

A population pharmacokinetic model of Whole-Blood and Intracellular Tacrolimus in Kidney Transplant Recipients

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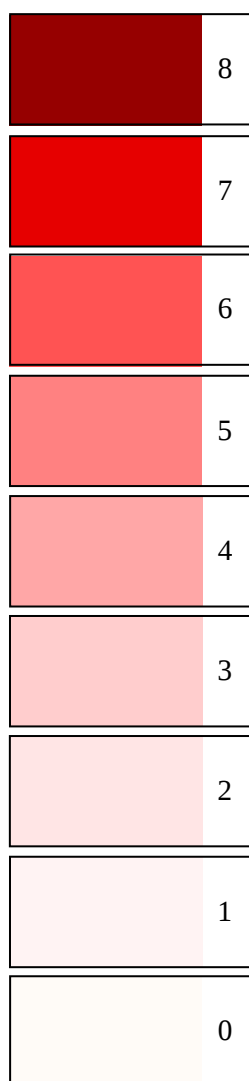
SUPPLEMENTARY CONTENT

Supplementary Figure S1. Red level scale

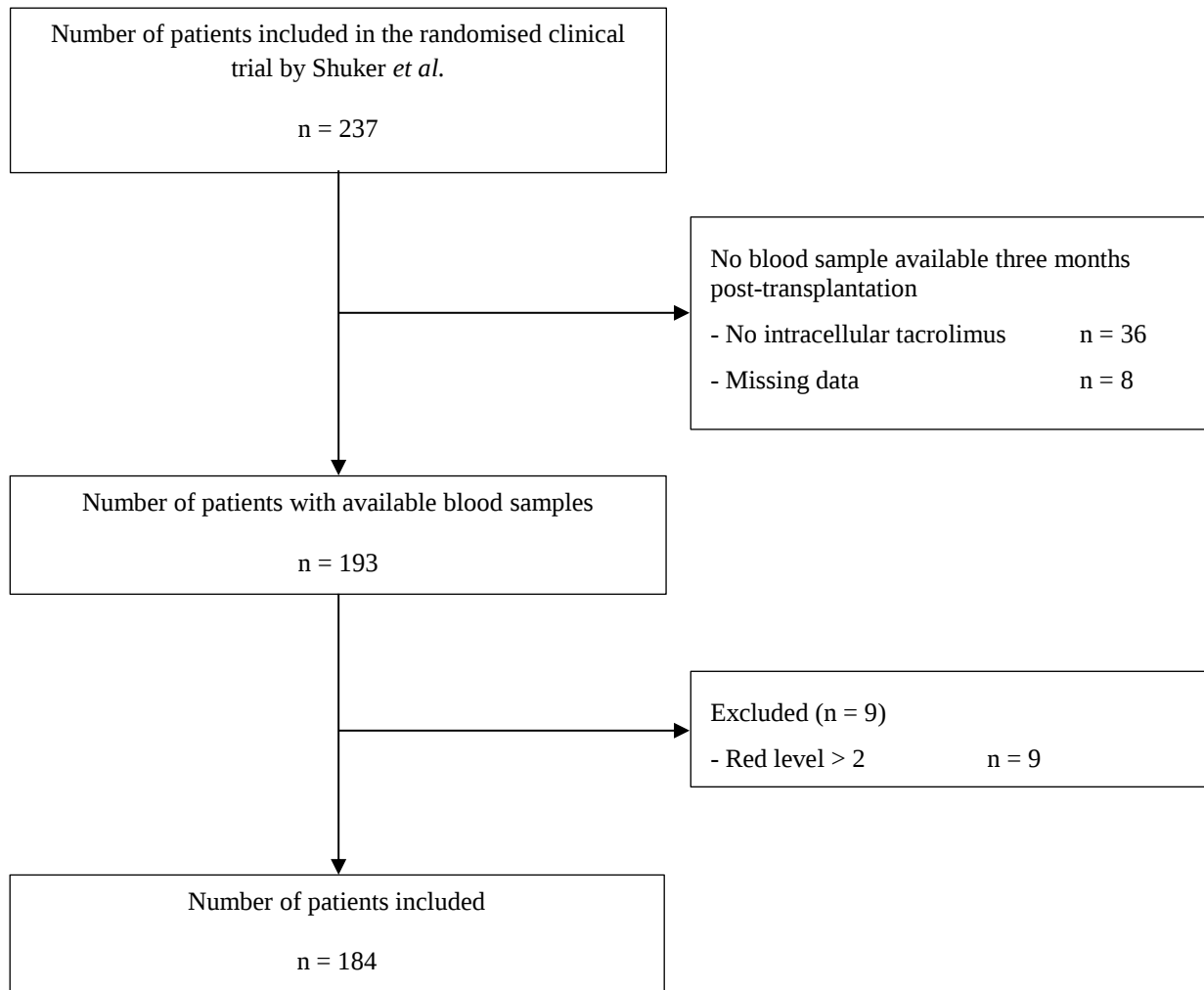
Supplementary Figure S2. Flowchart of patient inclusion and exclusion

Supplementary Table S1. Simulated intracellular tacrolimus concentrations

Supplementary Data S1. NONMEM code



Supplementary Figure S1. Red level scale



Supplementary Figure S2. Flowchart of patient inclusion and exclusion

Supplementary Table S1. Simulated intracellular tacrolimus concentrations

	IC (µg/L)	R _{WB-IC}
Hematocrit 0.28 L/L	199.2 (154.1 – 255.8)	0.054 (0.042 – 0.069)
Hematocrit 0.34 L/L	181.6 (140.6 – 233.3)	0.068 (0.053 – 0.087)
Hematocrit 0.43 L/L	168.2 (124.1 – 217.9)	0.081 (0.063 – 0.110)
Lean body weight 49.96 kg	160.1 (123.8 – 205.5)	0.080 (0.062 – 0.104)
Lean body weight 60.62 kg	186.1 (144.0 – 239.1)	0.066 (0.051 – 0.085)
Lean body weight 68.47 kg	201.2 (148.4 – 260.5)	0.057 (0.044 – 0.078)

Values are presented as median (IQR).

IC, intracellular tacrolimus concentration; R_{WB-IC}, whole blood to intracellular tacrolimus concentration ratio

Supplementary Data S1. NONMEM code

```
----- INPUT -----

$SIZES      LVR=60

$PROBLEM    TACROLIMUS IN PBMCS

$INPUT      ID TIME TATX AMT DV DVIC DVP MDV EVID II ADDL SS CMT TIM2 IOV
            ICL IV2 IV3 IQ CREA HCT ALB AGE LBW FAT NEXP CYP AVIER ABCB CC
            CT TT ABC2 AA GA GG BSA WGT BMI IBW DVID

$DATA       DATA.csv

$ABBREVIATED DERIV2=NO

----- PHARMACOKINETIC MODEL -----

$SUBROUTINE ADVAN6 TOL=5

$MODEL
NCOMPS=4
COMP (DEPOT,DEFDOSE)
COMP (CENTRAL)
COMP (PERI)
COMP (IC)

$PK
KA = 3.6
ALAG1 = 0.382
CL = ICL
V2 = IV2
V3 = IV3
Q = IQ
K24 = THETA(4)

RPIC = (THETA(5)*(LBW/59.5)**(THETA(6))*(HCT/0.34)**(THETA(7)))*EXP(ETA(1))

K12 = KA
K20 = CL / V2
K23 = Q / V2
K32 = Q / V3
K40 = K24
S2 = V2 / 1000

$DES
DADT(1) = -K12*A(1)
DADT(2) = K12*A(1)-(K23+K20)*A(2)+K32*A(3)
DADT(3) = K23*A(2)-K32*A(3)
DADT(4) = K24*(RPIC*(A(2)/V2)-A(4))
```

\$ERROR

IPRED = F

IF (CMT.EQ.2) Y=F + F*EPS(1)*THETA(1)

IF (CMT.EQ.4) Y=F + F*EPS(2)*THETA(2) +EPS(3)*THETA(3)

IF (CMT.EQ.0) IPRED=0

IF (CMT.EQ.1) IPRED=0

IF (CMT.EQ.3) IPRED=0

IF (CMT.EQ.2) W=SQRT(F*F*THETA(1)**2)

IF (CMT.EQ.4) W=SQRT(THETA(3)**2+F*F*THETA(2)**2)

IRES=DV-IPRED

IWRES=IRES/W

\$THETA

(0,0.1) ;1

(0,0.001) ;2

(0,20) ;3

(0.9) FIX ;4

(0,12900) ;5

(1) ;6

(-1) ;7

\$OMEGA

(0.2) ;1

\$SIGMA

1 FIX

1 FIX

1 FIX

\$EST METHOD=1 MAXEVAL=99999 SIG=3 PRINT=5 NOABORT POSTHOC INTERACTION

\$COVARIANCE PRINT=E UNCONDITIONAL