CYP3A5 genotypes and the impact of the phenotypes on tacrolimus levels in UCSF pediatric bone marrow transplant patients

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Background:

Tacrolimus (TAC), a calcineurin inhibitor, is commonly used after bone marrow transplantation (BMT) to prevent Graft vs. Host Disease (GvHD). Despite prophylactic immunosuppression treatment, an estimated 20-80% of allogeneic BMT recipients develop GvHD, and this observation is not unique to adults. In pediatrics, the clinical use of TAC is complicated by its variable pharmacokinetics, narrow therapeutic window, and weight-based dosing. Genetic polymorphisms in the CYP3A5 gene are known to influence TAC's pharmacokinetic profile, which subsequently may impact GvHD. A meta-analysis that included 23 studies in different patient populations (renal and liver transplantation; 22 in adults, 1 in pediatrics) showed that CYP3A5-expressors not only require higher TAC doses to achieve therapeutic levels but also experience significantly higher acute rejection rates within the first four weeks of transplantation compared to non-expressors (OR: 3.27; 95% CI: 1.57–6.81). Thus, refining the initial dosing regimen to achieve and maintain therapeutic levels is imperative to improve therapeutic outcomes. This study seeks to identify genetic and non-genetic predictors that determine TAC treatment in a unique pediatric BMT patient group.

Current CPIC Guidelines:

CYP3A5 Genotype	CYP3A5 Phenotype	CPIC recommendations
**1/*1*	Extensive metabolizers	Increase dose 1.5-2 times standard dosing (NTE 0.3 mg/kg/day)
**1/*3, *1/*6, *1/*7*	Intermediate metabolizers	
**3/*3, *6/*6 , *7/*7, *3/*6, *6/*7 , *3/*7*	Poor Metabolizers	Standard dosing (typical GvHD ppx: 0.03 mg/kg/day)

Objectives:

To identify the genetic and non-genetic factors associated with TAC concentration in pediatric BMT recipients.
To determine the effect on CYP3A5 phenotype on concentration of TAC in plasma when first pass metabolism is bypassed.

Primary Outcome:

The CYP3A5 phenotype's effects on the concentration of TAC measured 24 hours after initial IV infusion

Secondary Outcome:

The CYP3A5 phenotype's effect on time to achieving therapeutic TAC concentration.

Methods:

- Retrospective study in pediatric patients who received BMT at UCSF between 2013-2015.
- Electronic medical records were reviewed to determine patient eligibility, extract patient demographic information, and obtain relevant clinical data and lab results.
- CYP3A5 phenotypes were constructed using genotype data to define the following three alleles: *3, *6, *7.

Inclusion Criteria	Exclusion Criteria
• Age < 18 • Met requirements for BMT candidacy • BMT transplant procedure and subsequent hospital stay at UCSF facility • Given intravenous TAC	• Known TAC allergy or Contraindication • Hepatic dysfunction (Child-Pugh Class C or serum bilirubin >2mg/dL) • Liver transplant • On TAC therapy prior to BMT, or given PO TAC

Analysis:

- Analysis was stratified according to CYP3A5 metabolizer status: Extensive Metabolizers (EM), Intermediate Metabolizers (IM), and Poor Metabolizer (PM).
- TAC concentration at 24 hours post initial infusion and the time to therapeutic trough will be compared between the groups using ANOVA.
- If a significant difference between the groups is observed, post hoc analysis using individual independent t-tests will compare the average time to therapeutic TAC troughs between the different metabolizer levels.
- To correct for covariates such as age, concomitant azole antifungal therapy, and renal function, multivariate linear regression will be used to analyze differences in time to therapeutic TAC concentration.

Preliminary Results:

77 patients

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30 on TAC

Excluded: 47 on cyclosporine

↓

20 w/ PGx data

Excluded: 10 pts not sequenced

↓

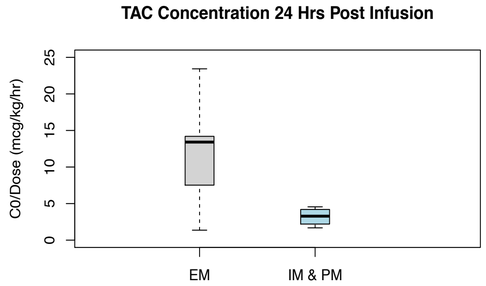
14 pts on IV TAC

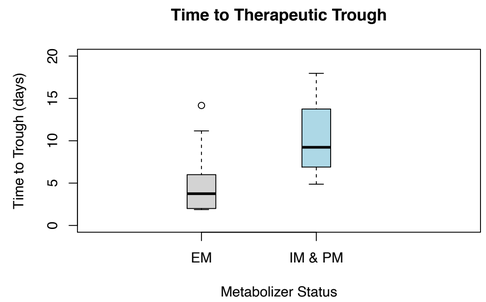
Excluded: 6 pts on PO

↓

13 met inclusion criteria
9 EM, 3 IM, 1 PM

Variables	EM	IM & PM	P-value
n	9	4	
Age, years mean ± SD	10.3± 5.7	9.87± 5.5	P=0.901
Gender, n (%)			
Female	5 (55.6%)	2 (50%)	P=0.853
Male	4 (44.4%)	2 (50%)	
Ethnicity, n (%)			
Caucasian	6 (66.7%)	1 (25%)	P=0.0296
Hispanic	3 (33.3%)	0 (0%)	
Asian	0 (0%)	2 (50%)	
Other	0 (0%)	1 (25%)	





Preliminary Results:

- Initial TAC concentration (24 hours after IV infusion): the difference between the two groups is significant (C_0/Dose ± SD: EM = 11.4 ± 6.53; IM&PM = 3.20 ± 1.26; P = 0.0329).
- The EM group had lower mean time to therapeutic trough compared to the IM&PM group; however, the difference was not statistically significant (Mean days to trough ± SD: EM = 1.80 ± 0.53; IM & PM = 1.30 ± 0.64; P = 0.167).

Conclusions & Future Direction:

- Preliminary results show that EM group had higher concentration and shorter time to therapeutic tough, which is the opposite of what we expect. This research is in progress. The sample size is too small, which makes the study underpowered to show a significant difference at this time.
- More subjects need to be screened for inclusion in the study, and the analysis will be done to compare the three phenotypic metabolizer status (EM, IM, and PM).
- IV formulation at 24 hours was chosen over oral to distinguish between GI and liver effects.
- This study can be further expanded to include patients who take oral tacrolimus in order to determine the effect of liver vs intestinal CYP3A5 on TAC's PK profile.

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