The Usefulness of Combining Clinical Therapeutic Drug Monitoring Data with Bottom-up System Data to Understand the Effect of Renal Impairment on the Non-renal Clearance of Drugs: Tacrolimus as a Drug Example

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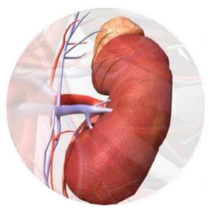
Introduction

- The impact of chronic kidney disease (CKD) on the liver's ability to metabolise CYP3A substrates is not well established[1].



- Hypotheses are:
  - ✓ Uraemic toxins can downregulate the expression of many CYP enzymes[2] and CYP3A in particular >> ↓ $CL_{int,H,\ unbound}$ (Not yet confirmed!)
  - ✓ Changes in protein binding in CKD[3] >> ↑ CL,h
- Tacrolimus has been chosen as CYP3A substrate in this study to understand the effect of CKD on hepatic CLint. It is also an immunosuppressant that is commonly used for renal transplantation[4].

Aim

The aims of this study were

1) to assess the value of combining **the top-down** and **bottom-up** approaches in order to develop a model that could recover the $CL_{int,H,unbound}$ from the C_{trough} of tacrolimus in blood, while accounting for other sources of *a priori* identified inter-patient variability.

2) to investigating the impact of CKD on the non-renal elimination of tacrolimus in renal transplant patients.

Methods

A- Patients and Clinical Data

- ✓ Data were obtained from Salford Royal Hospital.
- ✓ Data gathered from electronic records for 40 patients included demographics, co-morbidities, and concomitant medications (Fig.1).
- ✓ Blood results included serial:

serum liver function tests, haematocrit, albumin, eGFR calculated using CKD-EPI equation, and Cb_{trough} Tacrolimus levels

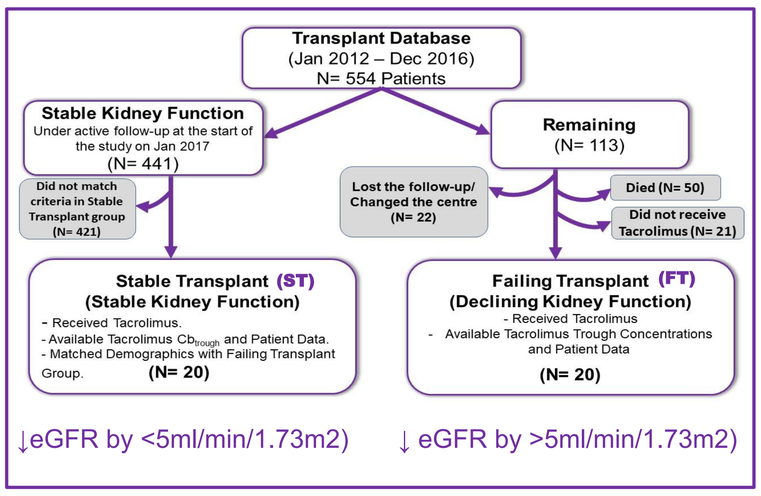
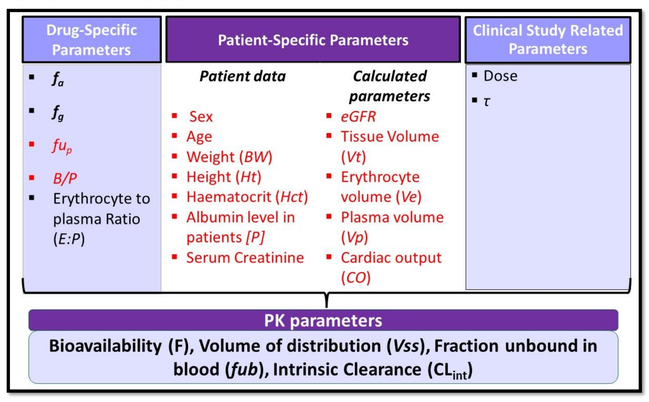


Fig. 1: Flowchart showing stepwise selection of patient data to be included in the study.

B- Model Structure and Parameters

- A single compartment model was used to describe the Cb_{trough} (Fig. 2).
- Blood binding (B/P, *fub)*, distribution volume (*Vss,b*), hepatic flow rate (Q_h), and renal clearance (CLr,b) have been calculated for every patient using clinical and demographic data to allow the estimation of $CL_{int,H,unbound}$ (Fig. 2).
- Other parameters such as *fa, fg*, and *E:P* were fixed for all patients to 1, 0.14, and 77.4 based on literature values [5-7].



$$Cb_{trough} = \frac{Dose \times F}{V_{SS,b}} \times \frac{e^{-k_{el} \times \tau}}{1 - e^{-k_{el} \times \tau}}$$

$F = f_a \times f_g \times f_h$

$k_{el} = (CL_{r,b} + CL_{h,b})/V_{SS,b}$

$V_{SS,b} = (Vp + (Ve \times E{:}P) + (\sum_t Vt \times Pt{:}p)/B/P$

$fh = 1-(CLh,b/Qh)$

$CL_{r,b} = fub \times eGFR$

$B/P = E{:}P \times Hct + (1 - Hct)$

$fub = fu_p / B/P$

$CL_{h,b} = Q_h \times fub \times CL_{int}/(Q_h + fub \times CL_{int})$

$Q_h = 0.227 \times CO$

$CO = (187 \times BW^{0.81})$

$fu_p = 1/(1 + [P]/[P]_{Healthy} \times ((1 - fu_{p,healthy}))/(fu_{p,healthy}))$

$V_p = V_b \times (1-Hct)$ $V_b\ (male) = 0.3669 \times Height\text{^}3 + 0.03219 \times BW + 0.6041$

$V_e = V_b \times Hct$ $V_b\ (female) = 0.3561 \times Height\text{^}3 + 0.03308 \times BW + 0.1833$

Fig. 2: Input and output parameters included into the model. Parameters in black font are fixed while parameters in red font varied among the patients.

- The model with the above parameters were introduced into Monolix® to estimate the population $CL_{int,H,unbound}$ using the maximum likelihood and the stochastic approximation of expectation and the maximization (SAEM) method.
- The $CL_{int,H,unbound}$ values and the observations were assumed to follow a log-normal distribution using the exponential model to describe between subject (i) and occasion (k) variability (BSA and IOV, respectively).

$$CL_{int_{i,k}} = CL_{int_{pop}} \times e^{\eta CL_{int,i} + kCL_{int},i}$$

- Kidney function related parameters such as eGFR and the stage of CKD were introduced as covariates in the model (Fig. 3).

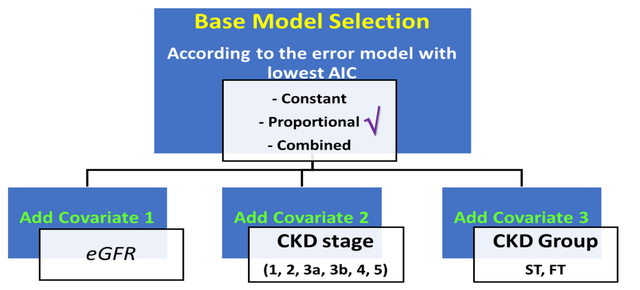


Fig. 3: Stepwise model development starting from base model followed by parallel addition and assessment of covariates.

Results

- The goodness-of-fit plots for the base model showed that the individual predictions were evenly spread around the unity line. Conditional weighted residuals were randomly scattered, indicating adequate precision and acceptable bias (Fig. 4).
- The hepatic unbound clearance was dropping slowly moving from normal kidney function to end-stage renal disease to reach a maximum drop by 37% (Fig. 5A).
- No difference statistically between the $CL_{int,H,unbound}$ for patients who failed transplantation and those with stable transplanted kidney function (Fig. 5B).
- There was a significant (p=0.0005) positive correlation (r= 0.21) between eGFR and tacrolimus $CL_{int,H,unbound}$ (Fig. 5C).

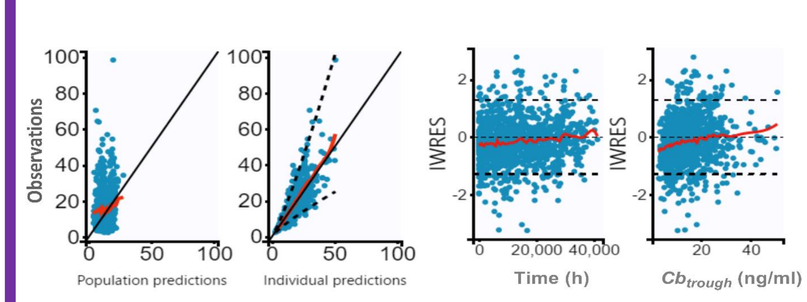


Fig. 4: Goodness of fit plots for the base model. Red line: Spline, Dashed: 90% CI, Solid black: Unity line, Blue dots: Observed data.

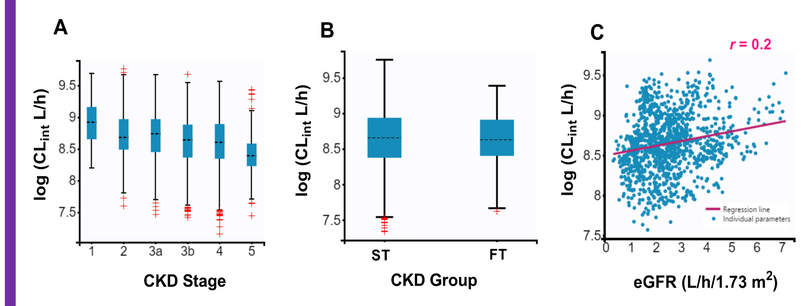


Fig. 5: Correlations between tacrolimus intrinsic clearance (CLint) and the different covariates introduced to the basic model. (**A**) Correlation with the stage of chronic kidney disease (CKD), (**B**) Correlation with CKD group; Stable Transplant (ST) or Failed transplant (FT), and (**C**) Correlation with estimated glomerular filtration rate (eGFR).

Conclusion

- ✓ The drop in $CL_{int,H,unbound}$ with renal disease can be important clinically in adjusting the dose of hepatically CYP3A eliminated drugs in CKD patients especially those with narrow therapeutic window and/or not frequently monitored.
- ✓ The strategy of bottom-up individualization of pharmacokinetic parameters using previously defined system components can assist in the determination of unknown parameters with higher certainty instead of depending only on clinical datasets.

References

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