PREDICTING THE IMPACT OF CYP3A5 POLYMORPHISM ON TACROLIMUS TROUGH CONCENTRATIONS IN BLACK AFRICAN TRANSPLANT RECIPIENTS

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BACKGROUND

- Tacrolimus (TAC) is an immunosuppressive agent widely used to prevent acute rejection following solid-organ transplantation. TAC has a narrow therapeutic index and exhibits considerable interpatient variability in pharmacokinetics (PK) (1).
- Maintaining therapeutic trough levels of TAC is essential, particularly during the initial period after transplantation to minimise the risk of organ rejection. Efficacy is increased when the trough (12-h post-dose) whole blood concentrations > 10 ng/mL and toxicity increases at concentrations > 20 ng/mL (1).
- TAC is primarily metabolised by CYP3A4 and CYP3A5 (2). Clinical studies observed that there was a link between the CYP3A5 genotype and the variable PK of TAC in different ethnic populations (1, 3, 4). Transplant recipients who express functional CYP3A5 (CYP3A5*1) require significantly higher TAC doses to achieve target levels compared to patients who do not express CYP3A5 (CYP3A5∗3 allele carriers) (1, 3).
- It is evident that the genotypes containing the CYP3A5*1 allele (heterozygotes or homozygotes) is present in 85% of black individuals but only ~15% of white individuals (1).
- Considering the significant impact of both ethnic and genetic factors on the PK of TAC, population based Physiologically Based Pharmacokinetic (POP-PBPK) modelling approaches could be useful to explain the inter-individual variability in PK, and to optimise the dose for TAC in different ethnic groups.

OBJECTIVES

- The aim of this study was to investigate the impact of polymorphic expression of CYP3A5 on the PK of TAC in black South African (SA) subjects compared to North European Caucasian (NEC) individuals. A clinical case study conducted in renal transplant recipients from Caucasian and African ethnic groups (3) was simulated.

METHODS

- The Simcyp Population-Based Simulator (version 15.1, Sheffield, UK) was used to simulate the time course of TAC in blood following an initial oral dose of 0.1 mg/kg.
- A virtual SA population considering population-specific demographics, physiology and CYP abundances, and the default NEC population (Simcyp, V15.1, UK) have been used to predict the trough blood concentrations of TAC in renal transplant recipients.
- The differences in CYP3A5 phenotype frequencies and comparison of hepatic CYP3A5 abundances in black SA and NEC populations are shown in Figure 1.

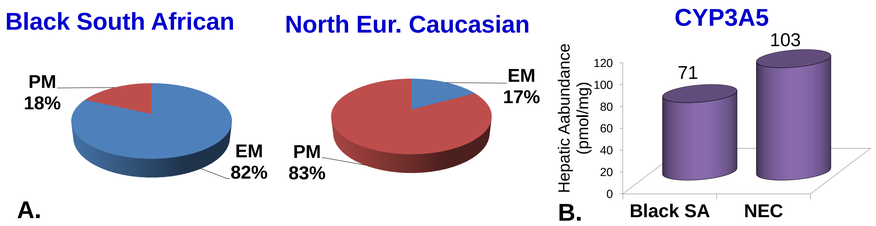
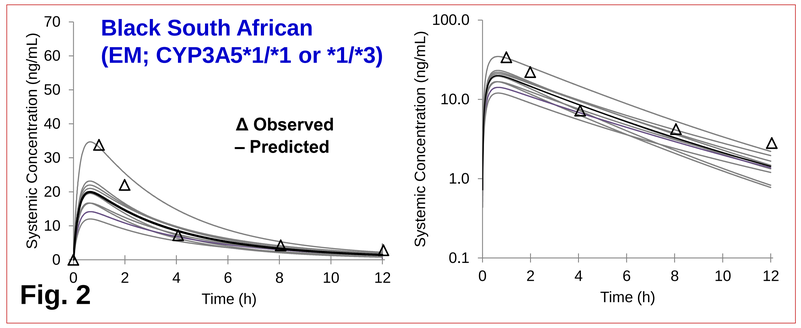


Figure 1: Differences in CYP3A5 phenotype frequency (A) and hepatic CYP 3A5 abundances in subjects who express the enzyme (B) between black SA and NEC populations. *EM – Extensive Metaboliser; PM- Poor Metaboliser.*

- Trial designs matched published clinical trials (3) in terms of initial dose, ethnicity (where possible), CYP3A5 phenotype, age, gender and number of subjects.
- There were no details available on the ethnicity of individuals with CYP3A5*1/*3 or CYP3A5*3/*3 carriers in the clinical study (3) and these subjects were assumed to be from black SA and NEC populations, respectively, in the simulations.

RESULTS

- Following an oral dose of 0.1 mg/kg, the predicted and observed (3) blood concentration-time profiles of TAC in black SA population and NEC populations are shown in Figures 2 & 3, respectively. There were significantly lower systemic exposure and trough blood levels observed for TAC in black SA subjects compared to NEC population (Table 1).
- The predicted median area under the time *versus* blood concentration curve ($AUC_{0\text{-}12h}$) and the trough blood concentrations (at 12 h post-dose) were markedly decreased (~ 66% and ~88%, respectively) in black SA subjects compared to those observed in NEC population. Similar trend was seen in the observed data (Figures 2-3; Table 1).
- Although the average predicted data is reasonably comparable with observed data in these populations (Figures 2-3; Table 1), there was higher inter-individual variability observed in the predicted data compared to clinical data (3).



Figures 2-3 : Predicted and observed TAC blood concentration-time profiles in black SA (Fig. 2) and NEC transplant recipients (Fig. 3).
Grey lines represent mean values for different individual trials (n = 9 -10); the black line indicates the overall mean for the virtual population (n = 90 or 100); open triangles indicate mean observed values in each population. EM – Extensive Metaboliser; PM- Poor Metaboliser.

Table 1: Predicted (median; 5th-95th percentile) and observed (median (range)) TAC pharmacokinetics in black SA and NEC transplant recipients.

	Black South African (EM; CYP3A5*1/*1 or *1/*3)		North Eur. Caucasian (PM; CYP3A5*3/*3)	
	Predicted	**Observed**	**Predicted**	**Observed**
TAC trough levels in blood at 12h post-dose (ng/mL)	0.9 (0.1-4.4)	2.5 (2.0–4.4)	7.8 (1.3-25.1)	7.5 (5.5–20.2)
$AUC_{0\text{-}12h}$ (ng/mL*h)	65.6 (18.1-209.2)	100.2 (64.4–224.4)	192.8 (56.5-618.1)	197.1 (110.8–323.6)

- Besides CYP3A5 polymorphism, other potential contributing factors such as polymorphic expression of drug transporters and the role of elevated levels of cytokines on the disposition of TAC (5) could be contributing to the interindividual variability in TAC PK in transplant recipients and these aspects need to be investigated for more mechanistic insights in to these ethnic differences.
- While these results are encouraging in describing the impact of CYP3A5 polymorphism on the variability of TAC PK, under-prediction of average trough levels and exposure to TAC in SA population, and high variability in the predicted data compared to observed data in both ethnic groups warrant further investigation.

CONCLUSION

- Overall, these simulations demonstrated the contribution of CYP3A5 polymorphism in the observed variability in TAC pharmacokinetics, and also highlight the potential application of POP-PBPK modelling for optimising drug dosage of TAC in different ethnic groups.

REFERENCES

1. Barry A and Levine M. Ther Drug Monit. 32(6):708, 2010.
2. Dai Y *et al.,* Drug Metab Dispos. 34(5):836, 2006.
3. Haufroid V *et al.,* Am J Transplant. 6(11):2706, 2006.
4. MacPhee IAM *et al.,* Transplantation. 74,1486, 2002.
5. Higginsa RSD and Fishmanb JA, American Journal of Transplantation. 6: 2556, 2006.