all-cause mortality). *F*-tests comparing average mean differences over time between the two treatment arms for serum creatinine, c-peptide and HbA1C were performed using log-transformed values; for each variable a repeated measures, linear model was assumed (using PROC MIXED in SAS, Statistical Analysis Systems), allowing for main effects of treatment arm and time posttransplant, a separate variance term for each of the 11 time points, and a separate intraclass correlation term for each pair of values separated by *k* time points, *k* = 1, ..., 10 (i.e. a heterogeneous Toeplitz variance–covariance structure). The effect of drug withholding on the time-to-failure events was modeled as a time-dependent covariate, and time-to-failure analyses of the two groups were compared while patients were maintained on the protocol (i.e. censored at the time of Rapamycin or MMF withholding).

Results

Patient demographics

The baseline demographics between the two groups (Table 1) were comparable. Although a slightly lower proportion of Hispanic participants was observed in the MMF arm (22% vs. 37% Rapamycin, *p* = 0.03), the total non-Caucasian population (Hispanic plus African American) was comparable: 44% and 35% Rapamycin vs. MMF (*p* = 0.22). As expected, the mean cold ischemia time for pancreas transplants was similar in both groups, as was the proportion of recipients with gastroparesis (>50%), coronary artery disease and those at high risk for cytomegalovirus (donor sero-positive to recipient sero-negative).

Immunosuppressive drug doses and target trough levels

There were no significant differences between groups for steroid or tacrolimus dosing. Mean tacrolimus and Rapamycin levels were usually maintained between 5 ng/mL and 7 ng/mL as per the protocol (Appendix Table A1). Mean MMF dosing fell from 1528 mg/day at month 1 to 792 mg/day by 96 months, mostly secondary to gastrointestinal side effects and leukopenia. During the first year following transplantation, the rate of withholding or discontinuing immunosuppressive agents due to any reason was 52% for MMF versus 29% for Rapamycin (*p* = 0.002). Despite a similar baseline prevalence of gastroparesis in both groups, MMF was withheld due to gastrointestinal toxicity in 28% (vs. 0% Rapamycin, *p* < 0.000001) during the first year. Conversely, Rapamycin was withheld due to wound healing

issues and/or fluid retention in 11% (vs. 0% MMF, $p = 0.002$) during the first year. No significant difference in drug withholding or discontinuation (due to any reason) was observed in the two arms beyond 1 year posttransplant ($p = 0.39$, 10% for MMF vs. 14% for Rapamycin).

Primary endpoint

Freedom from the first biopsy-proven acute kidney rejection at 12 months posttransplant was superior in the Rapamycin group compared with MMF (100% vs. 88%; $p = 0.001$), with 0/84 versus 10/86 patient events occurring in the Rapamycin and MMF arms during this time. Similarly, Rapamycin was superior for freedom from first biopsy-proven acute pancreas rejection at 12 months post-transplant compared to MMF (99% vs. 92%; $p = 0.04$), with 1/84 versus 7/86 patient events occurring in the Rapamycin and MMF arms during this time. There were no significant differences in rates of kidney or pancreas rejection between the groups beyond 12 months post-transplant. Kidney-specific (death-censored) freedom from biopsy-proven acute rejection at 120 months was higher in the Rapamycin versus MMF group (88% vs. 71% respectively; $p = 0.01$) (Figure 2A, with 8/84 vs. 22/86 events occurring in the two arms, respectively). Pancreas-specific (death-censored) freedom from biopsy-proven acute rejection at 120 months was also higher in the Rapamycin (99%) than MMF group (89%, $p = 0.01$) (Figure 2B, with 1/84 vs. 9/86 events occurring in the two arms, respectively). The grade of rejection for kidney and/or pancreas was mild in 9 (Rapamycin) and 27 (MMF). There were no episodes of moderate-to-severe acute rejection in the Rapamycin group versus four in the MMF treated group.

When clinically suspected first episodes of acute kidney rejection were included with biopsy-proven rejection episodes, there was a trend in favor of the Rapamycin arm at 12 months posttransplant ($p = 0.06$, with 5/84 vs. 13/86 patient events occurring in the Rapamycin and MMF arms during this time). However, there was no longer a significant difference in this outcome between the groups at 120 months ($p = 0.30$, Figure 2C, with a total of 20/84 and 27/86 patients treated for rejection in the two arms, respectively). When clinically suspected first episodes of acute pancreas rejection were included with biopsy-proven rejection episodes, there was a significant difference in favor of the Rapamycin arm at 12 months posttransplant ($p = 0.01$, with 6/84 vs. 18/86 patient events occurring in the Rapamycin and MMF arms during this time). This significant difference was still present in the Rapamycin arm at 120 months ($p = 0.007$; Figure 2D, with a total of 7/84 and 21/86 patients treated for rejection in the two arms, respectively). However, there were no significant differences in rates of kidney or pancreas rejection between the groups beyond 12 months posttransplant.

The patients in whom MMF was withheld experienced a higher rate of biopsy proven or clinically suspected acute rejection compared to those who did not have their MMF dosing interrupted ($p = 0.00002$ for kidney; $p = 0.02$ for pancreas). There was no difference in allograft outcome in those SPKT recipients who tolerated either MMF or Rapamycin without a period of withholding.

Kidney and pancreas transplant function

Mean serum creatinine increased by 0.3 mg/dL over the 10-year follow-up, with no significant difference between the groups (Figure 3A). There was also no significant difference at any time posttransplant between the two treatment arms in estimated glomerular filtration rate (using the abbreviated MDRD formula, data not shown). Similarly, there was no difference in urine protein/creatinine ratios between the groups over 120 months (1.33 Rapamycin (N = 27) vs. 1.80 MMF (N = 28), $p = 0.28$). There was also no difference between groups for proteinuria identified by urinalysis (Appendix Table A2). Furthermore, there was no difference in the percentage of patients receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blockade therapy (22% Rapamycin vs. 10% MMF, $p = 0.25$).

The level of fasting c-peptide was similar in both groups throughout follow-up (Figure 3B). Mean hemoglobin A1C was normal throughout follow-up in both arms; however, it was significantly lower in the MMF arm ($p = 0.00004$; Figure 3C). Five patients (Rapamycin) versus 3 (MMF, $p = 0.39$) developed type-2 diabetes with elevated HbA1C ($>6.1\%$) and persistent levels of normal or high c-peptide secretion. Three patients (MMF) developed type 1 diabetes recurrence (17).

Survival and allograft failures

There was no difference in patient survival between the two groups over 120 months (Table 2, Figure 4A). The majority of deaths were cardiovascular related (9/15-Rapamycin; 14/16-MMF). Similarly, there were no differences between the groups in death-censored or uncensored kidney or pancreas allograft survival (Table 2, Figure 4B–E). However, when allograft failure outcomes due to acute cellular rejection, humoral rejection, or chronic allograft injury were combined, Rapamycin was superior for kidney (6 allograft failures (Rapamycin) versus 16 allograft failures (MMF) ($p = 0.04$)), with a trend for pancreas (0 allograft failures (Rapamycin) versus 4 allograft failures (MMF) ($p = 0.06$)) survival.

Other clinical outcomes

There were no differences between groups for serious infections requiring hospitalization, including cytomegalovirus, polyoma and Epstein–Barr virus (Table 2). There were no lymphoproliferative disorders over the 10-year period (Table 2). The number of patients that had a wound infection requiring hospitalization during the first year posttransplant was similar in the two arms (5/84 for Rapamycin, and 5/86 patients for MMF); in addition, no patients required hospitalization (in either arm) for mouth ulcerations or lymphoceles. The number of patients who were reoperated for incisional hernia repair was similar in the two arms (12/84 for Rapamycin vs. 8/86 for MMF, $p = 0.31$), as was the number of patients who underwent enteric conversion (11/84 for Rapamycin vs. 10/86 for MMF, $p = 0.77$). Mean cholesterol and triglyceride levels were normal throughout follow-up in both arms, but were significantly higher in those patients on Rapamycin (Figures 5A and B). Levels of HDL and LDL cholesterol were not significantly different beyond 3 months posttransplant and were normal throughout the follow-up period. Furthermore, although there were higher percentages of patients taking lipid-lowering drugs during the first year in the Rapamycin

arm, at 96 months, there were no differences in the percentage of recipients taking lipid lowering drugs (45% Rapamycin vs. 50% MMF, $p = 0.76$).

Discussion

In this randomized, prospective, long-term, single center study of SPKT recipients, we demonstrated significantly reduced rates of biopsy-proven acute kidney and pancreas allograft rejection in patients on a tacrolimus-based regimen, assigned to Rapamycin compared to MMF. The differences were observed primarily during the first 12 months posttransplant and were driven by increased rates of rejection among MMF-treated patients in whom the drug was held for gastrointestinal and/or bone marrow toxicity. These results confirm our earlier observation with 42 patients (6) suggesting that the incidence of acute rejection would be limited mostly to those instances where the recipients' immunosuppression was significantly reduced. With longer term follow-up there were no differences in renal or pancreas transplant function, posttransplant diabetes mellitus, or proteinuria between the two groups. Similarly, there were no statistically significant differences in patient, kidney or pancreas transplant survival. This study demonstrates the safety and efficacy of *de novo* Rapamycin as an alternative to MMF for long-term maintenance immunosuppression in SPKT recipients on tacrolimus. Furthermore, the results suggest that Rapamycin may be preferred for SPKT recipients who are at high risk of MMF intolerance, for example, those with severe preexisting gastroparesis.

A previous retrospective study (10) suggested that the combination of tacrolimus and MMF was superior to tacrolimus and Rapamycin as maintenance immunosuppression in a steroid-free protocol for kidney transplant survival in SPKT recipients. Although not statistically significant, there appeared to be a higher rate of acute rejection at 72 months in the Rapamycin versus MMF group (10). Worse kidney transplant survival was also reported in a 3-year steroid-free prospective, randomized study of kidney transplant alone recipients from the same (8) and other groups (7,9). The kidney transplant population in these studies was not likely to have as high rates of gastroparesis as patients in our study. It is likely that the prevalence of gastroparesis in patients with type 1 diabetes in our study predisposed them to the higher incidence of gastrointestinal side effects which, in addition to leukopenia led to withholding of MMF more frequently than Rapamycin during the first 12 months posttransplant. Our results indicate that reduction or withholding of MMF contributed to the higher rate of acute rejection seen during the first 12 months in the MMF group, as inadequate MMF dosing has been associated with allograft loss due to acute rejection after kidney transplantation (18). With long-term follow-up, the higher rate of acute rejection in the MMF group has not adversely affected overall allograft or patient survival, in contrast to expectations (19). However, there is a suggestion that rejection-related allograft loss (i.e. acute rejection, humoral rejection, or chronic allograft injury) for kidney transplants favors Rapamycin over MMF with a similar trend for pancreas transplants. In those patients able to tolerate either agent without withholding, this advantage was lost.

Our study shows that Rapamycin targeted for relatively low levels compared to other studies (8,10) is associated with less rejection in tacrolimus-based SPKT when compared with MMF. These relatively low but effective levels may have provided other benefits. The

prolonged cold ischemia time (21 hours) for pancreas transplants and the racial/ethnic diversity in our c-peptide-defined type 1 diabetes patient population both contribute to a higher risk for acute rejection (10,20–22) for both groups in this study. Despite the concern that the lower rate of acute rejection seen in the Rapamycin arm would lead to complications related to over immunosuppression, there was a low incidence over 10 years of both viral infections (specifically BK/polyoma virus (22,23) and cytomegalovirus (21,23)) and lymphoproliferative disorders (24). Furthermore, the observed small rise in mean creatinine (0.3 mg/dL) over 10 years argues against the potential for synergistic nephrotoxicity from calcineurin inhibitors and Rapamycin (12,13,25). Finally, despite the association of Rapamycin with proteinuria in kidney transplant recipients (26), there was no difference favoring MMF. This is in contrast to reports associating Rapamycin with proteinuria, podocyte apoptosis and even focal segmental glomerulosclerosis after kidney transplantation (27).

Long-term patient survival following SPKT depends on allograft survival and prevention of cardiovascular events by controlling risk factors, such as insulin resistance and dyslipidemia. In our SPKT recipients, similar to our kidney transplant recipients (28), there was evidence of Rapamycin-related insulin resistance, i.e. higher levels of HbA1C, with similar c-peptide levels. Importantly, however, HbA1C levels were normal throughout. Rapamycin was also associated with higher levels of cholesterol and triglycerides than MMF; however, levels of HDL and LDL were equivalent in both arms after three months, and, importantly, all lipid levels were normal in both arms. Ultimately, our study demonstrates equivalence in patient survival for Rapamycin and MMF over 10 years, in contrast to a recent study involving kidney transplant alone recipients (29), in which a higher mortality rate was reported for patients receiving Rapamycin. Our study is limited by the relatively small numbers of patients that are from a single center where protocol biopsies were not performed. However, this is, to our knowledge, the only long-term, randomized, prospective study, comparing Rapamycin and MMF in tacrolimus-based SPKT.

The reduction in the rate of acute rejection following SPKT seen with Rapamycin (vs. MMF) along with the lower rates of rejection-related allograft loss for kidney, and trend for pancreas transplants, must be weighed against its potential negative metabolic consequences. Effective management of these risk factors, as evidenced by the normal HbA1C and lipid levels in this study, may translate to better cardiovascular protection which may require two decades to become apparent (30) with Rapamycin versus MMF in this tacrolimus-based SPKT population.

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Abbreviations

BPAR	biopsy-proven acute rejection
ESRD	end-stage renal disease
HbA1C	hemoglobin A1C
MMF	mycophenolate mofetil
SPKT	simultaneous pancreas kidney transplantation
T1DR	type 1 diabetes recurrence

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Appendix

Methods

Inclusion and exclusion criteria

Patient inclusionary criteria included recipient age 18–75 years; negative standard cross match for T cells; and women of childbearing potential agreeing to use an adequate method of contraception for the study duration.

Patient exclusionary criteria included previously received or receiving an organ transplant other than pancreas or kidney; an ABO incompatible donor kidney; current malignancy or a history of malignancy (within the past 5 years), except nonmetastatic basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been treated successfully; significant liver disease, defined as having during the past 28 days continuously elevated AST (SGOT) and/or ALT (SGPT) levels greater than three times the upper value of the normal range at this center; known hypersensitivity to thymoglobulin, daclizumab, tacrolimus, rapamycin, MMF, or corticosteroids; pregnant or lactating patients; screening/baseline (or within 96 h of transplant) total white blood cell count $<4000/\text{mm}^3$; platelet count $<100\,000/\text{mm}^3$; fasting triglycerides $>400\text{ mg/dL}$ ($>4.6\text{ mmol/L}$); fasting total cholesterol $>300\text{ mg/dL}$ ($>7.8\text{ mmol/L}$); fasting HDL-cholesterol $<30\text{ mg/dL}$; fasting LDL-cholesterol $>200\text{ mg/dL}$; and any form of substance abuse, psychiatric disorder or condition that, in the opinion of the investigator, may invalidate communication with the investigator.

Randomization codes

Randomization codes were kept in sealed, individual envelopes and were opened sequentially immediately prior to transplant, ensuring that the next treatment assignment was not known by the surgeon until the time of transplant.

Cytomegalovirus/pneumocystis carinii pneumonia prophylaxis

Prophylaxis for cytomegalovirus was with ganciclovir intravenously for 3 days, followed by daily valganciclovir orally for 3 months. In sero-positive donor to sero-negative recipients, treatment was for 6 months postoperatively. In patients treated with steroids or antilymphocyte therapy for an acute rejection episode, intravenous ganciclovir or valganciclovir was reinstituted. Single strength trimethoprim/sulfamethoxazole, 1 tablet orally (Monday, Wednesday, Friday) was given indefinitely for pneumocystis carinii pneumonia and nocardia prophylaxis.

Statistical analysis

Lastly, an analysis (using logrank tests) of first acute rejection rates based on actual treatment received was performed using a dichotomous time dependent covariate defined as whether the patient was receiving MMF (vs. Rapamycin) at follow-up time t (here, first acute rejections were compared according to which drug the patient was receiving immediately prior to the time of acute rejection, and any rejections and person-time of follow-up while patients were on neither drug were excluded from this analysis).

Results

Any withholding or discontinuation of rapamycin or mmf throughout the study period

Overall, during the 10-year study 62% (53/86) and 42% (35/84) of patients had MMF and Rapamycin withheld or discontinued due to any reason in the two arms ($p = 0.009$). Reasons for withholding/discontinuation included GI symptoms ($N = 27$ in MMF vs. $N = 2$ in Rapamycin, $p < 0.000001$), wound infection/fluid retention ($N = 0$ in MMF vs. $N = 10$ in Rapamycin, $p = 0.001$), other infection ($N = 2$ in MMF vs. $N = 9$ in Rapamycin, $p = 0.03$), leukopenia ($N = 10$ in MMF vs. $N = 4$ in Rapamycin, $p = 0.10$), insurance issue ($N = 6$ in MMF vs. $N = 1$ in Rapamycin), other ($N = 5$ in MMF vs. $N = 5$ in Rapamycin) and unknown ($N = 3$ in MMF vs. $N = 4$ in Rapamycin).

Among the 28 patients for whom Rapamycin was discontinued, 14, 3, 1 and 10 patients were switched to MMF, EC-MPS, AZA and no other immunosuppression, respectively. Among the 44 patients in whom MMF was discontinued, 27, 11 and 6 patients were switched to Rapamycin, EC-MPS and no other immunosuppression, respectively. The attempt to optimize immunosuppression (usually following a kidney or pancreas BPAR episode) was a common and equally likely reason for switching from Rapamycin to MMF (or EC-MPS) (9/84 in the Rapamycin arm) or from MMF to Rapamycin (9/86 in the MMF arm).

Timing of acute rejection

Among 30 patients who experienced a biopsy-proven acute rejection of the kidney, 10 (33%) occurred during the first year posttransplant (Appendix Tables A3 (panel A) and (panel B)). Among 10 patients who experienced a biopsy-proven acute rejection of the pancreas, 8 (80%) occurred during the first year posttransplant.

Therapy for acute rejection

Treatment for biopsy-proven rejection episodes included steroids, IVIG, switching to Rapamycin in the MMF group, and the use of antilymphocyte therapy in 6 (Rapamycin) and 19 patients (MMF) (Appendix Table A3 (panel B)). Intravenous immunoglobulin infusions and/or plasmapheresis and Rituximab (375 mg/m^2) were administered when there was evidence of antibody mediated rejection diagnosed by development of donor-specific antibodies in recipient sera and C4d staining on kidney transplant biopsy.

Impact of drug withholding on acute rejection rates over 10 years

For kidney transplants, 19/53 patients that had MMF withheld subsequently experienced a first acute rejection versus 8/86 patients who experienced acute rejection while receiving MMF. For pancreas transplants, 12/53 patients that had MMF withheld subsequently experienced a first acute rejection versus 9/86 patients who experienced acute rejection while receiving MMF. Such differences between patients in whom Rapamycin was withheld versus not withheld were not statistically significant ($p = 0.23$ for kidney; $p = 0.95$ for pancreas).

Analysis of freedom-from-acute rejection over 10 years while patients were maintained on the protocol

Freedom-from-clinically suspected or biopsy-proven acute rejection was not significantly different between the two treatment arms while patients were maintained on the protocol, i.e. did not have Rapamycin or MMF withheld ($p = 0.17$ for kidney, with 16/84 vs. 8/86 patients developing such acute rejection in the Rapamycin and MMF arms, respectively; $p = 0.25$ for pancreas, with 6/84 vs. 9/86 patients developing such acute rejection in the two arms, respectively). Freedom-from-biopsy-proven acute rejection was not significantly different between the two treatment arms while patients did not have Rapamycin or MMF withheld ($p = 0.81$ for kidney, with 6/84 vs. 4/86 patients developing such acute rejection in the Rapamycin and MMF arms, respectively; $p = 0.47$ for pancreas, with 1/84 vs. 2/86 patients developing such acute rejection in the two arms, respectively).

Analysis based on actual treatment received

Lastly, an analysis of first acute rejection rates based on actual treatment received (Rapamycin or MMF) yielded no meaningful differences (results not shown) beyond those already provided in the intent-to-treat analysis.

Causes of allograft failure

Causes of kidney allograft failure in the Rapamycin group were chronic allograft injury ($N = 6$), atherosclerosis ($N = 1$), complications following enteric conversion ($N = 1$), mycotic fungal aneurysm ($N = 1$) and noncompliance ($N = 1$). Causes of kidney allograft failure in the MMF group were chronic allograft injury ($N = 14$), acute rejection ($N = 1$), humoral rejection ($N = 1$) and noncompliance ($N = 2$). Causes of pancreas allograft failure in the Rapamycin group were thrombosis ($N = 2$), and in the MMF group acute rejection ($N = 1$), chronic allograft injury ($N = 3$), type 1 diabetes recurrence (T1DR) ($N = 1$) and noncompliance ($N = 2$). Noncompliance was documented and resulted in allograft loss due to rejection. Seven patients in the MMF group developed both kidney and pancreas allograft failure.

Table A1

Immunosuppressive drug dosing and trough whole blood concentrations (ng/mL)¹

		N	Rapamycin	N	MMF	p-Value
Mean drug dose $\pm$ SE						
Methylprednisolone (mg/kg) at	1 month	80	0.227 ± 0.014	85	0.230 ± 0.010	0.88
	3 months	75	0.123 ± 0.014	81	0.131 ± 0.012	0.63
	6 months	77	0.085 ± 0.009	79	0.087 ± 0.007	0.83
	12 months	73	0.063 ± 0.004	72	0.073 ± 0.006	0.19
	24 months	60	0.059 ± 0.003	62	0.064 ± 0.004	0.40
	36 months	53	0.061 ± 0.004	57	0.055 ± 0.002	0.16
	48 months	45	0.059 ± 0.003	49	0.058 ± 0.005	0.93
	60 months	37	0.066 ± 0.010	43	0.054 ± 0.003	0.26
	72 months	28	0.063 ± 0.006	30	0.057 ± 0.004	0.39

		N	Rapamycin	N	MMF	p-Value
Tacrolimus (mg/kg) at	84 months	21	0.053 ± 0.003	22	0.056 ± 0.005	0.66
	96 months	17	0.054 ± 0.005	19	0.048 ± 0.003	0.29
	1 month	82	0.118 ± 0.008	84	0.120 ± 0.008	0.80
	3 months	81	0.104 ± 0.008	83	0.108 ± 0.009	0.71
	6 months	79	0.097 ± 0.006	82	0.095 ± 0.007	0.81
	12 months	75	0.088 ± 0.006	79	0.086 ± 0.007	0.89
	24 months	66	0.073 ± 0.005	67	0.075 ± 0.006	0.86
	36 months	57	0.068 ± 0.006	62	0.073 ± 0.007	0.53
	48 months	50	0.061 ± 0.005	54	0.068 ± 0.005	0.38
	60 months	36	0.055 ± 0.005	41	0.057 ± 0.008	0.87
MMF (mg) at	72 months	28	0.049 ± 0.006	26	0.051 ± 0.005	0.78
	84 months	22	0.047 ± 0.007	21	0.050 ± 0.006	0.76
	96 months	17	0.048 ± 0.007	18	0.050 ± 0.007	0.86
	1 month			73	1528 ± 61	
	3 months			57	1307 ± 66	
	6 months			55	1073 ± 62	
	12 months			50	1035 ± 57	
	24 months			42	1055 ± 57	
	36 months			38	993 ± 61	
	48 months			34	926 ± 70	
Rapamycin (mg/kg) at	60 months			28	946 ± 70	
	72 months			20	838 ± 73	
	84 months			14	821 ± 100	
	96 months			12	792 ± 96	
	1 month	72	0.073 ± 0.004			
	3 months	67	0.061 ± 0.004			
	6 months	65	0.061 ± 0.004			
	12 months	61	0.056 ± 0.004			
	24 months	53	0.048 ± 0.004			
	36 months	44	0.046 ± 0.005			
Mean drug level ± SE	48 months	38	0.046 ± 0.005			
	60 months	29	0.042 ± 0.007			
	72 months	19	0.031 ± 0.004			
	84 months	15	0.030 ± 0.004			
	96 months	10	0.029 ± 0.006			
	1 month	83	7.61 ± 0.34	85	7.44 ± 0.27	0.70
	3 months	79	7.28 ± 0.31	82	7.82 ± 0.27	0.19
	6 months	78	6.87 ± 0.24	79	6.69 ± 0.29	0.62
	12 months	72	6.68 ± 0.26	77	6.77 ± 0.26	0.79
	24 months	63	6.42 ± 0.35	67	6.58 ± 0.25	0.71
Tacrolimus levels (ng/mL)	36 months	51	6.04 ± 0.35	57	5.99 ± 0.24	0.91

		N	Rapamycin	N	MMF	p-Value
Rapamycin levels (ng/mL)	48 months	46	5.72 ± 0.30	49	5.46 ± 0.35	0.58
	60 months	34	5.87 ± 0.35	40	5.80 ± 0.27	0.87
	72 months	26	5.30 ± 0.39	26	6.02 ± 0.41	0.21
	84 months	21	5.74 ± 0.43	20	6.25 ± 0.47	0.43
	96 months	15	5.73 ± 0.52	17	5.63 ± 0.31	0.86
	1 month	73	7.54 ± 0.66			
	3 months	61	7.03 ± 0.38			
	6 months	62	6.35 ± 0.36			
	12 months	55	7.07 ± 0.39			
	24 months	49	7.35 ± 0.62			
	36 months	38	6.88 ± 0.47			
	48 months	31	6.93 ± 0.71			
	60 months	19	6.96 ± 0.68			
	72 months	17	7.56 ± 1.03			
	84 months	16	5.51 ± 0.61			
	96 months	10	6.12 ± 1.01			

¹ Drug doses were measured as long as the patient had at least 1 functioning graft (kidney or pancreas).

Table A2

Distributions of urine protein values¹

Month	Urine protein value ²	Rapa	MMF	p-Value ³
1	Negative	(48/73)	(41/74)	
	Trace	82.2% (12/73)	73.0% (13/74)	0.18
	1+	(13/73)	(9/74)	
	2+	(0/73)	(9/74)	
	3+	(0/73)	(2/74)	
6	Negative	(31/37)	(31/46)	
	Trace	89.2% (2/37)	78.3% (5/46)	0.19
	1+	(3/37)	(7/46)	
	2+	(1/37)	(3/46)	
	3+	(0/37)	(0/46)	
12	Negative	(27/38)	(25/37)	
	Trace	94.7% (9/38)	86.5% (7/37)	0.22
	1+	(1/38)	(2/37)	
	2+	(1/38)	(2/37)	
	3+	(0/38)	(1/37)	
24	Negative	(27/35)	(28/32)	
	Trace	94.3% (6/35)	87.5% (0/32)	0.33
	1+	(2/35)	(2/32)	
	2+	(0/35)	(2/32)	
	3+	(0/35)	(0/32)	
36	Negative	(32/36)	(28/34)	
	Trace	94.4% (2/36)	91.2% (3/34)	0.60
	1+	(2/36)	(2/34)	

Month	Urine protein value ²	Rapa	MMF	p-Value ³
48	2+	(0/36)	(0/34)	0.95
	3+	(0/36)	(1/34)	
	Negative	(23/31)	(24/30)	
	Trace	80.7% (2/31)	80.0% (0/30)	
	1+	(3/31)	(1/30)	
60	2+	(3/31)	(3/30)	0.68
	3+	(0/31)	(2/30)	
	Negative	(17/23)	(19/29)	
	Trace	78.3% (1/23)	82.8% (5/29)	
	1+	(3/23)	(2/29)	
72	2+	(2/23)	(3/29)	0.35
	Negative	(15/18)	(13/16)	
	Trace	83.3% (0/18)	93.8% (2/16)	
	1+	(2/18)	(0/16)	
	2+	(0/18)	(1/16)	
84	3+	(1/18)	(0/16)	0.36
	Negative	(10/13)	(8/11)	
	Trace	76.9% (0/13)	90.9% (2/11)	
	1+	(3/13)	(0/11)	
	2+	(0/13)	(1/11)	
96	Negative	(6/8)	(7/9)	0.45
	Trace	75.0% (0/8)	88.9% (1/9)	
	1+	(2/8)	(0/9)	
	2+	(0/8)	(1/9)	

¹ This variable was measured as long as the patient had a functioning kidney graft.

² The qualitative urine protein values “Negative”, “Trace”, “1+”, “2+” and “3+” are approximately equivalent to the following quantitative values: 0, 15, 30, 100 and 500 mg/dL, respectively. The percentages shown are those for the negative and trace categories combined.

³ The p-values listed in this column represent the results of comparing the observed percentage of patients having either a negative or trace value for urine protein at each month, using the Pearson (uncorrected) chi-squared test.

Table A3

(Panel A) Distributions of first acute rejection episodes by group, organ, time of episode, maximum therapy given and grade (suspected or biopsy proven). (Panel B) Distributions of first biopsy-proven acute rejection episodes by group, organ, time of episode, maximum therapy given and grade

	Rapamycin (N = 84)		MMF (N = 86)	
	Kidney	Pancreas	Kidney	Pancreas
Panel A				
Acute rejection N (%)				
During months 0–3	4	4	8	5
During months 4–6	0	2	5	8

	Rapamycin (N = 84)		MMF (N = 86)	
	Kidney	Pancreas	Kidney	Pancreas
During months 7–12	1	0	0	5
During months 13–36	6	1	7	2
Beyond month 36	9	0	7	1
Total # of patients with acute rejection	20	7	27	21
Maximum therapy for rejection				
Steroids	8	4	9	16
Steroids+IVIG	0	1	1	0
Addition of rapamycin	0	0	2	3
Antilymphocyte therapy	12	2	15	2
Grade of rejection				
Suspected or borderline ¹	13	6	7	13
Mild (kidney I/IIA, pancreas III)	7	1	18	6
Moderate/severe (kidney IIB/III, pancreas IV)	0	0	2	2
Panel B				
Acute rejection N (%)				
During months 0–3	0	1	4	1
During months 4–6	0	0	6	4
During months 7–12	0	0	0	2
During months 13–36	5	0	5	1
Beyond month 36	3	0	7	1
Total # of patients with acute rejection ²	8	1	22	9
Maximum therapy for rejection				
Steroids	2	1	5	4
Addition of rapamycin	0	0	1	2
Antilymphocyte therapy	6	0	16	3
Biopsy-proven rejection				
Mild (kidney I/IIA, pancreas III)	8	1	20	7
Moderate/severe (kidney IIB/III, pancreas IV)	0	0	2	2

¹ Only those clinically suspected or borderline acute rejections in which empiric treatment was given were included here. Note that one patient (MMF) with a borderline kidney rejection was actually diagnosed in the pathology report as having “Borderline AMR, C4d+”.

² The first biopsy-proven acute rejection episode of the kidney for one patient (Rapamycin) and two patients (MMF) occurred following a first, clinically suspected acute rejection episode. The first biopsy-proven acute rejection episode of the pancreas occurred in one patient (MMF) following a first, clinically suspected acute rejection episode.

Figure 1.
Protocol.

Figure 2.

SPKT recipients treated with Rapamycin versus MMF: (A) % biopsy-proven acute rejection free in kidney transplants; (B) % biopsy-proven acute rejection free in pancreas transplants; (C) % clinically suspected or biopsy-proven rejection free in kidney transplants; (D) % clinically suspected or biopsy-proven rejection free in pancreas transplants.

Figure 3. SPKT recipients treated with Rapamycin versus MMF: mean levels of (A) serum creatinine, (B) c-peptide and (C) HbA1C in those groups.

Figure 4.

SPKT recipients treated with Rapamycin versus MMF: (A) % patient survival; (B) % kidney death-censored graft survival; (C) % kidney death-uncensored graft survival; (D) % pancreas death-censored graft survival and (E) % pancreas death-uncensored graft survival.

Figure 5. SPKT recipients treated with Rapamycin versus MMF: mean levels of (A) cholesterol, (B) triglycerides.

Table 1

Pretransplant and early outcome variables

	Rapamycin (N = 84)	MMF (N = 86)
A. Baseline variables ¹		
Age (in years) mean $\pm$ SD	41.5 $\pm$ 8.2	43.4 $\pm$ 9.5
Median (range)	40 (26–61)	43 (22–60)
Race/ethnicity (%)		
Caucasian	47 (56%)	55 (64%)
Hispanic	31 (37%)	19 (22%)
African American	6 (7%)	11 (13%)
Other	0 (0%)	1 (1%)
Gender		
Males	50 (60%)	55 (64%)
Females	34 (40%)	31 (36%)
Panel reactive antibodies <5%	78/81 (96%)	77/82 (94%)
Donor age (in years)	24.5 $\pm$ 10.3	22.7 $\pm$ 10.9
Median (range)	23 (1–50)	20 (1–51)
Kidney: cold ischemia time in hours	N = 84 20.9 $\pm$ 5.1	N = 85 21.4 $\pm$ 5.2
Median (range)	21 (10–31)	21 (6–31)
Pancreas: cold ischemia time in hours	N = 42 20.6 $\pm$ 3.5	N = 44 21.4 $\pm$ 4.8
Median (range)	21 (11–27)	22 (9–32)
Kidney: warm ischemia time in minutes	N = 58 66.9 $\pm$ 22.1	N = 57 66.7 $\pm$ 16.9
Pancreas: warm ischemia time in minutes	N = 48 48.5 $\pm$ 18.3	N = 47 53.0 $\pm$ 42.5
Total # of HLA mismatches	4.63 $\pm$ 1.00	4.47 $\pm$ 1.10
Pretransplant weight (kg)	71.9 $\pm$ 16.4	71.5 $\pm$ 13.6
Pretransplant body mass index	26.0 $\pm$ 5.1	25.6 $\pm$ 4.5
Clinical symptoms		
Retinopathy	79 (94%)	74 (86%)
Peripheral neuropathy	64/82 (78%)	62/84 (74%)
Gastroparesis	49/81 (60%)	44/82 (54%)
Postural hypotension	35/80 (44%)	32/80 (40%)
Age at diagnosis of type 1 diabetes (years)	14.0 $\pm$ 7.8	15.0 $\pm$ 9.2
Pre-Tx duration of type 1 diabetes (years)	27.6 $\pm$ 7.8	28.4 $\pm$ 8.8
Pre-Tx history of coronary artery disease	22 (26%)	20 (23%)
B. Pre-Tx CMV antibody status		
Donor –/Recipient –	14 (17%)	16 (19%)
Donor –/recipient +	21 (25%)	13 (15%)
Donor +/recipient –	26 (31%)	29 (34%)
Donor +/recipient +	23 (27%)	28 (33%)
C. Early outcome variables		
Slow graft function	2 (2%)	2 (2%)
Delayed graft function	0 (0%)	0 (0%)

	Rapamycin (N = 84)	MMF (N = 86)
Nonfunctioning graft	0 (0%)	0 (0%)

¹ All comparisons of means and percentages of the baseline and early outcome variables between the two treatment arms were nonsignificant, with the exception of the percentage of Hispanics in the two arms ($p = 0.03$).

Table 2Outcomes for SPKT recipients at 10 years posttransplant^I

Outcome	Rapamycin (N = 84)	MMF (N = 86)	Log-rank test p-value
Patient survival	67%	73%	0.99
Kidney graft survival			
Death censored	74%	70%	0.16
Death uncensored	51%	58%	0.75
Pancreas graft survival			
Death censored	98%	84%	0.12
Death uncensored	65%	64%	0.77
Type 1 diabetes recurrence	0	3	0.09
Type 2 diabetes	5	3	0.39
Posttransplant	0	0	1.00
lymphoproliferative			
disorder			
Viral infections			
Cytomegalovirus	2	1	0.55
Epstein–Barr virus	1	0	0.30
BK (polyoma)	1	1	0.96

^I Actuarial freedom-from-the event at 120 months posttransplant is included for patient and graft survival; number of patients with the event is included for all other calculations.