Dose rationale and metrics of target exposure for mycophenolate and tacrolimus in paediatric patients undergoing solid organ transplantation

Pietro Laddomada[1] | Alessandro Di Deo[1] | Bianca Maria Goffredo[2] | Sara Cairoli[2] | Raffaele Simeoli[2] | Oscar Della Pasqua[1]

[1] Clinical Pharmacology & Therapeutics Group, University College London, United Kingdom

[2] Bambino Gesù Children's Hospital IRCCS, Rome, Italy

INTRODUCTION

Tacrolimus (TAC) is often prescribed often in combination with mycophenolic acid (MPA) to patients who undergo solid organ transplantation (SOT)[1]. Despite its efficacy, TAC has a narrow therapeutic range (C_{trough} 5-15 ng/mL), however dose adjustment recommendations based on therapeutic drug monitoring (TDM) do not consider the effect of combination therapy with MPA (target C_{trough} 1-3.5 mg/L). This practice in TDM has persisted despite the use of immunosuppressant combinations, making it challenging to establish the adequate exposure range.

OBJECTIVES

1. Assess the effect of demographic and clinical factors on the pharmacokinetic disposition of TAC in paediatric patients undergoing SOT.
2. Revisit the therapeutic range for TAC and MPA when used in combination.
3. Explore the feasibility of a model-based approach for dose adjustment to reduce TAC C_{trough} fluctuations, considering the concurrent levels of MPA and intraindividual variability in the predicted exposure profile over time.

METHODS

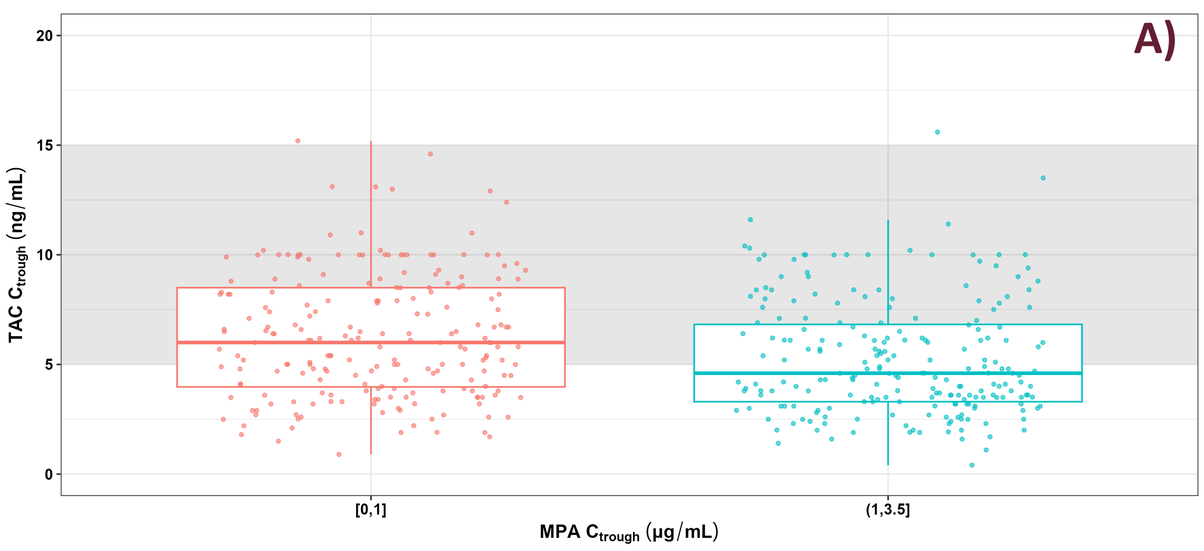
This was a retrospective, single-centre, observational study in paediatric and adult SOT (N=96, *Table 1*). Sparse TDM data for both TAC and MPA were used in conjunction with clinical and demographic data collected at different follow-up visits. A nonlinear mixed effects modelling approach was implemented using prior parameter distributions from pharmacokinetic models for TAC[6,7] and MPA. C_{trough} was chosen as a metric of interest, and simulation scenarios were evaluated including regimens for both drugs.

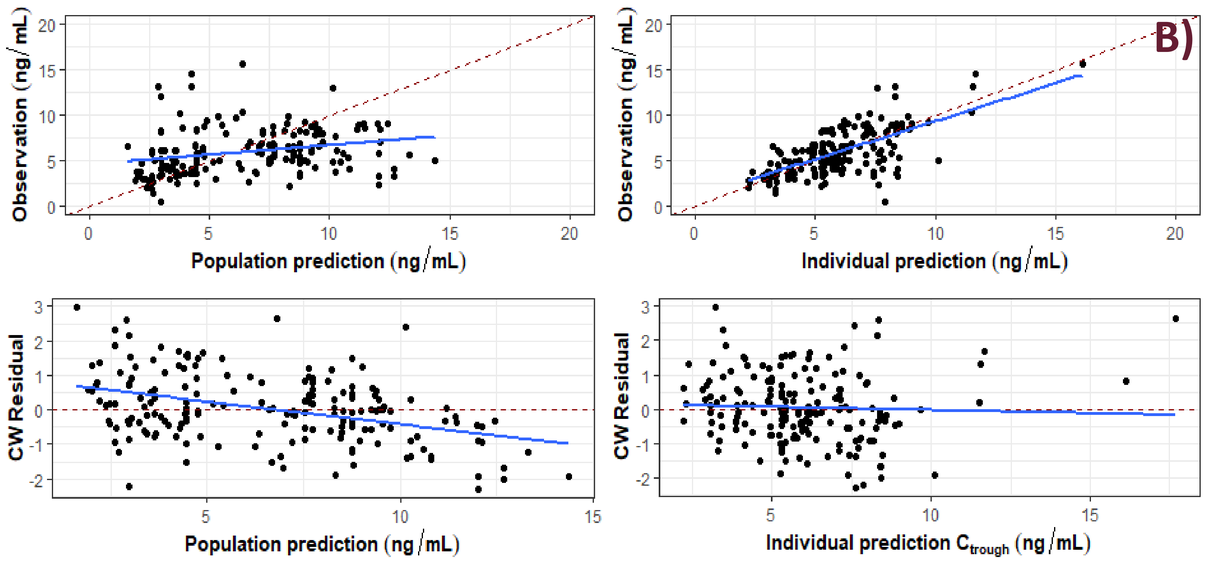
A model-based algorithm was subsequently tested for a more effective dose-adjustment.

Baseline Characteristics	Mean (min-max)	Median (IQR)
Age [y]	7.2 (0.8-17.6)	6.45 (2.3-12.1)
Days after transplant	676 (8-2702)	227 (109-1074)
Weight [kg]	24.6 (6.8-55.0)	19.5 (13.6-39.0)
BSA [m²]	0.9 (0.3-1.5)	0.8 (0.6-1.3)
BMI [kg/m²]	17.3 (0.2-32.5)	17.3 (15.0-19.3)
Creatinine [mg/dL]	0.51 (0.12-1.85)	0.41 (0.26-0.67)
AST [U/L]	55 (9-804)	34 (26-49)
ALT [U/L]	67 (7-716)	37 (23-65)

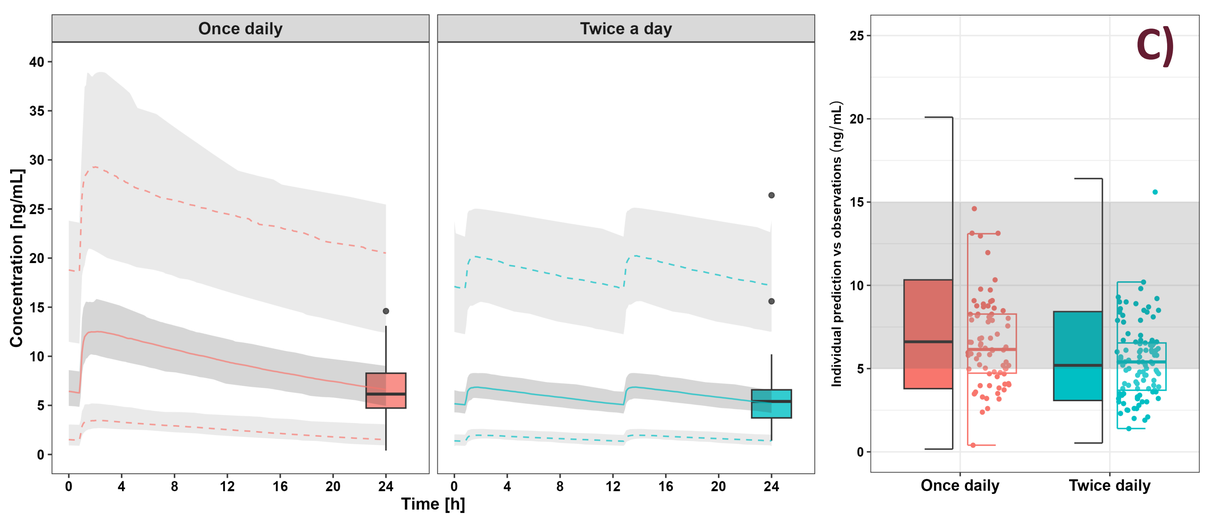
Table 1. *Clinical and demographic baseline characteristics.*

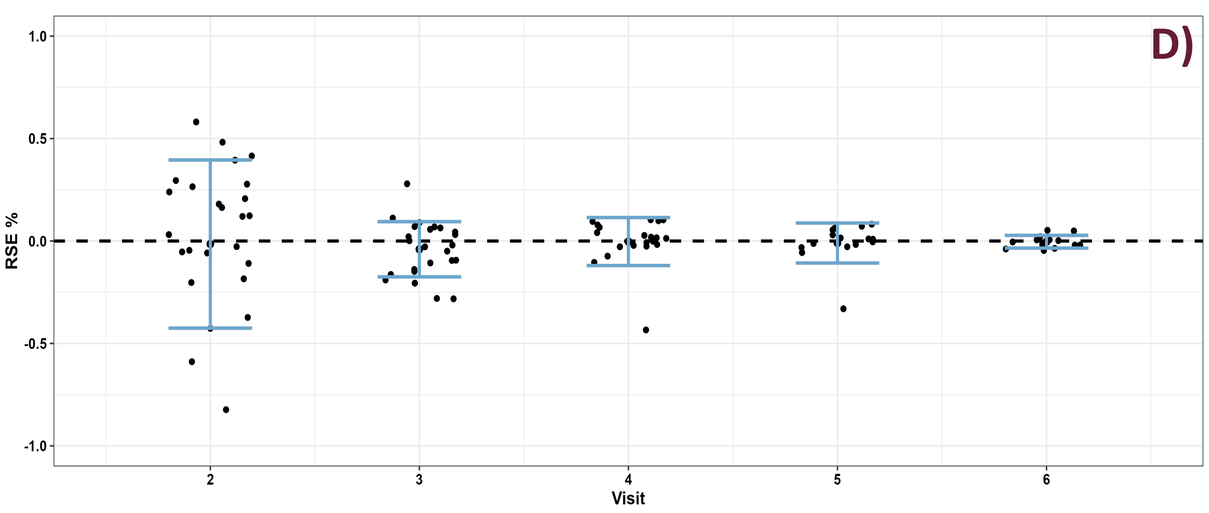
RESULTS





Exploratory analysis revealed TAC under-exposure (IQR 3.2-6.1 ng/mL) when MPA C_{trough} is in the therapeutic range *(Figure A)*. Yet, no organ rejection was recorded for any patients. The pharmacokinetics of TAC and MPA was described by one- and two-compartment models, respectively. Inclusion of body weight and dose-dependent bioavailability were found to be significant covariates for TAC, despite considerable IIV and IOV in disposition properties *(Figure B)*.





The VPC shows that the median values and the dispersion of the data appear to be well captured by the model *(Figure C)*. In addition, as the number of visits increases, the model improves performance in predicting patients TAC C_{trough} *(Figure D)*.

CONCLUSION

In contrast to empirical dose adjustment, based on a predetermined mg/kg dosing regimen, the utilization of a model-based dosing algorithm for TAC ensures the integration of the effect of baseline covariates that are currently disregarded. Moreover, the proposed approach allows the accurate prediction of TAC C_{trough} , thereby ensuring tailored interventions in a rigorous manner. Whilst a prospective evaluation of the performance of the proposed dosing algorithm has been planned, these results indicate a significant reduction in the proportion of patients who are under/overexposed to TAC when used in combination with MPA.

1. *J. R. Scalea, S. T. Levi, W. Ally, and K. L. Brayman, "Tacrolimus for the prevention and treatment of rejection of solid organ transplants," 2015, doi: 10.1586/1744666X.2016.1123093.* ***2.*** *P. Lancia, E. Jacqz-Aigrain, and W. Zhao, "Choosing the right dose of tacrolimus", doi: 10.1136/archdischild-2013-305888.* ***3.*** *M. Brunet et al., "Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report," 2019. [Online].* ***4.*** *P. E. Wallemacq and R. K. Verbeeck, "Comparative Clinical Pharmacokinetics of Tacrolimus in Paediatric and Adult Patients".* ***5.*** *A. Prytuła and T. Van Gelder, "Clinical aspects of tacrolimus use in paediatric renal transplant recipients", doi: 10.1007/s00467-018-3892-8.* ***6.*** *W. Zhao et al., "Population pharmacokinetics and pharmacogenetics of once daily prolonged-release formulation of tacrolimus in pediatric and adolescent kidney transplant recipients," Eur J Clin Pharmacol, vol. 69, no. 2, pp. 189–195, Feb. 2013, doi: 10.1007/s00228-012-1330-6.* ***7.*** *A. Di Deo et al. "A model-based algorithm for mycophenolate dose adjustment in paediatric transplantation patients", Clinical Pharmacology Report, Clinical Pharmacology & Therapeutics, UCL,[Unpublished].*

Pietro Laddomada p.laddomada@ucl.ac.uk