GENDER PHARMACOKINETICS ANALYSIS OF TACROLIMUS IN KIDNEY TRANSPLANT PATIENTS

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Objectives

- Monitoring of tacrolimus blood concent-rations is of utmost importance in the management of renal transplant patients because of its the narrow therapeutic range and highly variable pharmacokinetics.
- Adverse effects depend of concentration and total body exposure of tacrolimus.
- As accurate tacrolimus blood concentra- tion monitoring is necessary in the early post-transplant days, there is a need to find a new predictable method for routine clinical use.

- **THE AIM** of this study was to detect systemic exposure to tacrolimus after first oral dose and in steady state in a group of men and women, using $AUC_{0\text{-}12}$ as a predictor of tacrolimus exposure.
- The secondary objective was to find the best sampling time to predict the exposure of tacrolimus in kidney transplant patients.

Methods

Our study was conducted on 24 kidney transplant recipients (13 men/11 women) on quaternary immunosuppressive therapy. [methylprednisolone 0.5 g / day, i.v. and mycophenolate mofetil (1.5 g / day, per oral) for 3 days and basiliximab (20 mg, i.v.) on the first and the fourth day] The first tacrolimus oral dose (0.05 mg/kg) was given on day 5 post-transplant. Blood concentrations were measured by microparticle enzyme immunoassay method. AUC ($AUC_{0\text{-}12}$) for each patient was calculated from a plot of tacrolimus concentration versus time from 0 to 12 hour after the first dose and in steady state. Associations between each sampling time point of concentrations and 12 hours after the administration AUC ($AUC_{0\text{-}12}$) were evaluated by Pearson correlation coefficients. Abbreviated sampling equations were derived by multiple stepwise regression analyses.

Results

- $AUC_{0\text{-}12}$ showed remarkable interindividual variations after the first oral Tac dose. Interindividual variation was lower in a steady state.
- There is statistical difference between men and women after first oral dose ($p<0.01$), but this difference is lost in the steady state.
- The most important time point influencing $AUC_{0\text{-}12}$ was the concentration of tacrolimus measured 4 hours after administration (C_4), whereas in steady state the most important time point were the concentrations 8 (C_8).
- In women recipients C_2 seems to be indicator of total body exposure to tacrolimus after first oral dose and this is also confirmed in a steady state.
- The three-point sampling method is needed for calculating AUC after first oral dose in man, whereas in the steady state, concentration.
- C_8 seems to be a good indicator of abbreviated AUC for a tacrolimus monitoring strategy in men.

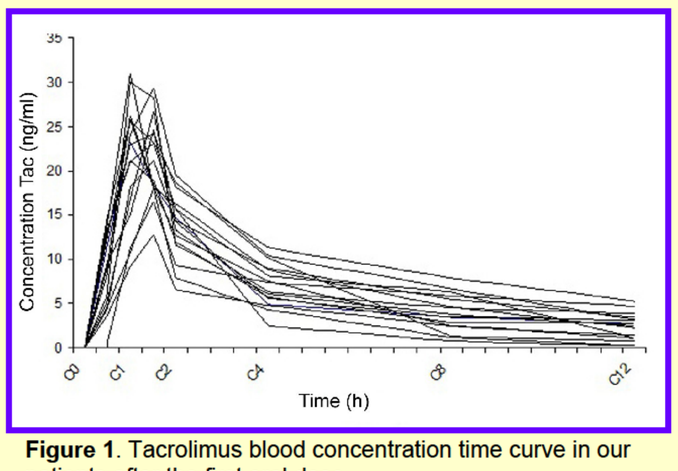

Figure 1. Tacrolimus blood concentration time curve in our patients after the first oral dose

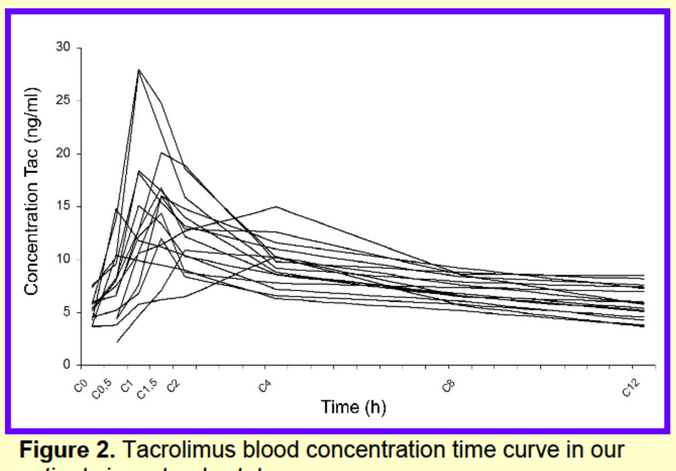

Figure 2. Tacrolimus blood concentration time curve in our patinets in a steady state

Table 1. Tacrolimus pharmacokinetic parameters in patients after the first oral dose and steady state

Female			
$AUC_{0\text{-}12}$ (ngh/ml)		$AUC^{ss}_{0\text{-}12}$ (ngh/ml)	
AUC ±SD	60,50±20,8	107,72±23,44	AUC^{ss}±SD
Min	48,25	73,45	Min^{ss}
Max	78,97	129,35	Max^{ss}
Male			
$AUC_{0\text{-}12}$ (ngh/ml)		$AUC^{ss}_{0\text{-}12}$ (ngh/ml)	
AUC ±SD	93,80±19,1	101,26±16,91	AUC^{ss}±SD
Min	75,95	74,7	Min^{ss}
Max	128,62	125,13	Max^{ss}

$AUC_{0\text{-}12}$ - abbreviated 12- hour area under the curve after first dose
$AUC^{ss}_{0\text{-}12}$- abbreviated 12-hour area under curve in a steady state

Table 2. Regression Equations of the relationship between predicted area under curve (AUCp) and actual 12-hr AUC and the associated coefficient of multiple regression values in females and man

Result of regression analysis after first dose in females	r	r^2	Result of regression analysis after first dose in man	r	r^2
$AUC_p = 22{,}879 + 3{,}453 * C_2$	0,911	0,830	$AUC_p = -2{,}406 + 7{,}351 * C_4 + 1{,}209 * C_1 + 4{,}043 * C_{12}$	0,977	0,954
Result of regression analysis in a steady state	r	r^2	Result of regression analysis in a steady state	r	r^2
$AUC_p = 38{,}163 + 5{,}373 * C_2^{ss}$	0,913	0,834	$AUCp = -4{,}442 + 14{,}602 * C_8^{ss}$	0,926	0,858
independent variables - C_2, C_2^{ss}, C_0^{ss}		*r - correlation coefficient*	*independent variables - $C_4, C_1, C_{12}, C_2, C_8, C_8^{ss}$*		
dependent variables - AUCp		*r - determination coefficient*	*dependent variables - AUC_p*		

Conclusions

- Our results show significant tacrolimus pharmacokinetics differences between men and women.
- Also, our research shows the need for gender dependent choice indicator of total body exposure to tacrolimus in kidney transplant patients.

References

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