Application of PBPK modelling for prediction of tacrolimus exposure in CYP3A combined genotype groups (CYP3A4*22 and/or CYP3A5*3) and a renal transplant population

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Aim

To assess the impact of CYP3A genotypes on tacrolimus clearance in a renal transplant population using PBPK Modelling.

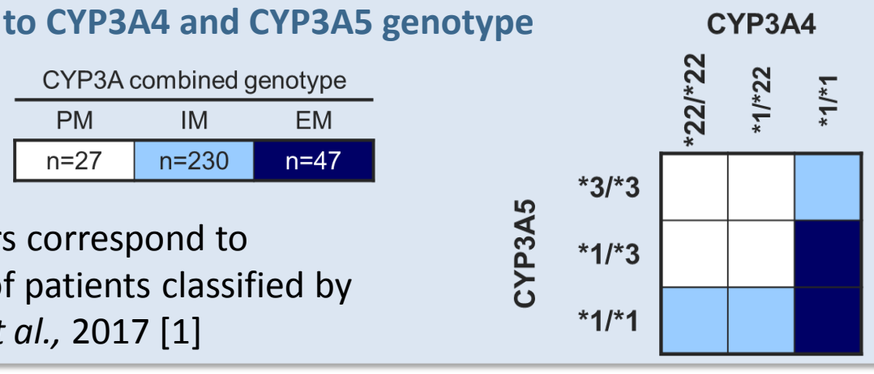
Background

Identified SNPs do not fully explain huge variability in drug metabolism by CYP3A4 and CYP3A5. Tacrolimus (metabolized by CYP3A4/CYP3A5) is subject to large variability in exposure, narrow therapeutic index and potential DDIs. Population PK models show impact of CYP3A4*22 and CYP3A5*3 on tacrolimus CL_{PO} in renal transplant patients [1,2].

Methods

Prior metabolic, protein binding and physicochemical data were collated from literature and incorporated into a minimal PBPK model with single additional compartment (sac) within the Simcyp Simulator (Version 17). fu and Vsac were optimized to reflect the observed plasma concentration-time profile of tacrolimus in renal transplant patients. Retrograde Vmax inputs were required to recover observed CL_{PO}.

Figure 1. Classification of individual patients as CYP3A EM, IM or PM according to CYP3A4 and CYP3A5 genotype



n numbers correspond to number of patients classified by Andreu *et al.,* 2017 [1]

Liver and intestinal CYP3A4 and CYP3A5 protein abundances were reduced to reflect the ratio of tacrolimus CL_{PO} *in vivo* [1] for IMs and PMs to EMs (Table 1).

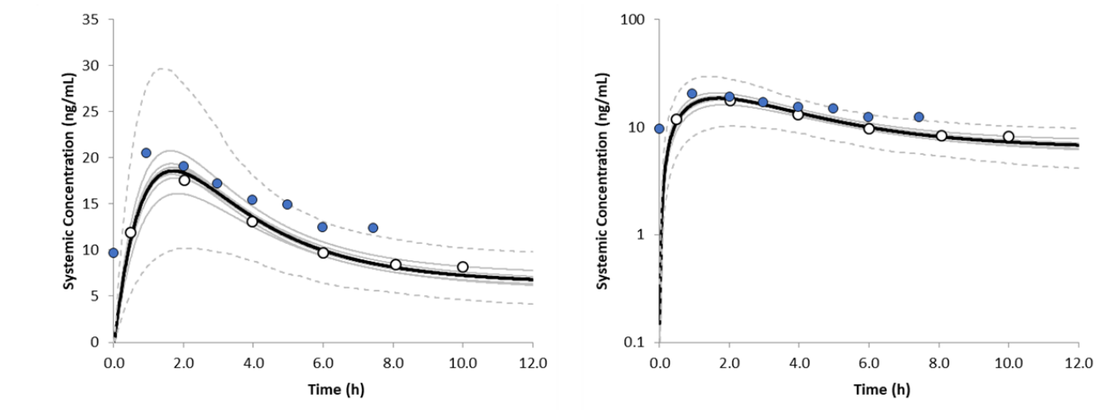
Table 1. Liver and intestinal CYP3A4 and CYP3A5 protein abundances (pmol per mg microsomal protein) input in CYP3A EM, IM and PM simulations (Model 1)

	CYP3A4 abundance		CYP3A5 abundance	
	Liver	Gut	Liver	Gut
EM	137	66.2	115	24.6
IM	84	40	57.5	12.3
PM	61	29	0	0

Results

PBPK Model Verification 1 - Simulated mean Cmax and AUC were within 20% of the observed values (Fig. 1) [1,2]

Figure 2. Simulated and observed plasma concentration-time profile of tacrolimus after a single 5 mg oral dose

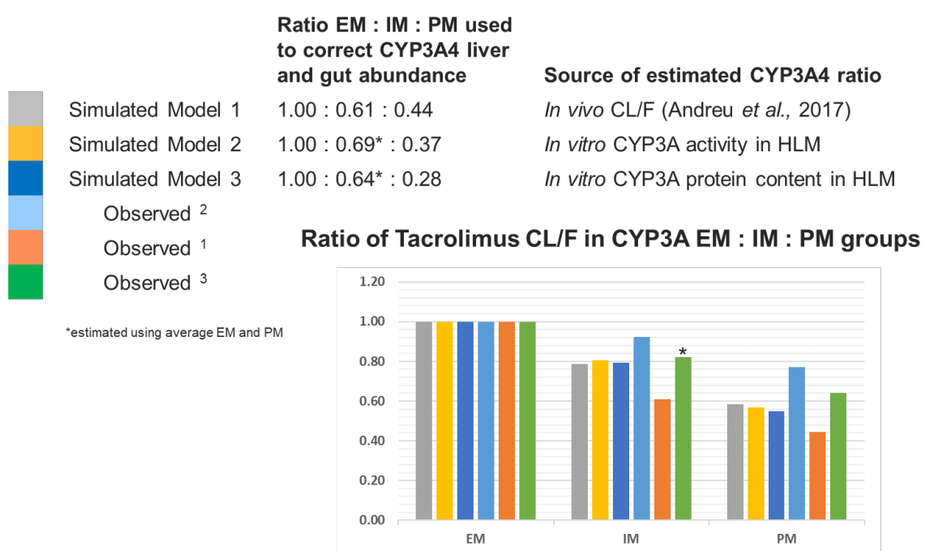


Simulated (black line) and observed (data points) mean plasma concentration-time profiles of tacrolimus in a global renal transplant population (CYP3A EM, IM and PM) after a single oral dose of 5 mg (10 trials of 30 subjects, 18-65 yrs, 50% female). The open (n=304) and blue (n=101) circles are median observed data [1,2]. The grey lines represent the predictions from individual trials and the dashed lines the 5th and 95th percentiles around the simulated mean.

Results (con't)

PBPK Model Verification 2 - Tacrolimus clinical CL_{PO} data in renal transplant populations were variable. The developed model allowed recovery of ratios of CL_{PO} for CYP3A IM and PM renal transplant patients : EM within the range seen in clinical studies (Fig. 2)

Figure 2. Simulated and Observed Ratio of Tacrolimus CL_{PO} in CYP3A EM : IM : PM groups of renal transplant patients



PBPK Model Application - A weak-to-moderate interaction was observed in simulations where tacrolimus (single 5mg oral day 6) was co-administered with ketoconazole (200mg qd 7 days). Simulated mean blood AUC ratio was 1.58 (range 1.25-2.41), 1.31 (1.08-1.73) and 1.14 (0.99-2.52) for CYP3A EMs, IMs and PMs, respectively.

Conclusions

- Tacrolimus clinical data in renal transplant populations were variable.
- The developed PBPK model allowed recovery of:
  - plasma concentration-time profile for tacrolimus after a single 5 mg dose in renal transplant patients
  - ratios of CL_{PO} for CYP3A EM : IM : PM renal transplant patients (within the range seen in clinical studies)
- The developed model also allowed investigation of a theoretical DDI with ketoconazole (clinical data were lacking).
- To our knowledge, this is the first time a PBPK model has been developed specifically to look at the impact of CYP3A4*22 and CYP3A5*3 on the exposure of a CYP3A substrate
- The PBPK model could be further refined with more data in order to:
  - Assess impact of CYP3A4*22 / CYP3A5*3 for other CYP3A substrates
  - Help understand CL_{PO} variability in organ transplant patients
  - Investigate changes in exposure as a result of additional DDIs

References

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