# Population pharmacokinetic analysis of tacrolimus TDM data in stable kidney transplant patients

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## Objectives

The aim of the study was to explore pharmacokinetic characteristics of tacrolimus and potential factors that significantly contribute to its variability in stable kidney transplant patients.

## Methods

- TDM data for period about one year after transplantation
- $C_{trough}$ in whole blood were assessed using CMIA method (ARCHITECT, Abbot Laboratories)
- NONMEM® (version 7.2.0), PSN® (version 3.5.3)
- Graphic presentation - Xpose®, R®, Pirana®
- FOCEI; ADVAN2 TRANS2
- Internal validation: bootstrap -1000 samples, Numerical predictive check (NPC) - 1000 samples

## Results

Table 1. Patients' and immunosuppressive therapy characteristics

| Characteristic | | Number (%) / Average ± Sd | Range |
|---|---|---|---|
| Gender | Male | 26 | |
| | Female | 19 | |
| Graft origin | Living donor | 30 | |
| | Cadaver | 15 | |
| Post transplantation days | | 389.14 ± 33.75 | 328 – 470 |
| Age (years) | | 40.83 ± 10.22 | 20 – 61 |
| Body weight (kg) | | 69.78 ± 12.94 | 45 – 95 |
| Haematocrit | | 0.40 ± 0.06 | 0.28 – 0.58 |
| Proteinaemia (g/l) | | 71.76 ± 3.70 | 63 – 80 |
| Toatl cholesterole (mmol/l) | | 5.39 ± 1.15 | 2.9 – 9.17 |
| Triglycerides (mmol/l) | | 1.96 ± 1.01 | 0.14 – 7.19 |
| Aspartate aminotransferase (IU/l) | | 19.68 ± 6.96 | 9 – 41 |
| Alanine aminotransferase (IU/l) | | 23.84 ± 12.61 | 2 – 73 |
| Tacrolimus | Dose (mg/day) | 4.52 ± 2.26 | 1 – 11 |
| | Concentation (ng/ml) | 6.69 ± 2.63 | 2.6 – 19.6 |
| Mycophenolate mofetil dose (mg/day) | | 1134.26 ± 270.05 | 750 – 2000 |
| Corticosteroids dose (mg/day) | | 8.49 ± 1.99 | 5 – 12.5 |

- interindividual variability – exponential error model
- residual variability – proportional error model
- bootstrap – 999 successful runs

Table 2. Inclusion of covariate during model building process

| Model | OFV | Δ OFV |
|---|---|---|
| Base | 344.212 | |
| Forward inclusion of DTAC | 319.929 | 24.283 |
| Forward inclusion of WT | 305.93 | 13.999 |
| Full | 305.93 | |
| Backward exclusion of DTAC | 340.362 | 34.432 |
| Backward exclusion of WT | 319.929 | 13.999 |
| FINAL | **305.93** | |

Table 3. Final model parameters of real and bootstrap simulated data

| Parameter | FINAL MODEL | | BOOTSTRAPING | |
|---|---|---|---|---|
| | Estimate | 95% CI | Median | 95% CI |
| $\theta_{CL}$ [a] (l/h) | 4.27 | 2.853 - 5.687 | 4.27 | 3.033 – 6.082 |
| $\theta_{DTAC}$ [b] | 1.51 | 1.364 - 1.656 | 1.52 | 1.38 – 1.73 |
| $\theta_{WT}$ [b] | 1.82 | 1.355 - 2.285 | 1.80 | 1.33 – 2.38 |
| $\omega^2_{CL}$ [c] | 0.0202 | 0.00685 – 0.0335 | 0.0177 | 0.00595 – 0.0325 |
| Wp [d] | 0.302 | 0.224 - 0.380 | 0.298 | 0.224 - 0.382 |

a- typical value of tacrolimus clearance;
b- influential factors for covariates (DTAC – daily tacrolimus dose, WT – body weight);
c- variance for clearance;
d- residual variability (Wp – proportional error).

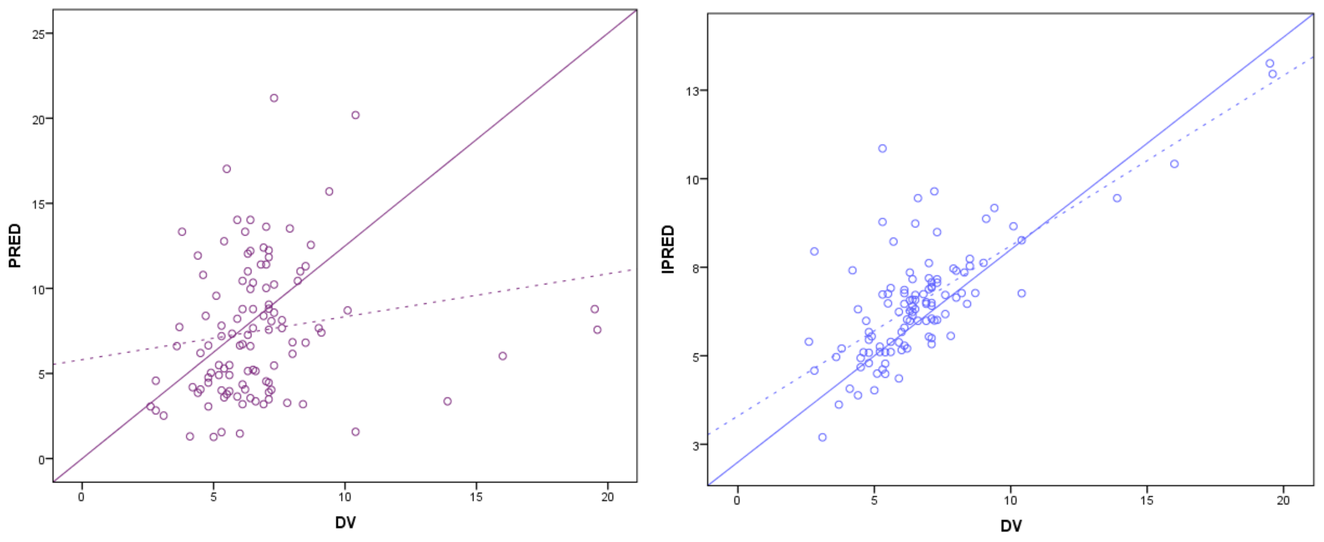


Figure 1. Population (PRED) and individual model predicted (IPRED) concentration versus observed concentration (DV) (ng/ml)

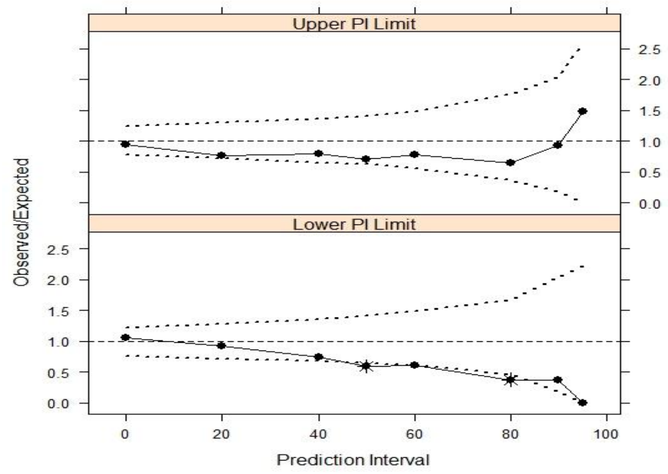


Figure 2. NPC of the final model . Circles present lower and upper limits of prediction intervals (%) observed in the data. Dashed lines indicate 95% CIs of the lower and upper limits of simulation-based prediction intervals (%).

## Conclusions

Tacrolimus CL/F was found to increase with WT and DTAC. Relationship between CL/F and DTAC may be due to so-called TDM effect. Other analyzed covariates did not influence tacrolimus CL/F significantly.

References
1. Golubović B, Vučićević K, Radivojević D, Kovačević Vezmar S, Prostran M, Miljković B. Total plasma protein effect on tacrolimus elimination in kidney transplant patients – population pharmacokinetic approach. Eur J Pharm Sci. 2014; 52: 34–40.
2. Ahn, J.E., Birnbaum, A.K., Brundage, R.C., 2005. Inherent correlation between dose and clearance in therapeutic drug monitoring settings: possible misinterpretation in population pharmacokinetic analyses. J Pharmacokinet Pharmacodyn 32, 703-718.

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