Model-Informed Precision Dosing of Tacrolimus in Lung Transplantation Early After Surgery Using Model-Predictive Control in the TDMore Framework

KU LEUVEN

Nicolas Luyckx (1), Andreas Lindauer (1), Robin Vos (2), Dirk Kuypers (3)

(1) Calvagone SAS, France; (2) Department of Respiratory Diseases University Hospital Leuven and BREATHE KU Leuven, Belgium; (3) Department of Nephrology, University Hospital Leuven, Belgium

INTRODUCTION

Tacrolimus is a critical immunosuppressant drug used in transplantation, but its narrow therapeutic index and highly variable bioavailability make dosing challenging [1]. To address this, KU Leuven and UZ Leuven have collaborated to develop a **model-informed precision dosing (MIPD)** tool for tacrolimus in renal transplant recipients during the first 14 days post-transplantation [2]. This project has led to the creation of the **tdmore** [3] package in R, which allows for maximum a posteriori Bayesian estimation of individual parameters, including a novel estimation technique called **model-predictive control (MPC)** [4] and the exploration of new dosing regimens [5]. The current work aimed at applying the same approach for patients undergoing **lung transplantation**.

Objectives

- To develop a **population PK model for tacrolimus in lung transplant recipients** and identify predictive factors for inter- and intra-individual variability.
- To develop a **computer-aided dose-individualization strategy** using the MPC approach for this patient population and evaluate its predictive performance retrospectively.

METHODS

Tacrolimus trough concentration (4027) data from **322 lung transplant patients** (2015-2020) were analyzed after excluding 38 due to age, re-transplantation, dosing time, or outliers. Data were divided into:

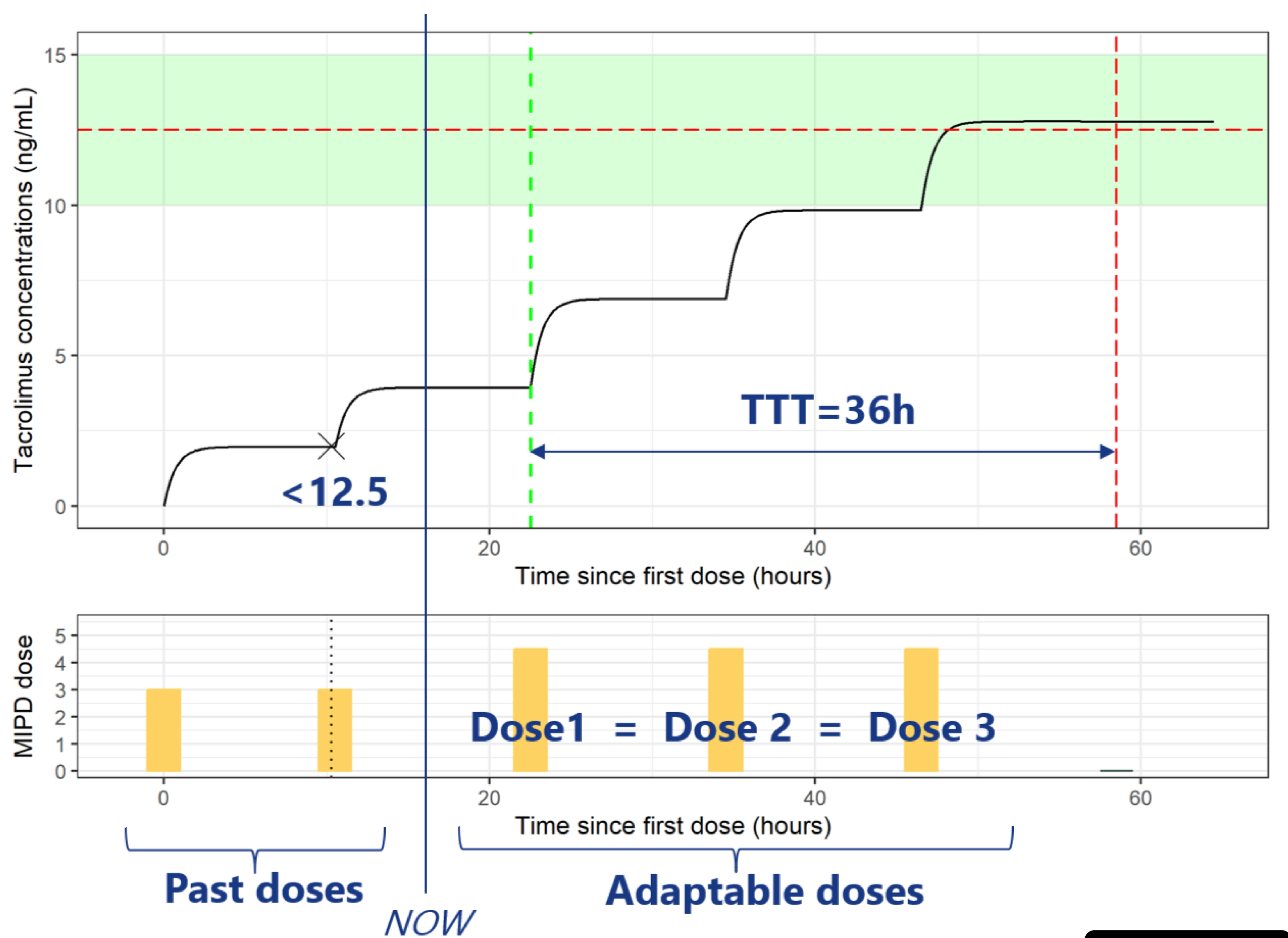
- **Estimation dataset** (~65% of the data): 209 patients
- **Validation dataset** (~35% of the data): 113 patients

Analysis involved developing a structural population PK model with **NONMEM**, automatic covariate modeling, model refinement, and validation through visual checks.

The best models were tested in **tdmore** [6] using the **MPC** technique:

1. One-day predictive performance on these models was assessed.
2. Dose adaptation simulations were run to assess the efficacy of various dose-individualization strategies.

To avoid giving a too high dose when the observed levels are below a certain **threshold** (e.g., the target value), the concept of **time-to-target (TTT)** was introduced, whereby the next doses are adjusted to meet the target concentration not 12 hours after the following dose but some time (TTT) further in the future (see Figure below). As further precautionary measures, **dose caps** and **maximum fold-increase** in doses were also explored.

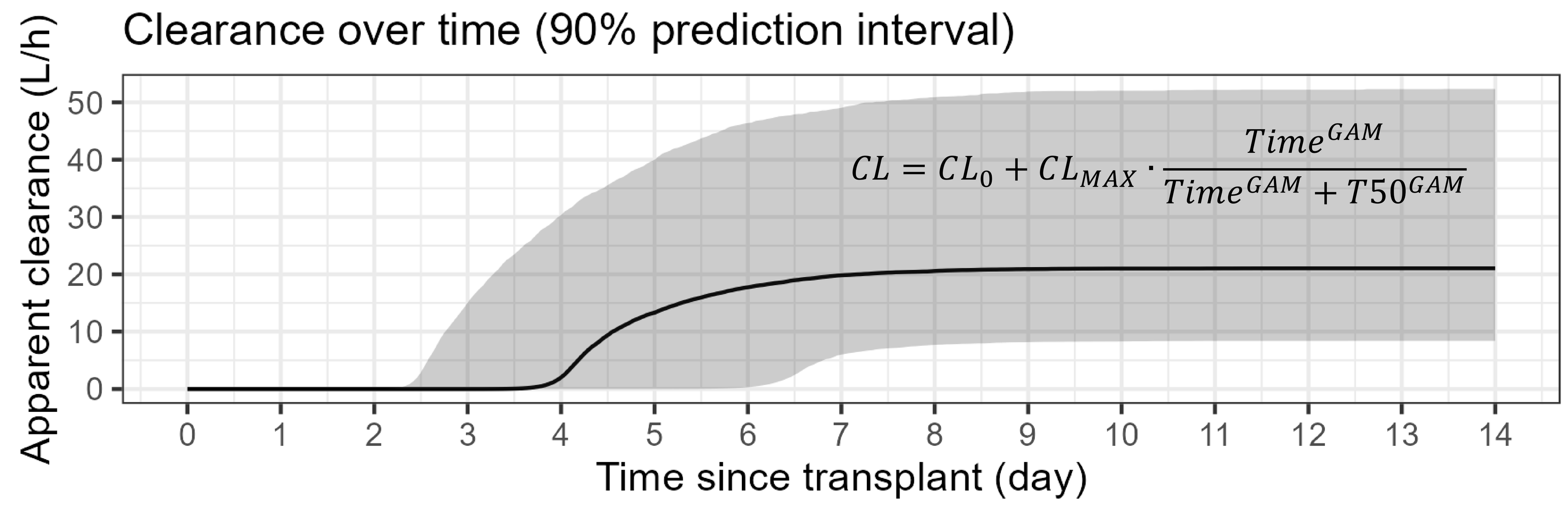


More info on how model-predictive control (MPC) works:

RESULTS

Modelling

A **one-compartment model** with **time-varying** (apparent) **clearance** provided the best fit to the tacrolimus data.



CL0 and CLmax were not separately identifiable and CL0 was fixed to a small number. The significant covariates retained were body weight, age, formulation, **bilirubin** and **triazoles** comedication.

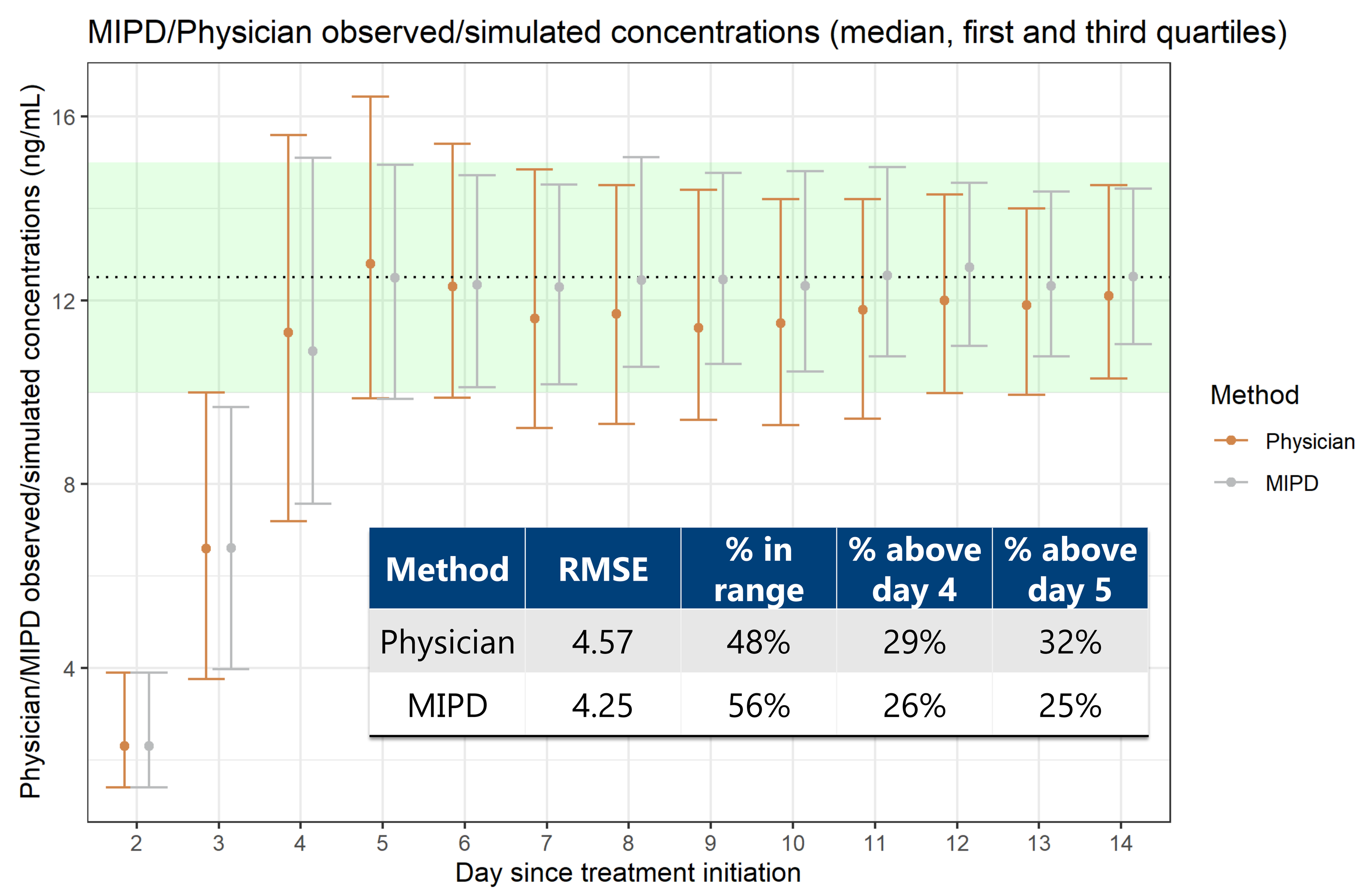
Predictive performance

Models including the time-varying clearance outperformed the base model (RMSE=3.84). The **reduced model** (no bilirubin measurement, RMSE=3.62) performed almost as well as the **full-covariate model** (RMSE=3.60) and was deemed the most convenient model to use in practice.

Dose adaptations

Simulations, based on the retrospective data and the reduced model, identified the following **ideal parameters** for the MIPD algorithm:

- Ideal time-to-target (TTT) of 36 hours
- Target threshold of 12.5 ng/mL
- Maximum allowed BID dose of 9 or 10 mg
- Maximum fold-increase of 1.5



Method	RMSE	% in range	% above day 4	% above day 5
Physician	4.57	48%	29%	32%
MIPD	4.25	56%	26%	25%

CONCLUSION

A one-compartment PK model with time-varying apparent clearance and body weight, age, formulation, bilirubin and co-medication with triazole antifungals provided a good fit to the tacrolimus concentration data. The **MIPD** algorithm potentially **increases the percentage of patients** with tacrolimus levels within the therapeutic range from day 4 onwards by approx. 48% (current practice) to 56%, while reducing the percentage above the therapeutic range from respectively 29% to 26% and 32% to 25% at day 4 and day 5, the 'over-shooting' days.

REFERENCES

[1] Kirubakaran, R et al. Clin Pharmacokinet (2020), 59(11): p. 1357-1392.
[2] Faelens, R. et al. CPT:PSP (2022), 11(3): p. 348-361.
[3] https://github.com/tdmore-dev/tdmore (original repository)
[4] https://www.page-meeting.org/pdf_assets/3300-2019_reworked.pdf
[5] Faelens, R., Tdmore: In silico evaluation of precision dosing. (2021)
[6] https://github.com/Calvagone/tdmore (updated repository)