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Short Communication

LCPT in tacrolimus fast-metabolizing pancreas recipients compared to high-dose prolonged release tacrolimus versus non-fast metabolizers: a single-center experience

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Abstract

We compared conversion to LCPT vs high-dose prolonged release (PR) tacrolimus (Tac) in Tac fast- versus non-fast-metabolizing patients. A total of 45 pancreatic graft recipients (43 combined kidney-pancreas, two pancreas transplants alone) were retrospectively analyzed. Immunosuppression consisted of a lymphocyte-depleting agent, Tac + MMF + steroids. In response to subtherapeutic Tac levels despite incremental increase in PR-Tac dosage, 15 patients were converted to LCPT (median day 10.9; range day 5-21), after being identified as Tac fast metabolizers (Group 1) from the ratio of concentration/dosage (c/d) <1.05 (median: 0.69; range 0.3 – 0.9). Another 15 patients with a median c/d ratio of 0.22 (range 0.4 – 0.9) were given high-dosed IR-/PR-Tac (Group 2). Group 3 consisted of 15 non-fast-metabolizing patients (median c/d ratio 1.75; range 1.2 – 3.8). At 17.2 months, all study patients are alive. In Group 1, no pancreatic or renal graft was lost. In Group 2, two pancreata were lost to thrombosis, in Group 3 one pancreas was lost to necrotizing pancreatitis and one to thrombosis, one kidney because of primary non-function. All patients with a pancreas graft in situ are insulin-free. Complications were comparable between all groups. LCPT is a promising alternative for Tac fast metabolizers in pancreatic transplantation.

Keywords: Pancreas transplantation; LCPT; tacrolimus; fast metabolizer

Abbreviations: c/d: concentration/dosage; CMV: cytomegalovirus; CT: computed tomography; CYP: cytochrome P; DSA: donor-specific antibody; HLA: human leukocyte antigen; IR: immediate release; MMF: mycophenolate mofetil; PR: prolonged release; PRA: panel-reactive antibodies; PTA: pancreas transplantation alone; SPK: simultaneous pancreas-kidney transplantation; Tac: tacrolimus

Introduction

Pancreatic transplantation is an effective therapy for type 1 diabetes and kidney failure. A stable therapeutic trough level of tacrolimus (Tac) is a key factor for graft survival in these patients. Previous studies identified a subgroup of patients, in whom a therapeutic Tac level range cannot be achieved despite a dose increase in Tac immediate-release (IR) or prolonged-release (PR) formulations. These Tac „fast metabolizers" are characterized by a Tac concentration/dose (c/d) ratio <1.05, based on a genetic variation of cytochrome P (CYP) 450 3A5 [1-5]. The CYP 3A5*1 allele is associated with rapid Tac metabolism, whereby the inferior susceptibility of LPCT to the CYP 3A5 genotype probably results from LCPT absorption in the more distal gastrointestinal tract, where CYP 3A5 activity is decreased [4,5]. A randomized multicenter study and several published clinical trials suggest LCPT as a feasible immunosuppressant in kidney, liver and pancreas transplantation since it features 30% increased bioavailability [1-11].

In contrast to published trials assessing LCPT in larger cohorts of kidney and liver transplant patients, only small populations in pancreatic transplantation have been previously reported (2-4, 6-10). Promising results have been achieved after conversion from

PR-Tac to LCPT for tremor or lesser bioavailability. Kerstenetzky et al. postulated the need for further studies on LCPT in pancreatic recipients [10]. In our retrospective center analysis, we investigated pancreas graft recipients after conversion from PR-Tac to LCPT for subtherapeutic Tac levels despite a dose increase in oral PR Tac. Patient, pancreas and renal graft survival and postoperative complications were assessed. This cohort was compared to Tac fast metabolizers, who were given high-dose IR/ or PR-Tac and a control group of normal metabolizers.

Materials and Methods

Table 1.

Demographic data		Group 1 n=15	Group 2 n=15	Group 3 n=15
Recipient	Male / female	11/4	8/7	8/7
Diabetes mellitus type 1	15	15	15	15
Transplantation	1st transplantation	SPK 12 / PTA 1	SPK 8 / PTA 1	SPK 12
	2nd transplantation	SPK 2 (simultaneous) (explantation of 1st kidney each)	SPK 4 (simultaneous explantation of each 3 previous 1st renal grafts and one previous 1st pancreas graft)	SPK 3 (simultaneous explantation of each 2 previous 1st renal and pancreas grafts)
	3rd transplantation		SPK 1 (simultaneous explantation of previous 2nd renal graft; all other grafts already being explanted earlier)	
	Combined 2nd kidney + 4th pancreas transplantation		SPK 1 (simultaneous explantation of previous 1st kidney and 3rd pancreas graft)	
Age in years median (range)		48.5 (25-64)	46.9 (30-64)	44.3 (30-69)
PRA	Negative	14	12	15
PRA	Positive	1 (26%; 1st SPK)	3 2% / 38% / 50% (2nd SPK each)	0
HLA MM locus A median (range)		1.3 (0-2)	1.3 (1-2)	1.5 (1-2)
HLA MM locus B median (range)		1.8 (1-2)	1.7 (1-2)	1.6 (0-2)
HLA MM locus DR median (range)		1.7 (1-2)	1.4 (0-2)	1.6 (0-2)
Cold ischemia time in hours: minutes median (range)	Pancreas	10:32 (05:24 - 16:41)	11:06 (06:44 - 16:22)	09:52 (06:55 -13:54)
	Kidney	12:06 (07:35 - 20:49)	12:48 (04:40 - 18:56)	12:48 (07:38 - 16:08)
Immunosuppression	Thymoglobuline / ATG	14 / 1	12/3	11/4
	MMF	15	15	15
	Steroids	15	15	15
Donor data	Male / female	10/5	9/6	5/10
	Age in years median (range)	29.4 (10-46)	30.7 (16-49)	28.1 (5-45)

Abbreviations: ATG, antithymocyte globulin; HLA MM, HLA mismatch; MMF, mycophenolate mofetil; PRA, panel reactive antibodies; PTA, pancreas transplantation alone; SPK, simultaneous pancreas kidney transplantation.

Between February 2016 and March 2019, 45 type 1 diabetic patients (43 simultaneous pancreas-kidney transplantations (SPK), two pancreas transplantations alone (PTA)) underwent pancreatic transplantation at our center. Details on transplantation and demographic data are depicted in Table 1. The surgical procedures were performed according to standard techniques (renal anastomosis: left iliacal vessels; pancreatic anastomosis: right A. iliaca com./V. cava inferior; exocrine drainage: pancreatoduodenojejunostomy). For pancreas retransplantation, previous grafts were resected for technical reasons (Table 1).

Immunosuppression consisted of a lymphocyte-depleting agent, PR-Tac (in 15 / 14 / 14 patients in Groups 1 / 2 / 3, respectively) or immediate-release (IR)-Tac (1 patient each in Groups 2 and 3 for logistic reasons), MMF, steroids (Table 1). The targeted Tac level (ng/mL) was 12-14 during the first month and

4-6 after one year. The initial dose of oral PR-Tac was 0.07 mg/kg and was gradually increased in order to achieve the targeted Tac trough level. In response to subtherapeutic Tac levels despite an incremental increase in PR-Tac dosage, 15 patients were converted to LCPT (median day 10.9; range day 5-21). They were identified as Tac fast metabolizers (Group 1) from a c/d ratio <1.05 (median: 0.69; range 0.3 – 0.9). Another 15 fast metabolizers (median c/d ratio 0.22; range 0.4 – 0.9) received a high dose of PR-Tac (Group 2). Group 3 consisted of 15 Tac non-fast-metabolizing patients (median c/d ratio 1.75; range 1.2 - 3.8). Details are depicted in Table 2.

Table 2.

	Group 1 n=15	Group 2 n=15	Group 3 n=15
Tacrolimus			
c/d ratio median (range)	0.69 (0.3 - 0.9)	0.22 (0.4 - 0.9)	1.75 (1.2 - 3.8)
Tac level ng/mL median (range) at day of conversion to LCPT	7.4 (4.1-10.1)		
Day of conversion to LCPT median (range)	10.9 (5-21)		
Dosage mg of IR-/PR-Tac median (range)	16.3 (8-24) prior to conversion to LCPT	15.3 (8-26) prior to 1st day	9.3 (3-14) prior to 1st day
Dosage mg/kg of IR-/PR-Tac median (range)	0.22 (0.11 - 0.32)	0.20 (0.11 - 0.35)	0.12 (0.04 - 0.10)
Initial dosage of LCPT mg/ kg median (range)	0.23 mg/kg (0.13 - 0.35)		
Day of 1st therapeutic Tac level ng/ mL median (range)	2.3 (1 - 6) after conversion to LCPT	11.6 (6 - 21) post transplant	5.7 (2 - 9) post transplant
Month 12 Tac level ng/mL median (range)	7.9 (5.7 – 11.5)	7.1 (5.6 – 8.8)	7.8 (5.1 – 12.4)
Month 12 Tac dosage mg median (range)	LCPT: 5.8 (2.0 - 16.0)	4.7 (2.0 - 7.0)	3.5 (2.0 - 5.0)
Month 12 Tac dosage mg/kg median (range)	0.08 (0.03 - 0.21)	0.06 (0.03 -0.09)	0.05 (0.03 - 0.07)
Month 24 Tac level ng/mL median (range)	6.7 (5.3 – 7.9)	6.4 (3.8 – 8.1)	5.9 (2.7 – 8.3)
Month 24 Tac dosage mg median (range)	LCPT: 2.4 (2.0 - 2.75)	2.6 (1.0 - 7.0)	2.5 (1.5 - 3.0)
Month 24 Tac dosage mg/kg median (range)	0.03 (0.03 - 0.04)	0.03 (0.01 - 0.09)	0.03 (0.02 - 0.04)

Abbreviations: c/d, concentration/dosage; IR, immediate release; PR, prolonged release; Tac, tacrolimus.

CYP 3A5 genotyping was not performed for logistic reasons. The standard antimicrobial prophylaxis consisted of piperacillin-tazobactam or ciprofloxacin, anidulafungin, and CMV prophylaxis consisted of gancyclovir / valgancyclovir.

All groups were comparable regarding postoperative regulation of digestion. All patients were heparinized and later converted to oral anticoagulation, depending on the individual risk for bleeding, coronary heart disease or peripheral vasculopathy. Postoperative graft monitoring included assessment of serum creatinine, urea, blood glucose, HbA1c, C-peptide, amylase, lipase, ultrasound and CT imaging for cases with inconclusive ultrasound findings regarding pancreatic perfusion. Delayed pancreatic graft function was defined as the need for exogenous insulin in blood glucose >180 mg/dL until day 14 and >250 mg/dL thereafter. Delayed renal graft function was defined as the requirement for ≥2 dialysis posttransplant. All renal rejections were diagnosed clinically (apart from one biopsy-proven case) and were determined from a decrease in urine output / increase in serum creatinine / deteriorated sonographic graft perfusion. All pancreatic rejections were diagnosed clinically and were determined from an increase in serum amylase, lipase / hyperglycaemia. Subtherapeutic Tac levels mostly preceded rejection. No biopsies of pancreatic grafts were performed because the risk for bleeding and pancreatic fistula was considered to be significant.

Long-term pancreas function was calculated according to the Igls Score [12]. Anti-HLA DSA testing (ELISA or Luminex) was performed according to the availability of the test at the center performing the follow-up visits.

Steroid withdrawal was performed individually depending on side-effects, stability of Tac level, incidence of infections and rejections.

Statistical methods

A descriptive analysis was performed for data assessment since the assessment was done in a relatively small study population.

Results and Discussion

At an observation time of median 17.6 (range 6 - 24) months all study patients are alive. In Group 1 no pancreatic or renal graft was lost. Patients with subtherapeutic Tac levels despite a gradual increase in PR dosage were switched to LCPT at day 10.9 (median). Consequently, the Tac level reached the target on day 2.3 (median) after switching (Figures 1a, 1b; Table 2): the dosage of PR-Tac at conversion was 0.22 mg/kg (median) and converted to LCPT at a starting dosage of 0.23 mg/kg (median). A total of four pancreatic and one clinically suspected renal rejections were reversed with steroids and an increase in Tac level. In three cases, pancreatic rejection occurred as a result of a low Tac level (median 8.7 ng/mL) and prior to conversion to LCPT. Median creatinine between months 1 and 24 was normal, all patients were insulin-free and classified as „optimal" function according to the Igls Score (Figures 2a, 2b). Analysis of DSA against HLA Class I (ELISA) was negative in 11 patients and not performed in four for logistic reasons. One re-SPK patient reconverted herself from LCPT to IR-Tac at month 2 for recurring diarrhea. Reconversion did not bring an improvement, and a psychosomatic disorder was eventually diagnosed and considered to contribute to the somatic disturbances. Concerning concomitant immunosuppression at month 12, 12 patients were on MMF, three were converted to azathioprine for diarrhea and one was steroid-free.

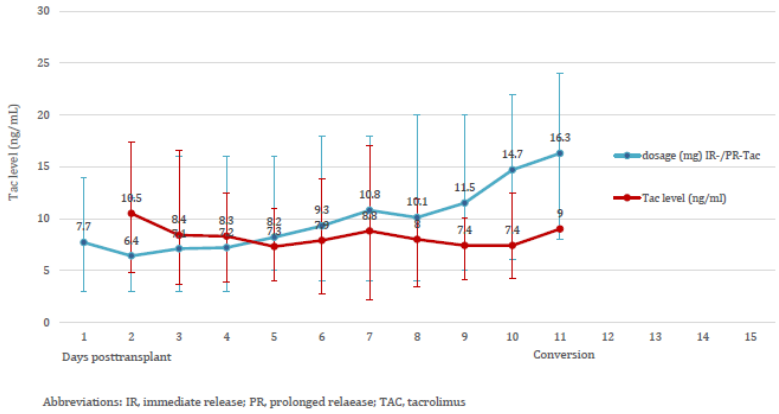

Figure 1a: Tacrolimus levels (median; range) and dosage (median; range) of IR-/PR-Tac.

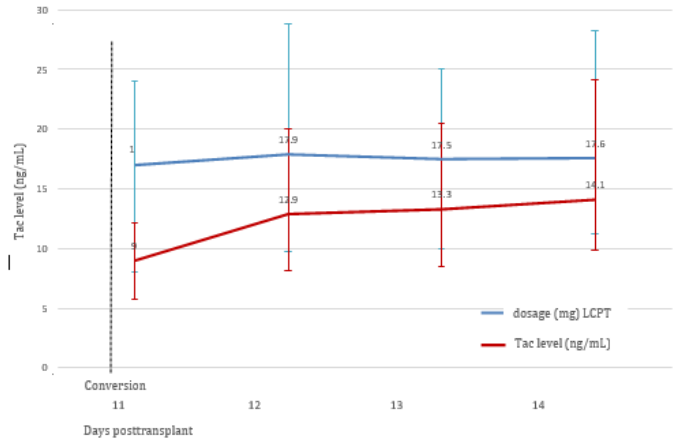

Figure 1b: Tacrolimus levels (median; range) and dosage (median; range) of LCPT.

In Group 2, no renal but two pancreatic grafts were lost at month 1 and 2. Both organs were lost as a result of venous thrombosis. One PTA had DSAs against HLA Class I+II in the Luminex assessment. In the other PTA, DSAs were not assessed. Both grafts were eventually removed. Two pancreatic rejections and one case each of biopsy-proven (Banff IIa) renal rejection were reversed with steroids (plus IR-/PR-Tac adaption to a therapeutic level), and an additional series of ten immune aphereses was performed in the latter patient. Median Tac level at time of rejection was 10.2 ng/mL. Three of the four patients with positive DSAs against HLA Class I+II (Luminex; 3 patients preoperatively sensitized with PRA 2%/ 38% / 50% PRA; all second SPK; one renal acute rejection Banff IIa) had stable graft function, while one patient lost his graft due to thrombosis (PTA; preoperatively PRA-negative). Median creatinine between months 1 and 24 was normal; the Igls Score for the remaining pancreatic grafts was "optimal" (Figures 2a, 2b). At month 12, three patients were converted from MMF to azathioprine for diarrhea, five were steroid-free.

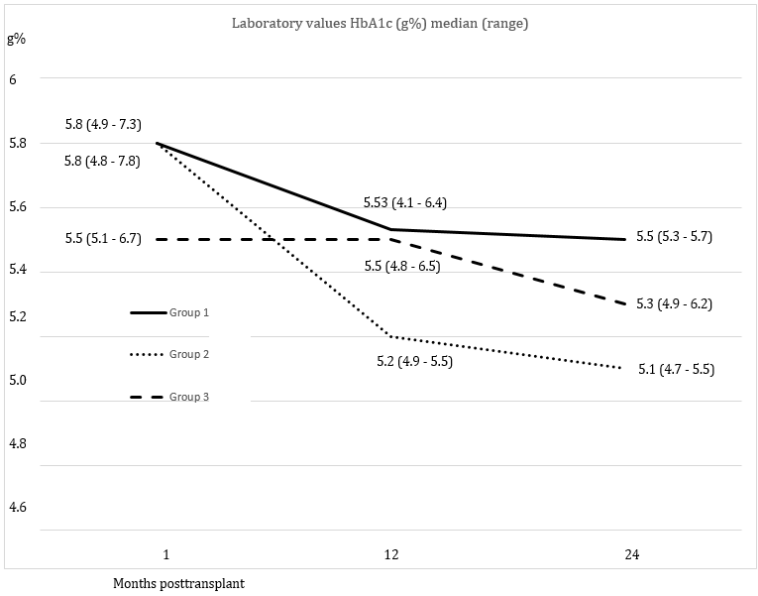

Figure 2a.

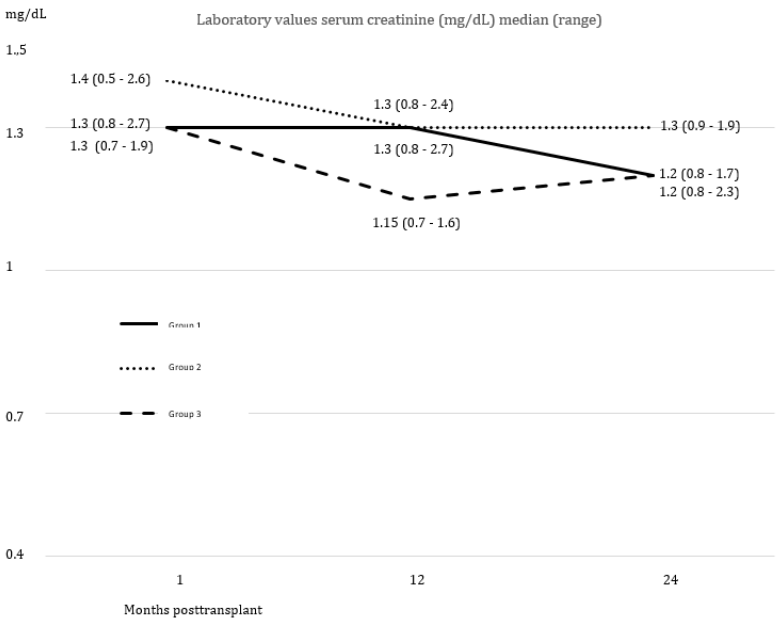

Figure 2b.

In Group 3, one renal graft was lost because of primary non-function (while pancreas function was good), one pancreas was lost as a result of necrotizing pancreatitis (month 2; positive HLA Class I + II antibodies in Luminex) and one after thrombosis (month 12; negative HLA Class I antibodies in ELISA). The latter two were re-SPKs, and both were removed. The remaining pancreas grafts display "optimal" function as shown by the Igls Score (Figure 2a). Median serum-creatinine between months 1 and 24 was normal (Figure 2b). Five pancreatic rejections were reversed with pulsed steroids and PR-Tac dosage adaptation to the therapeutic range. Median Tac level at time of rejection was 10.0 ng/mL. Of two patients with positive DSAs against HLA Class I+II (Luminex), one patient lost the pancreatic graft as a result of thrombosis at month 2 (second SPK; stable kidney graft; preoperatively PRA-negative). The function of the remaining pancreatic grafts is „optimal" as seen from the Igls Score (Figure 2a). Nine patients had no DSAs against HLA Class I (ELISA) and one patient had DSAs against Class I+II (Luminex). One patient was converted from IR-Tac to CyA for suspected drug fever. As this assumption could not be proven, he was reconverted to IR-Tac for hirsutism as a probable CyA side-effect and Tac was tolerated well. At month 12 one patient was switched from MMF to azathioprine for diarrhea, and one patient was steroid-free. In all three groups the infectious and other complications were controllable (Table 3).

Table 3.

		Group 1 n=15	Group 2 n=15	Group 3 n=15
Results				
Observation time	Months median (range)	13.6 (6-24)	22.0 (6-24)	17.2 (6-24)
Patient survival		100%	100%	100%
Graft survival	Pancreas	100%	86.7 % (13/15)	86.7 % (13/15)
	Kidney	100%	100%	93.3 % (14/15)
Cause of graft loss	Pancreas		Venous thrombosis each (month 1, 2; one PTA)	1 necrotizing pancreatitis (month 2) / 1 venous thrombosis (month 12)
	Kidney			Initial non function (month 1)
Initial function	Pancreas	100% (15/15)	66.7 % (10/15)	80 % (12/15)
	Kidney	64.3% (9/14)	71.4 % (11/14)	60 % (9/15)
Acute rejection	Pancreas (clinically)	4 (all reversible)	2 (all reversible)	
	Kidney (clinically)	1 (reversible)	1 (reversible)	5 (all reversible)
Kidney biopsy proven			1 (BANFF IIa; reversible)	1 (reversible)
Infectious complications bacterial	Acute cystitis	7 (2 recurring)	7 (1 recurring)	7
	Peripancreatic abscess	1		4
	Bronchitis	1	3	
	Urosepsis		2	
	Enteritis	1	2	
	One case each:	Dental focus / gastritis osteomyelitis / bronchitis / tonsillitis / laryngitis	Otitis media / leg ulcers / gastritis / chronic cholecystitis (cholecystectomy)	Pancreatic abscess /otitis media /toe gangraena
Infectious complications viral	Herpes stomatitis	1	4	1
	BK-viremia	2	2	
	CMV antigen positive		2	1
	Influenza B			1
	Rhinitis		1	3
Infectious complications fungal	One case each:	Candida stomatitis	Vaginitis/onychomycosis	Vaginitis / Candida-oesophagitis / candidemia
Surgical complications	Haematoma	3	2	3
	Surgical site infection		1	2
	Incisional hernia	1	3	
	Pancreatic anastomosis bleeding (clipped)	3		2
	Seroma	2	1	1
	One case each:	Iatrogenous urethral lesion	Lymphocele / kidney vein thrombosis / kidney vein stenosis (stent) / hernia umbilicalis / haemorrhoides	Sigmoid perforation / kidney arterial kinking / iatrogenous pneumothorax /burst abdomen
Cardiac complications	One case each:	Bradycardia	Acute coronary syndrome	Myocardial infarction / hypotension / tachycardia
Neurological/psychological complications		Tremor (2), venous thrombosis (2)	Dysaesthesia (1) / agitation (1) / depression (1)	Orthostatic syncope (1)
Rheological complications	Shunt thrombosis		3	
	One case each:			Thrombosis (A. radialis)
Peripheral angiopathy	One case each:	Foot amputation (osteomyelitis)	Claudicatio	Toes necrosis

Gastrointestinal complications	Elevated liver enzymes	3 (Azathioprine 2; Pantoprazole 1)	1 (Pantoprazole)	2
	Diarrhea	1	2	2
Haematological complications	Leucopenia <2500 L.	4	3	
Tumor			1 cancer native kidney (month 21)	
Other complications	One case each:	Pruritus / nausea / hyperpotassemia / dystelectasis	Hypocalciemia / traumatic bone fracture/ coxarthrosis	Hirsutism / erythrocytosis/ suspected drug fever (not proven)
Comment		Pregnancy (posttransplant month 22) stable		
DSA monitoring Test: ELISA	HLA Class I negative (ELISA)	11	5	9
	Not done	4	4	3
Test: Luminex	HLA Class I + II negative		1	1
	HLA Class I + II positive		4 (1 pancreas lost; 3 patients: pretransplant PRA positive)	2 (1 pancreas lost)
	HLA Class I negative, Class II positive			

Abbreviations: BK, polyomavirus; CMV, cytomegalovirus; DSA, donor specific antibodies

The following aspects are noteworthy for discussion

Tac fast metabolism is a pharmacokinetic phenomenon resulting from a genetic variation in the CYP 3A5 system, whereby patients with the CYP 3A5*1 allele are considered to meet the Tac trough levels with LCPT since it is resorbed in the distal gastrointestinal tract, where less CYP 3A5*1 is expressed (1-5). CYP 3A5 genotyping might be considered at the time of patient registration on the waiting list. In our study population, no genotyping was done and we defined Tac fast metabolizers with a c/d ratio <1.05 (1-5.) The c/d ratio seems to be a feasible denominator at about day 5, when postoperative bowel function has recovered. Promising results were published in kidney and liver transplant patients, where Tac fast-metabolizing recipients were effectively treated with LCPT, but only relatively small groups of Tac fast-metabolizing pancreatic graft recipients have been reported so far (2-4, 6-11). We therefore retrospectively analyzed our center cohort by comparing 15 Tac fast-metabolizing pancreatic graft recipients converted to LCPT and patients treated with high-dose IR-/PR-Tac and regular Tac metabolizers.

Tac fast metabolizers were kept on IR-/PR Tac, but a significant dose increase was applied. The therapeutic Tac level was reached on day 11.6 (median; Table 2). In Group 3 (regular Tac metabolizers), the therapeutic level was reached at day 5.7 (median; Table 2). The importance of a stable therapeutic Tac level was illustrated by the number of rejections seen in patients with subtherapeutic Tac levels, although reversed with pulsed steroids plus an increase in Tac level up to a therapeutic range. In the LCPT group no pancreatic or renal graft was lost, in contrast to two pancreatic graft losses each in Groups 2 and 3. Due to the relatively small patient population statistical significance was not calculated. All LCPT patients had stable pancreas and renal function.

Tremor as an established indication for conversion to LCPT was not relevant in this series [10]. Complications were comparable between all groups.

Conclusion

From our study we can summarize that conversion from PR-Tac to LCPT in fast metabolizing pancreatic graft recipients is feasible and safe. Long-term results are warranted.

Disclosure

The authors of this manuscript have no financial or other conflicts of interests to disclose.

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