Supplementary information

European Journal of Drug Metabolism and Pharmacokinetics

Extremely high variability of whole-blood tacrolimus pharmacokinetics early after thoracic organ transplantation

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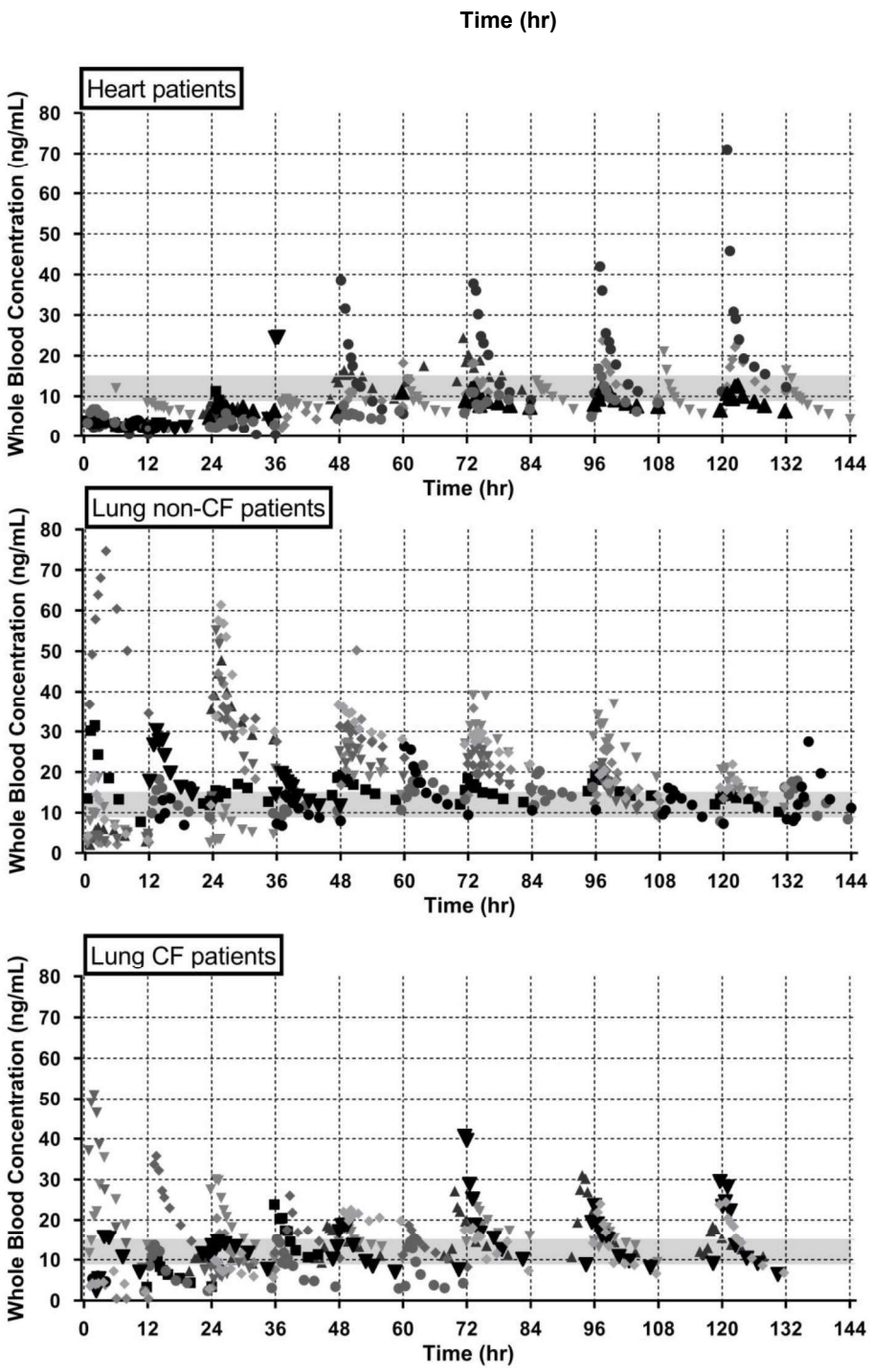

Fig. S1 Whole-blood tacrolimus concentrations over time subdivided into group of patients: 10 heart transplant patients, 10 lung transplant patients without CF, and 10 lung transplant patients with CF. The grey bar corresponds with the therapeutic range (9-15 ng/ml).

Table S1. Definitions of the covariates

Covariate	Definition
Baseline creatinine clearance	The baseline creatinine clearance was the last clearance before surgery or, when there was no measured clearance, clearance was calculated with the "CKD Epidemiology Collaboration equation (CKD EPI)" [1]
ARC	Creatinine clearance >130 ml/min [2]
AKI	Decrease of 50% in creatinine clearance or the use of CVVH [3] Creatinine clearance calculation: $C_{cr} = \frac{U_{cr} \text{ x 24-hour volume in ml}}{P_{cr} \text{ x 24 x 60 min}}$
Renal recovery	Serum creatinine below or equal to 125% of the baseline creatinine [4]
CKD	eGFR categories; G1=normal GFR: ≥90 ml/min/1.73 m^2, G2=mildly decreased: 60–89 ml/min/1.73 m^2, G3a/b=mildly to severely decreased: 30-59 ml/min/1.73 m^2, G4= severely decreased: 15-29 ml/min/1.73 m^2, G5= Kidney failure: <15 mL/min/1.73 m^2. eGFR = 141 x [min(Scr/κ),1)α x max(Scr/κ),1)-1.209] x Age-0.993 x 1.018 [if female] x [1.157 if Black] α is 0.329 for females and 0.411 for males; min indicates minimum of Scr/κ or 1, and max indicates maximum of Scr/κ or 1
SIRS	Presenting 2 or more of the following criteria: body temperature <36 °C or >38 °C, heart rate >90 /min for lung recipients and >100 /min for heart recipients, respiratory rate >20/min, PaCO2 <32 mmHg, mechanical ventilation and leucocyte count <4 $X10^9$ /L or >12 $X10^9$ /L
Shock	Mean arterial pressure <60 mmHg or use of norepinephrine, epinephrine, phenylephrine, vasopressin, dobutamine or milrinone
SOFA score	Sequential Organ Failure Assessment measured per day. The total SOFA was

	calculated as the sum of all daily SOFA scores during the intensive care stay for each patient.
Diarrhea	Defecation >2 times/day
Ileus	No defecation for ≥3 days or gastric retention of ≥500 mL/day
Liver injury	Bilirubin >34 μmol/L or an ALT >90 U/L for men and >70 U/L for women
Drugs potentially increasing tacrolimus blood concentrations by inhibition or substrate competition of the CYP3A4/5 and ABCB1 enzymes	Tobramycin, erythromycin, neomycin, trimethoprim/ sulfamethoxazole, fluconazole, voriconazole, (es)omeprazole, amlodipine, nicardipine, diltiazem, haloperidol, amiodarone
Drugs potentially decreasing tacrolimus blood concentrations by induction of CYP3A4/5 or ABCB1 enzymes	Corticosteroids and rifampicin

AKI= acute kidney injury, Ccr=creatinine clearance, Ucr=urine creatinine concentration, Pcr= plasma creatinine concentrations, CKD=chronic kidney dysfunction, (e)GFR=(estimated) glomerular filtration rate, SIRS=systemic inflammatory response syndrome, Scr=serum creatinine, min=minute, CYP=Cytochrome P450, ABCB1=p-glycoprotein

Table S2. Patient's characteristics indicated per day

	N=30 (%)	Median (1st and 3rd quartile)
SOFA scores per day		
Day1		9 (7;17)
Day2		8 (5;10)
Day3		5 (3;8)
Day4		5 (3;15)
Day5		4 (3;11)
Day6		4 (2;9)
Frequency of Ileus per day		
Day1	27 (90%)	
Day2	24 (80%)	
Day3	14 (47%)	
Day4	5 (17%)	
Day5	2 (7%)	
Day6	2 (7%)	
Frequency of diarrhea per day		
Day1	0 (0%)	
Day2	2 (7%)	
Day3	8 (27%)	
Day4	9 (30%)	
Day5	11 (37%)	
Day6	10 (33%)	
Frequency of liver dysfunction per day		
Day1	7/30 (23%)	
Day2	6/30 (20%)	
Day3	3/27 (11%)	
Day4	3/21 (14%)	
Day5	4/17 (24%)	
Day6	3/17 (18%)	
Frequency of ECMO use per day		
Day 1	8 (27%)	
Day 2	7 (23%)	
Day 3	5 (19%)	
Day 4	4 (19%)	
Day 5	3 (18%)	
Day 6	3 (18%)	
Number of drugs increasing tacrolimus concentration (min-max)		
Day1		2 (1-4)
Day2		1 (0-2)
Day3		1 (0-4)
Day4		1 (0-5)
Day5		0 (0-6)
Day6		1 (0-4)

Number of patients with drugs increasing tacrolimus concentration		
Day1	30 (100%)	
Day2	23 (77%)[a]	
Day3	23 (85%)[a]	
Day4	17 (81%)[a]	
Day5	14 82%)[a]	
Day6	16 (94%)[a]	
Number of drugs decreasing tacrolimus concentration (min-max)		
Day1		0 (0-0)
Day2		1 (1-2)
Day3		1 (0-1)
Day4		1 (0-1)
Day5		1 (0-1)
Day6		1 (0-1)
Number of patients with drugs decreasing tacrolimus concentration		
Day1	0 (0%)	
Day2	30 (100%)	
Day3	26 (96%)	
Day4	21 (100%)	
Day5	17 (100%)	
Day6	17 (100%)	
Renal function		
Baseline Creatinine clearance (ml/min/1.73m2)		85 (73;116)
Pharmacogenetic analyses		
Slow metabolizers of CYP 3A5	21 (70%)	
Slow metabolizers of CYP3A4		
Homozygosity CYP3A4*22	0 (0%)	
Heterozygosity and Homozygosity of POR*28	18 (60%)	
PPARα	16 (53%)	
Decreased ABCB1 activity		
Decreased PXR activity	18 (60%)	
G1199A homozygosity	0 (0%)	
C1236T homozygosity	6 (20%)	
G2677T homozygosity	8 (27%)	
C3435T homozygosity	8 (27%)	
OATP1B1 homozygosity	0 (0%)	

[a] *of the patients still at the ICU*

Reference list

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