Impact of CYP3A5 Phenotype on Tacrolimus Management after Kidney Transplant

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Objectives

- Determine if CYP3A5 extensive metabolizers require more trough measurements and dose adjustments to maintain target exposure compared to intermediate or poor metabolizers

- Determine if CYP3A5 metabolizer status affects time in therapeutic range (TTR) and time to first therapeutic level

- Determine if kidney graft outcomes vary by CYP3A5 metabolizer status

Study Population And Target Trough Concentrations

- Inclusion Criteria
  - Patients enrolled in the GEN03 GWAS study and transplanted at HCMC
  - Received de novo immunosuppression with tacrolimus-based regimen
  - At least 6 months of follow-up within the HCMC transplant clinic

- Final number included = 78 patients

- Tacrolimus trough concentrations maintained at 4-8 ng/mL and those at high risk of rejection maintained at trough of 8-12 ng/mL for 3 months followed by goal 5-10 ng/mL

Methods

Retrospective observational study using GEN03 Study Data and genotype data from GWAS chip and supplemented with chart review

Data Utilized from GEN03 Genomics Study	Data Abstracted from Chart Review
Demographics and transplant history Serum creatinine at 1, 3, and 6 months	Tacrolimus dose adjustments Tacrolimus trough measurements Total daily dose prior to trough Target trough concentration range Recommended new total daily dose, if trough out of range

CYP3A5 metabolizer diplotypes taken from GWAS chip and phenotypes created

Poor Metabolizer (PM) N = 55	Intermediate Metabolizer (IM) N = 17	Extensive Metabolizer (EM) N = 6
*3/*3, n = 53 *3/*6, n = 1 *3/*7, n = 1	*1/*3, n = 15 *1/*6, n = 1 *1/*7, n = 1	*1/*1, n = 6

Outcomes by Metabolizer Status in First 6 Months Post-Transplant

- Number of trough measurements
- Number of dose adjustments
- Tacrolimus time in therapeutic range
  - Defined using Rosendaal's method
- Time to therapeutic tacrolimus target
  - Defined as number of days from transplant to first tacrolimus level within target range
- eGFR at 6 months
  - Estimated using MDRD study equation

Statistical Analysis

- Primary outcomes are number of trough levels and dose adjustments
  - Quasi-likelihood based Poisson regression (proc genmod, SAS v9.4)
  - Covariates in the model
    - Age at transplant, gender, BMI at baseline and history of diabetes at baseline
    - Did not adjust for race, as the CYP3A5 phenotypes are highly colinear with race
    - Did not adjust for CYP inhibitors
- Secondary outcomes are time in therapeutic range and time to first therapeutic trough, eGFR
  - **Guillaume to provide name of analysis**

Results

Table 1. Baseline characteristics stratified by phenotype

	Poor Metabolizer (n = 55)	Intermediate Metabolizer (n = 17)	Extensive Metabolizer (n = 6)
% Male	54.5	64.7	83.3
Age at Tx, y (mean + SD)	50.9 (14.2)	46 (14.5)	44.5 (10.7)
BMI at Tx (mean + SD)	28 (5.9)	28.8 (5.5)	31.1 (6.2)
Cause of Kidney Disease, n (%)			
Congenital	11 (20)	1 (5.9)	0
Diabetes	12 (21.8)	2 (11.8)	1 (16.7)
Glomerular Disease	13 (23.6)	9 (52.9)	3 (50)
Hypertension	4 (7.3)	2 (11.8)	1 (16.7)
Polycystic Kidneys	8 (14.5)	1 (5.9)	0
Tubular and Interstitial	3 (5.5)	0	0
Other/Unknown	4 (7.3)	2 (11.8)	1 (16.7)
Deceased Donor, n (%)	24 (43.6)	6 (35.3)	5 (83.3)
Re-Transplant, n (%)	9 (16.4)	1 (5.9)	1 (16.7)
BPAR, n (%)	2 (3.6)	0	0
Graft Failure, n (%)	2 (3.6)	0	0

Table 2. Primary Outcomes by CYP3A5 Phenotype

	Poor Metabolizer (n = 55)	Intermediate Metabolizer (n = 17)	Extensive Metabolizer (n = 6)	P value[a]
No. of Dose Adjustments	6.1 (2.6)	7.6 (3.2)	9.5 (4.2)[b]	0.0089
No. of Trough Measurements	19.5 (3.9)	18.9 (6.0)	24 (4.3)	0.049

All values expressed as mean (SD), [a]EM compared to PM

Table 3. Secondary Outcomes by CYP3A5 Phenotype

	Poor Metabolizer N = 55	Intermediate Metabolizer N = 17	Extensive Metabolizer N = 6	P value
Time to first therapeutic trough in days, median (range)	6 (2 – 61)	5 (2 – 31)	2 (2 – 29)	TBD
Time in therapeutic range in percent, median (range)	49.7 (12.4-94)	46.1 (25.4-75.4)	48.6 (37.3-75.1)	TBD
eGFR at 6 months in mL/min/1.73m^2, mean (SD)	60.5 (20.3)	64.1 (16.7)	43.8 (13.5)	0.047

eGFR calculated using Modification of Diet in Renal Disease (MDRD) study equation

Conclusions

- EMs required 4 additional measurement compared to PMs
- EMs required 3 additional dose adjustments compared to PMs
- ADDITIONAL conclusions on TTR, time to first

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Percent of Tacrolimus Trough Measurements Within Goal by CYP3A5 Phenotype						
	Month 1 N = 465	Month 2 N = 347	Month 3 N = 279	Month 4 N = 142	Month 5 N= 98	Month 6 N = 89
Poor Metabolizer (N=55)	**0.48**	0.57	0.62	0.58	0.61	0.7
Intermediate Metabolizer (N=17)	**0.43**	0.45	0.66	0.68	0.47	0.83
Rapid Metabolizer (N=7)	**0.28**	0.55	0.58	0.91	0.42	0.71

Tacrolimus Troughs (ng/mL) in First 6 Months by CYP3A5 Phenotype

Phenotype	Month 1 N = 465	Month 2 N = 347	Month 3 N = 279	Month 4 N = 142	Month 5 N= 98	Month 6 N = 89
Poor Metabolizer (N=55)	7.9 (2 – 23.1)	8.5 (2 – 21.9)	8.3 (2.1 – 25.6)	7.5 (2 – 19.5)	6.8 (2 – 15.5)	6.5 (2.2 – 11)
Intermediate Metabolizer (N=17)	6.9 (2 – 18.6)	7.8 (2.6 – 21.9)	8.4 (4.5 – 15.4)	7.9 (3.2 – 19.3)	8.4 (3.5 – 12.3)	7.25 (4.3 – 9.1)
Rapid Metabolizer (N=7)	7 (2.1 – 15.8)	9.6 (4.9 – 23)	9.6 (6.7 – 18.6)	7.9 (5.5 – 8.7)	8.4 (5.6 – 11.6)	8.5 (5.3 – 15.6)

Month 1 is POD 0-30, Month 2 is POD 31-60, Month 3 is POD 61-90, Month 4 is POD 91-120, Month 5 is POD 121-150, Month 6 is POD 151-180

All values are expressed as median (range)

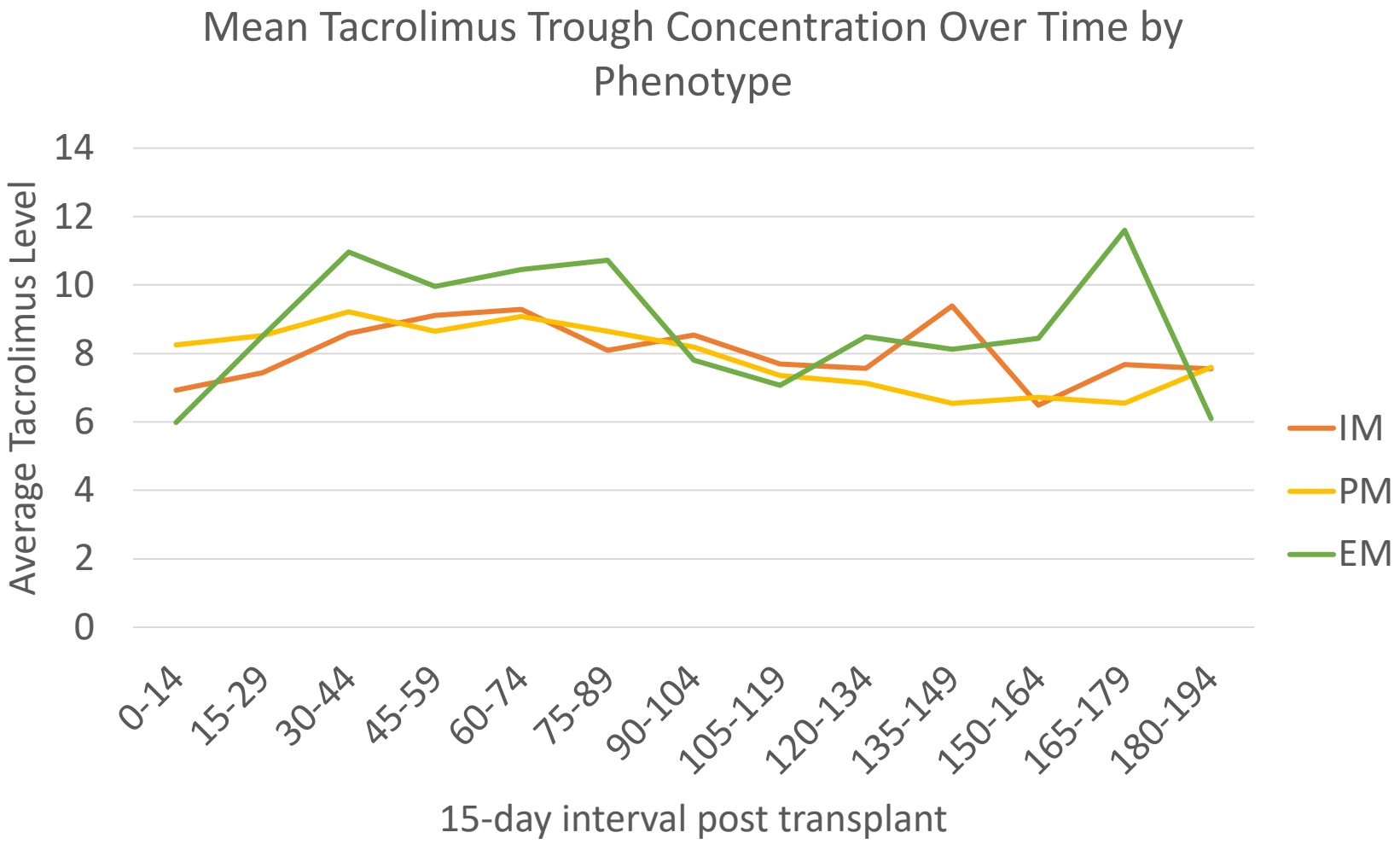
Median % Away from Target Trough

Phenotype	Month 1 N = 465	Month 2 N = 347	Month 3 N = 279	Month 4 N = 142	Month 5 N= 98	Month 6 N = 89
Poor Metabolizer (N=55)	19.2 (0.8 -138.8)	17.5 (0.8 – 173.8)	13.8 (1 – 113.8)	15.5 (1 – 95)	19.5 (1.3 – 55)	12.5 (2 – 53.3)
Intermediate Metabolizer (N=17)	28.8 (2.5 – 88.8)	25 (1.3 – 82.5)	12.8 (1.3 – 66.3)	24.4 (3 – 60.8)	16 (3.8 – 30)	5 (5-14)
Rapid Metabolizer (N=7)	32.5 (4.2 – 73.8)	15 (5 – 91.7)	16.3 (2.5 – 55)	3.8 (3.8 – 3.8)	15 (3.8 – 45)	89.7 (56 – 123.3)

Month 1 is POD 0-30, Month 2 is POD 31-60, Month 3 is POD 61-90, Month 4 is POD 91-120, Month 5 is POD 121-150, Month 6 is POD 151-180
All values are expressed as median (range) percent that tacrolimus trough concentrations were out of the target goal range

For every level that was out of the target trough range, I had excel calculate the percent out of range So the median here is the median percent out of goal range for every trough level that was not in goal. Values were taken as **absolute value** (could be below or above goal range).

Tacrolimus Levels Over Time By Phenotype



Notes from 4/20/21 Meeting – PAJ, GO

- In Time to frist therapeutic level say “Days” in header and move median (range) to bottom, and change to CYP3A5 Phenotype
- Go back and look to see how many EM patients were goal 8-12 (if any), and see what their starting dose was (weight based)
  - Add weight based starting dose (actual body weight)
- Limitation in TTR that we may have excluded actionable trough levels
- Put “p value = ?” for TTR and time to first therapeutic
- Make the point that TTR isn’t great
- Ask Tracy if all these levels were measured on the same assay
  - When did we move to mass spec?