

Multiple response modelling of mycophenolic acid pharmacokinetics in adult patients with transplanted kidneys by a population approach

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Introduction

Mycophenolic acid (MPA): immunosuppressant drug preventing graft rejection

- inhibits inosine-monophosphate dehydrogenase (IMPDH)
- acts inside peripheral blood mononuclear cells (PBMCs) ^[1]
- highly bound to plasma proteins
- narrow therapeutic index requires therapeutic drug monitoring (TDM) ^[2] based on total MPA AUC₀₋₁₂ in plasma ^[3] → **Interest of TDM at cellular level ?**

Aims

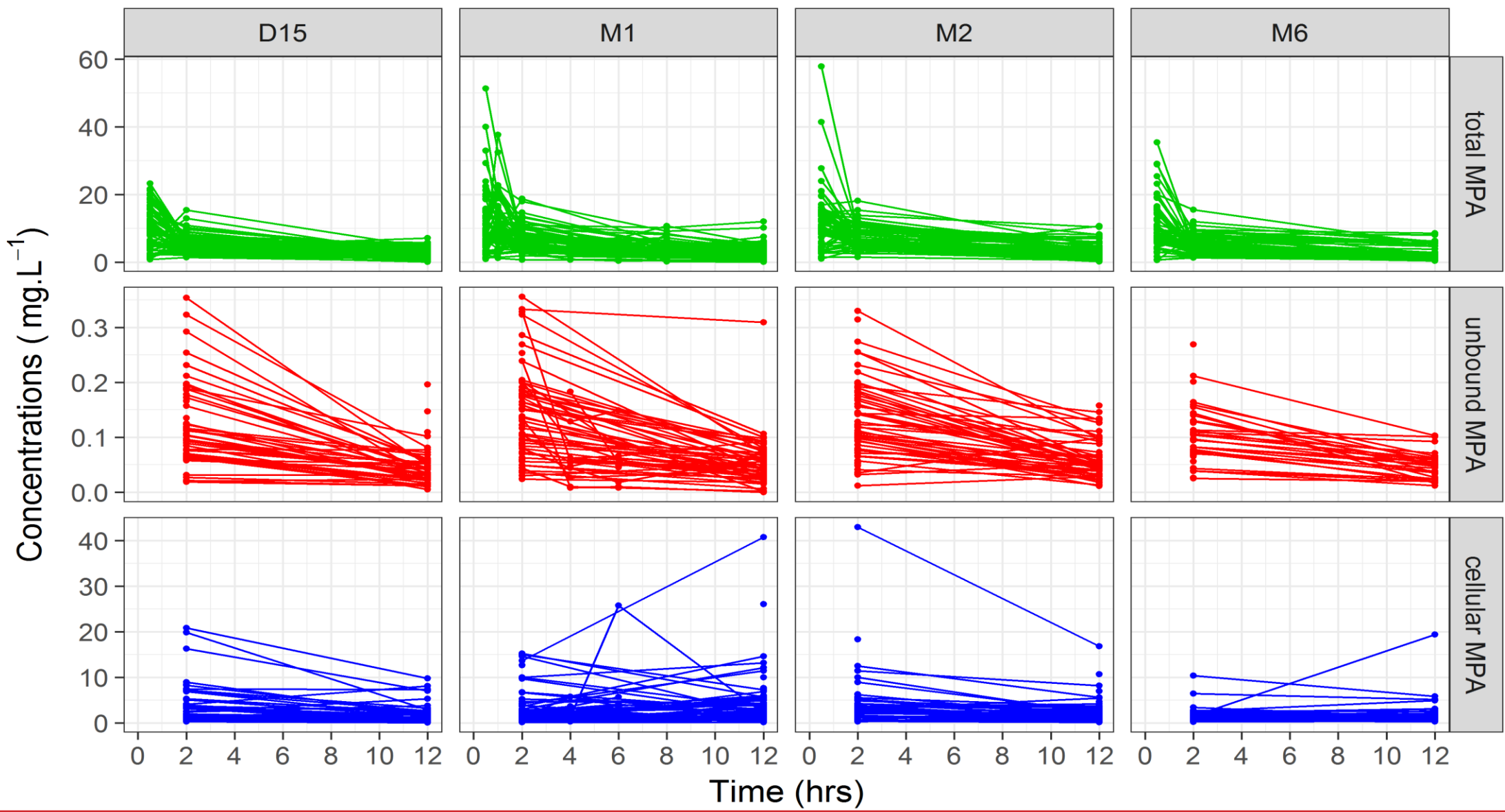
1. to build a model describing data collected in study CIMTRE in adult kidney transplant recipients
2. to predict exposition (AUC₀₋₁₂) to plasma MPA **total** and **unbound** and **cellular** MPA
3. to evaluate associations with the occurrence of graft rejections

Data

Occasion	Sampling time (hrs)						
	0.5	1	2	4	6	8	12
Day 15 (D15)	71		71/68/56				71/67/52
Month 1 (M1)	73	73	73/73/57	13/13/11	13/13/12	13	73/73/63
Month 2 (M2)	70		70/70/60				70/70/57
Month 6 (M6)	57		57/56/44				57/57/34

Number of **total**/**unbound**/**cellular** MPA samples

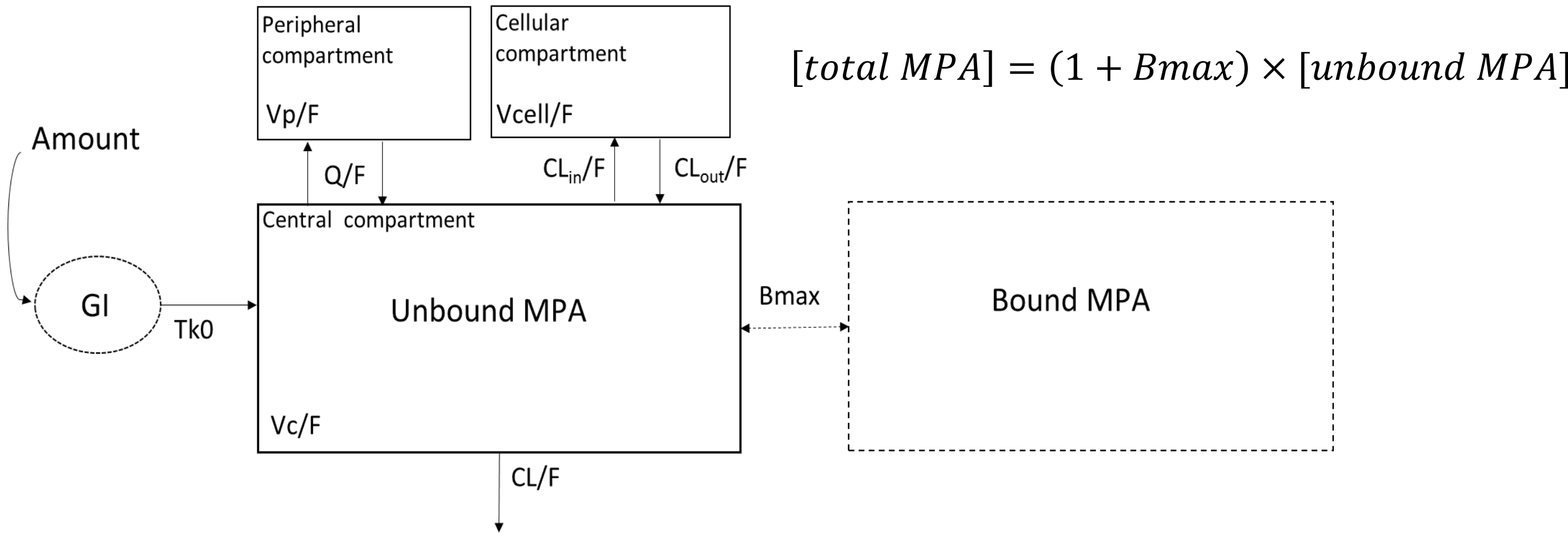
- Covariate: human serum albumine (HSA), creatinine clearance (CrCL) at each occasion and genotype of ABCB1, MRP1 and OATP1B3 transporters ^[4,5,6]



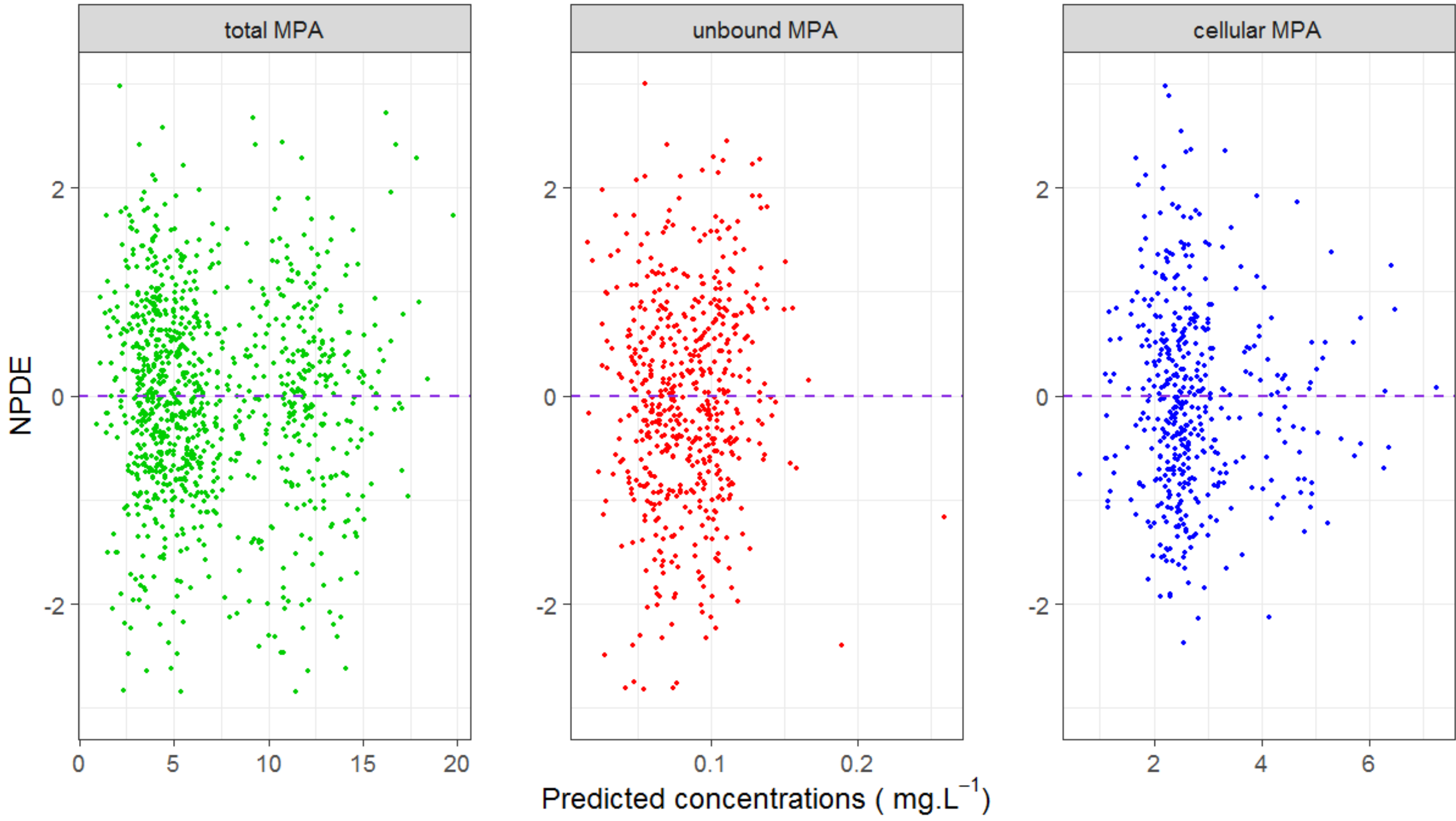
Modelling

- Steady state reached at M2
- Structural model selection on BIC and goodness-of-fit plots
- Covariate model selection on Wald test
- Parameter estimation with SAEM algorithm using the Monolix® software
- Logistic regression model using R software
 - occurrence of graft rejection explained by **total**/**unbound**/**cellular** MPA AUC₀₋₁₂

Results

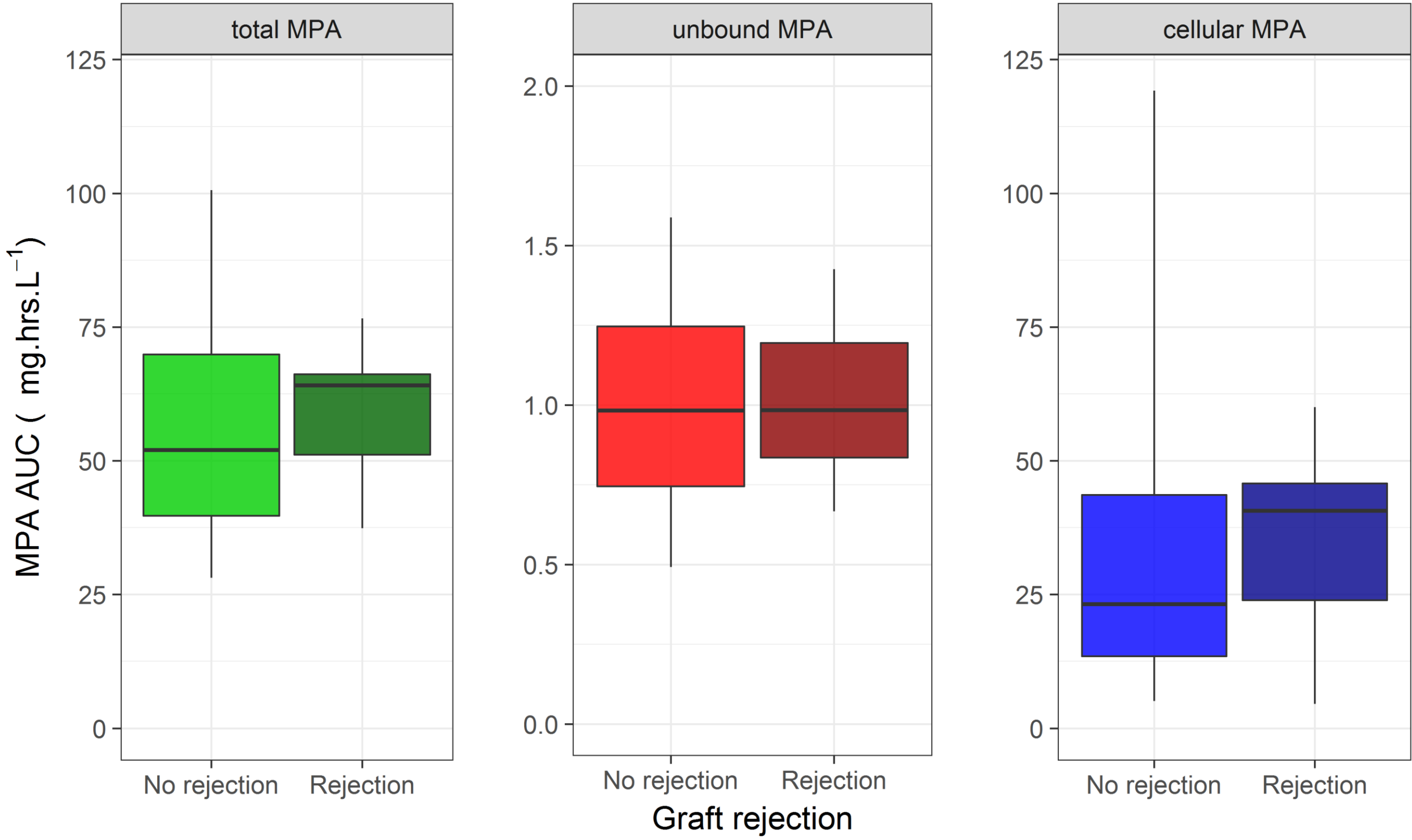


- Satisfactory goodness of fit plots



MPA exposition:

- MPA exposures in the plasma and in PBMCs at D15 versus organ rejection at the end of the CIMTRE study (M6)



- Median [range] MPA AUC₀₋₁₂ at D15
 - **total** = **54.50 [40.20–69.30]** mg.hrs.L⁻¹ → In upper range of therapeutic window (30 to 60 mg.hrs.L⁻¹) ^[2]
 - **unbound** = **0.98 [0.76–1.25]** mg.hrs.L⁻¹
 - **cellular** = **24.20 [13.70–45.20]** mg.hrs.L⁻¹

Conclusions

- First population PK model describing plasma total and unbound plus cellular MPA with PK parameter estimates close to values from the literature ^[6]
- No significant association between graft rejection and plasma **total** and **unbound** and **cellular** MPA exposure, although few graft rejections (n=13)
- Perspective: to explore association between adverse events and plasma **total** and **unbound** and **cellular** MPA exposure

References

[1] Jeong H, Kaplan B. Therapeutic Monitoring of Mycophenolate Mofetil. Clin J Am Soc Nephrol. 2007;2:184–91. [2] van Hest RM, Mathot RAA, Pescovitz MD, Gordon R, Mamelok RD, van Gelder T. Explaining Variability in Mycophenolic Acid Exposure to Optimize Mycophenolate Mofetil Dosing: A Population Pharmacokinetic Meta-Analysis of Mycophenolic Acid in Renal Transplant Recipients. J Am Soc Nephrol. 2006;17:871–80. [3] Pawinski T, Durlak M, Szlaska I, Urbanowicz A, Majchrnak J, Gralak B. Comparison of mycophenolic acid pharmacokinetic parameters in kidney transplant patients within the first 3 months post-transplant. J Clin Pharm Ther. 2006;31:27–34. [4] Picard N, Yee SW, Woillard JB, Lebranchu Y, Le Meur Y, Giacomini KM, et al. The role of organic anion-transporting polypeptides and their common genetic variants in mycophenolic acid pharmacokinetics. Clin Pharmacol Ther. 2010;87:100–8. [5] Atcheson BA, Taylor PJ, Mudge DW, Johnson DW, Hawley CM, Campbell SB, et al. Mycophenolic acid pharmacokinetics and related outcomes early after renal transplant. Br J Clin Pharmacol. 2005;59:271–80. [6] van Hest RM, van Gelder RM, Vulto AG, Shaw LM, Mathot RAA. Pharmacokinetic modelling of the plasma protein binding of mycophenolic acid in renal transplant recipients. Clin Pharmacokinet. 2009;48:463–76.