Conversion From Twice-Daily to Once-Daily Tacrolimus in Simultaneous Pancreas-Kidney Transplant Patients

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ABSTRACT

Background. Data on the effectiveness of once-daily tacrolimus (Tac-QD) in simultaneous pancreas-kidney (SPK) transplant patients are limited, which is of particular concern because diabetic gastroparesis may affect absorption. The aim of this study was to evaluate the clinical impact of converting SPK patients from twice-daily (Tac-BD) to Tac-QD.

Methods. From November 2008 to August 2011, 27 SPK recipients (out of 130) were converted from Tac-BD to Tac-QD. Demographics, prescribed doses, trough levels, and creatinine, glucose, and Hb_{A1c} values were collected prospectively at the time of conversion and at 1, 2, 3, 6, and 12 months after conversion.

Results. The mean time from transplantation to conversion was 35.81 ± 27.31 months, with 20 patients (74.07%) converted to Tac-QD >12 months after transplantation. There were no significant differences in the tacrolimus dose and trough levels before and after conversion and at all points during the follow-up. Creatinine, glucos,e and Hb_{A1c} levels remained stable throughout. Eight patients (29.63%) with gastroparesis had clinical outcomes, drug doses, and trough levels similar to all other patients.

Conclusions. Stable SPK recipients can safely be converted from Tac-BD to Tac-QD, with no clinical impact on the transplant function. Gastroparesis does not appear to influence tacrolimus dose requirements or trough levels.

TACROLIMUS in its twice-daily formulation (Tac-BD; Prograf), along with mycophenolate mofetil (MMF), has been the mainstay of immunosuppression for solid organ transplantation for more than a decade [1]. A once-daily oral preparation of tacrolimus (Tac-QD; Advagraf) has been introduced in clinical practice in recent years, and published reports suggest that it is as safe and effective as Tac-BD for renal as well as liver transplant recipients [2–4]. However, there is a paucity of data for simultaneous pancreas-kidney (SPK) transplant recipients, with only 1 small study suggesting that Tac-QD could be used in this patient group [5]. The perceived benefits of Tac-QD are a reduction in pill burden, which may translate into better patient compliance [6], thus minimizing the risk of graft dysfunction. There have been concerns, however, that converting stable patients on an mg:mg basis, as recommended in the manufacturer's guidance, may lead to reduced tacrolimus exposure, placing SPK transplant patients at risk of inadequate immunosuppression [7]. Patients who undergo SPK transplantation have a higher incidence of gastroparesis and gut motility dysfunction secondary to diabetic autonomic neuropathy. This may be particularly relevant with Tac-QD, which is absorbed more distally in the gut than the Tac-BD preparation. The diabetogenic effects of immunosuppressive drugs are also important, particularly in pancreatic transplantation, and the influence of Tac-BD on insulin production and diabetes are well recognized [8]. The effect of Tac-QD, however, is less well described.

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The aim of the present study was to evaluate the clinical impact of converting stable SPK transplant patients from Tac-BD to Tac-QD and the effect this had on their glucose homeostasis and outcome.

PATIENTS AND METHODS

Twenty-seven SPK recipients, out of the 130 transplantations performed from 2002 to 2010, were converted from Tac-BD to Tac-QD from November 2008 to August 2011 and followed for ≥1 year after conversion. Conversion was at physician's latitude or if requested by the patients. Ethical approval for this study was obtained from the local Research Ethics Committee. Data on tacrolimus dose, tacrolimus trough level (C_0), creatinine, serum glucose and Hb_{A1c}, episodes of biopsy-proven acute rejection before and after conversion to Tac-QD, and patient and graft survivals were collected prospectively as part of routine clinical care and analyzed retrospectively. For the purpose of this study, these data were recorded just before conversion and then at 1, 2, 3, 6, and 12 months after conversion to Tac-QD. Tacrolimus C_0 was measured with the use of a tandem mass spectrometry method. Data are expressed as mean ± SD unless otherwise stated and analyzed with the use of IBM SPSS version 19.

Transplant Technique and Immunosuppression

Pancreatic transplantation was performed via a right paramedian incision with intraperitoneal implantation, with the use of a donor iliac Y-graft to the splenic and superior mesenteric arteries and anastomosis to the recipient's common iliac artery. Venous outflow was achieved by systemic drainage into the inferior vena cava and exocrine drainage was achieved via a side-to-side loop enteroduodenostomy. The renal grafts were placed extraperitoneally in the left iliac fossa with the renal artery and vein anastomosed to the iliac artery and vein, respectively. The ureter was anastomosed to the bladder with the use of a 2-layer technique over a double J stent.

Standard immunosuppression consisted of induction with 20 mg basiliximab (days 0 and 4), 0.1 mg/kg/d Tac-BD (Prograf), 1 g MMF (Cellcept) twice daily, and 20 mg prednisolone once daily, tapered to 5 mg at 3 months. The target range for tacrolimus trough level was 10–14 μg/L in the 1st month after transplantation and 8–12 μg/L from 2–8 months. Thereafter, the maintenance target trough range was 5–10 μg/L.

RESULTS

Twenty-seven SPK recipients (14 male and 13 female) were converted from Tac-BD to Tac-QD. The demographic data are presented in Table 1. The mean time from transplantation to conversion was 35.81 ± 27.31 months (range, 0–101 mo), and the mean follow-up time after conversion was 27.70 ± 8.31 months (range, 16–49 mo). Twenty patients (74.07%) were converted >12 months after transplantation, and 7 patients were converted in the early post-transplantation follow-up (3 patients [11.11%] in the 1st 3 months, 2 patients [7.41%] in 4–6 months, and 2 patients [7.41%] in 7–12 months). One patient experienced delayed pancreatic graft function, and all of the remaining patients had immediate pancreatic graft function. All patients were insulin independent at the time of discharge from hospital from the index admission.

Table 1. Patient Demographics

Age, y, mean ± SD (range)	44.07 ± 9.02 (25–61)
Sex	
Female	13
Male	14
BMI, kg/m^2, mean ± SD (range)	24.31 ± 3.73 (18.51–30.83)
Renal replacement therapy	
Preemptive Transplant	8
Hemodialysis	7
Peritoneal dialysis	12
Gastroparesis	
Yes	8
No	19
Cold ischemia time, h:min, mean ± SD (range)	
Kidney	14:06 ± 02:31 (07:06–17:53)
Pancreas	12:37 ± 01:56 (10:14–16:51)
Rejection episodes	
Before conversion	4
After conversion	2
Time to conversion, mo, mean ± SD (range)	35.81 ± 27.31 (0–101)
Converted back to Prograf	8
Days until converted back, mean ± SD (range)	192.50 ± 231.173 (29–742)
Donor age, y, mean ± SD (range)	35.92 ± 13.66 (9–54)
HLA mismatch A/B/DR, mean	1.08/1.5/1.42
Donor sex	
Male	11
Female	15
Donor cause of death	
Intracranial hemorrhage	13
Head trauma	11
Meningitis	1
Hypoxic brain injury	1
Unknown	1
Delayed graft function, n (%)	
Kidney	10 (37.04%)
Pancreas	1 (3.70%)

Ten patients experienced delayed renal graft function after SPK transplantation.

Eight patients (29.63%) had documented gastroparesis, based on clinical symptoms and preoperative investigations.

Eleven patients (40.74%) were converted on an mg:mg basis, and 11 patients were converted within ±1 mg of their preceding Tac-BD dose. Four patients (14.82%) had their dose changed by >1 mg when converted to Tac-QD. Ten patients (37.0%) had no dose adjustments in the 12 months after conversion. Three patients (11.11%) had >3 dose changes in the 1st 12 months after conversion. Patients converted early to Tac-QD required more dose changes than those who were converted late (2.29 ± 2.36 vs 0.95 ± 1.10), although this was not statistically significant ($P = .054$; 1-way analysis of variance [ANOVA]).

A total of 8 patients (29.63%) were converted back to Tac-BD at a mean time of 192.50 ± 231.17 days after the initial conversion to Tac-QD. The reasons for conversion