

Joint model for longitudinal exposure to mycophenolic acid and rejection survival in the first year after renal transplantation

Zeinab DAHER ABDI¹, Marie ESSIG^{1,2}, Yannick LE MEUR³, Pierre MARQUET^{1,4} and Annick ROUSSEAU¹

¹Inserm UMR-S850, Laboratory of medical Pharmacology, Faculty of Medicine, Limoges, France; ²Department of Nephrology, University Hospital, Limoges, France; ³Department of Nephrology, University Hospital, Brest, France; ⁴Department of Pharmacology, University Hospital, Limoges, France

BACKGROUND AND OBJECTIVES

Previous studies have reported conflicted results concerning the relationship between mycophenolic acid (MPA) exposure and the risk of acute rejection in the first year after renal transplantation¹. The randomized clinical trial FDCC² (dose fixed vs concentration controlled) concluded to a significant association between very early (i.e. on day 3 after transplantation) MPA inter-dose area under the plasma concentration vs time curve (AUC) and acute rejection in the first year post-transplantation; however this statistical association seemed only true in high-risk immunological patients. The present study aimed at modelling the effect of MPA exposure on rejection free survival within the first year post-transplantation by comparing two approaches: i) a survival model with independent-time covariate(s) and ii) a joint model for longitudinal and survival data so as to take into account the time-course of MPA exposure.

METHODS

- We re-analyzed data from adult kidney transplant recipients enrolled in the randomized clinical trial APOMYGRE³ (NCT0019967) conducted in our team. This 12 month, randomized, prospective multicenter (11 centers) trial compared target MPA AUC and fixed dose in de-novo renal transplant patients. All patients received mycophenolate mofetil (i.e., the prodrug of MPA) associated with cyclosporine. Cyclosporine (8 ± 2 mg/kg/day) was commenced within 3 days post-transplant and adjusted to maintain target cyclosporine 2-h post-dose levels. In all the included patients, MPA AUC_{0-12h} had been estimated using Bayesian estimators⁴ at 6 occasions (W1, W2, M1, M3, M6 and M12 post-transplantation).
- Nonmem VII, PsN and Xpose4 was used for the modelling process.
- An exponential baseline hazard model was used to predict the risk of rejection with an interval censored approach.
- MPA exposure was incorporated in the survival model using either:
 - i) a single MPA AUC_{0-12h} value estimated within the first week (i.e. AUC_{w1}) or
 - ii) the longitudinal MPA exposure modelled by a non-linear mixed effect model using the MPA AUC bayesian estimates calculated within the first year post-transplantation (then the joint likelihood was maximized using the laplacian approximation)
- The recipient age and the number of HLA mismatches were tested as covariates in the survival model.
- Visual predictive checks (VPC) based on simulated vs non-parametric estimates of survival (Kaplan-Meier plots) were used for model evaluation.

RESULTS

Patient characteristics

- A total of 126 trajectories of which 121 included at least 3 MPA AUC measurements (i.e. corresponding to at least three visits) were analyzed in this study.
- All acute rejections were diagnosed by renal biopsy except three cases with contra-indications.

Number of kidneys	126
Follow-up time after transplantation	W1, W2, M1, M3, M6, M12
Acute rejection episodes	22
Recipient age (mean ± SD)	49.61
Number of HLA mismatches A/ B/ DR:	
- ≤ 3	- 47
- > 3	- 79

Table 1: Patients and study data. W: week, M: month.

Survival submodel

- An interval censored approach was used for the time when rejection occurred: [t-3days;t] interval for t<15 days and [t-15days;t] interval for t≥15 days, with t equal to the time of diagnosis of acute rejection.
- VPC Kaplan-Meier plots showed that the survival model which incorporates the longitudinal MPA AUC profiles (Fig.2a) describes the rejection free survival better than the survival model which included a MPA AUC value estimated in the first week post-transplantation (Fig.2b). No significant effect of the recipient age was obtained. Inclusion of the number of mismatches HLA in the model improved the VPC Kaplan-Meier plot. (Fig. 2c).
- The equation of the selected joint model was:

$$h(t) = h_0 \cdot \text{Exp}(\beta_1 \times \text{AUC}_{\text{MPA}}(t) + \beta_2 \times \text{HLA}_{\text{mis}})$$

Where h_0 is the baseline hazard, β_1 and β_2 the regression coefficients estimating respectively the effect of the longitudinal MPA AUC and the number of HLA mismatches on the risk of rejection.

Longitudinal submodel

- An exponential mixed effect model was retained to describe the longitudinal MPA exposure:

Equation : $\text{AUC}_{\text{MPA}}(t) = E_0 + E_1 \cdot \text{Exp}(-kt)$
- VPC graphs of the selected exponential mixed effect model showed that approximately 90% of the observed MPA AUC were within the 90% prediction interval.

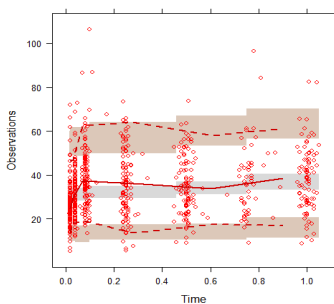


Fig. 1: Visual predictive check of the selected longitudinal MPA exposure model (n=1000 simulations). The solid red line represents the median observed AUC, and the grey field represents a simulation-based 95% confidence interval for the median. The observed 5% and 95% percentiles are presented with dashed red lines, and the 95% confidence intervals for the corresponding model predicted percentiles are shown as brown fields. The observed AUCs are represented by red circles.

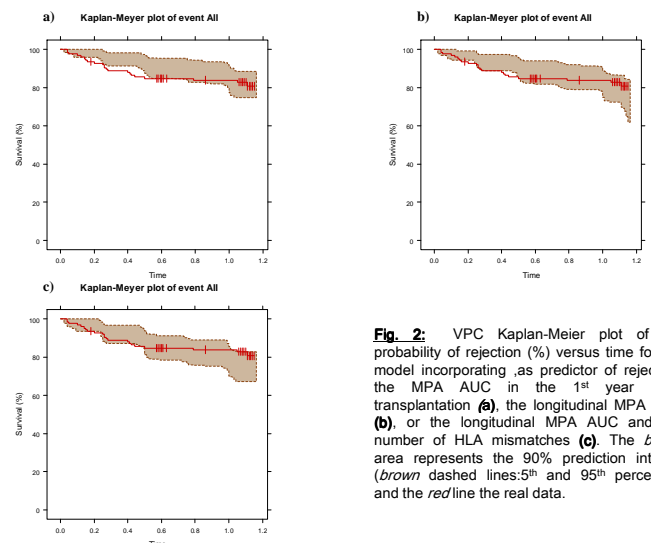


Fig. 2: VPC Kaplan-Meier plot of the probability of rejection (%) versus time for the model incorporating ,as predictor of rejection, the MPA AUC in the 1st year post-transplantation (a), the longitudinal MPA AUC (b), or the longitudinal MPA AUC and the number of HLA mismatches (c). The brown area represents the 90% prediction interval (brown dashed lines:5th and 95th percentile) and the red line the real data.

CONCLUSION

- The developed joint model suggested that optimum MPA exposure is critical over the first year and not only in the very early post-transplantation period
- Using this joint model, simulations can be performed leading to MPA target levels minimizing the risk of rejection.

REFERENCES

1. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clin Pharmacokinet.* 2007;46(1):13-58.
2. van Gelder T, Silva HT, de Fijter JW, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. *Transplantation.* 2008;86(8):1043-1051.
3. Le Meur Y, Büchler M, Thierry A, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am. J. Transplant.* 2007;7(11):2496-2503.
4. Prémaud A, Le Meur Y, Debord J, et al. Maximum a posteriori bayesian estimation of mycophenolic acid pharmacokinetics in renal transplant recipients at different postgrafting periods. *Ther Drug Monit.* 2005;27(3):354-361.