Changes in Physician Prescribing Patterns in Response to Therapeutic Drug Monitoring of Tacrolimus in Pediatric Patients

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INTRODUCTION

Tacrolimus is an immunosuppressive drug used to prevent organ rejection among patients undergoing allogenic and solid organ transplantation. Due to high intersubject variability in tacrolimus pharmacokinetics, individualization of patient dosing regimens is necessary for optimal therapy. The objective of this study was to characterize prescribing practices in response to tacrolimus concentrations obtained from children who underwent bone marrow, heart, kidney, and liver transplantation. Depending on patient characteristics and organ transplanted, a starting dose of about 0.075 mg/kg/day is recommended.

METHODS

This was a retrospective cohort study conducted among 17 Utah hospitals in the Intermountain Network. The cohort included children <19 years of age who received ≥2 tacrolimus doses. Physician action was assessed by observing changes in dosing immediately before and after a tacrolimus trough concentrations were measured. A categorical variable for trough concentrations was created in which: 0 (Below Recommended Level (about 5µg/mL, depending on transplant type factors in the tacrolimus label), 1 (Recommended), and 2 (More than Recommended (above about 20 mcg/mL).

Patient Characteristic	Mean	Std Dev	Minimum	Maximum
Average Age	9.92	5.98	0.00	18.00
# of encounters	3.19	3.37	1	23
Total # of Doses	41	68	2	762
Ave. Conc. (µg/mL)	9.79	3.57	1.80	34.55
Ave. Dose (mg/kg/day)	0.085	0.10	0.00	0.81

Table 1: Statistics of the pediatric patients

ACTION/ TROUGH CONCENTRATION	Below Rec.	Recommended	Above Rec.	Number of trough Samples
BONE MARROW				264
INCREASE DOSE	32%	33%	58%	
SAME DOSE	27%	32%	42%	
DECREASE DOSE	41%	35%	0%	
HEART				1317
INCREASE DOSE	55%	30%	27%	
SAME DOSE	25%	43%	32%	
DECREASE DOSE	20%	27%	41%	
KIDNEY				908
INCREASE DOSE	38%	27%	28%	
SAME DOSE	58%	53%	39%	
DECREASE DOSE	4%	23%	33%	
LIVER				2455
INCREASE DOSE	48%	35%	28%	
SAME DOSE	33%	38%	30%	
DECREASE DOSE	18%	27%	40%	

Table 2: Doctors' responses to concentration level for different transplant types.

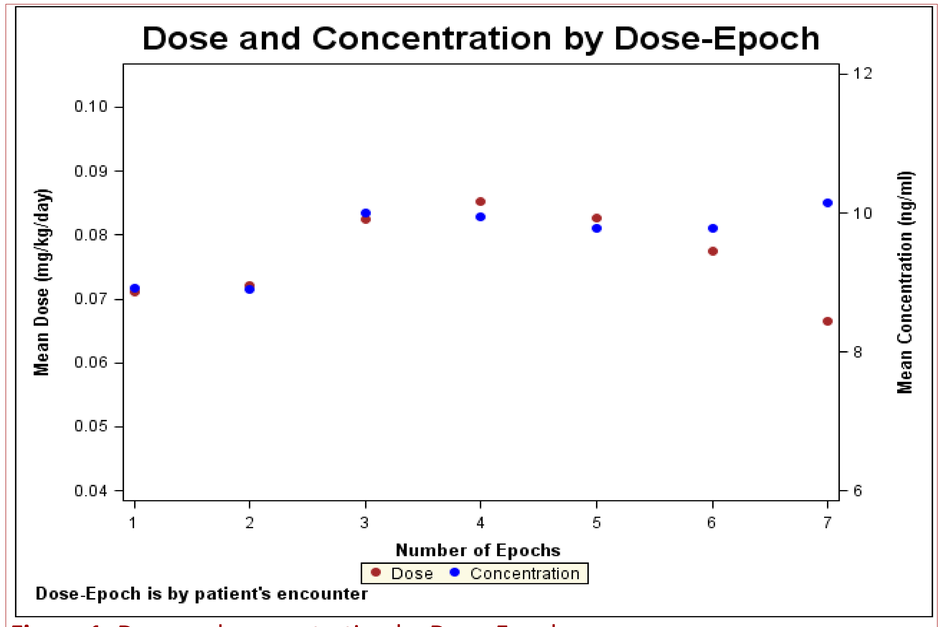

Figure 1: Dose and concentration by Dose-Epoch

RESULTS

- Patient characteristics can be found in Table 1.
- There were 307 children who met inclusion criteria. The children had an average age of 9 yrs and an average of 3 encounters (range 1-23).
- The average dose was .08 mg/kg/day and the median trough concentration was 9.71 mcg/mL.
- Decisions were characterized by dosing epoch, reflecting a set of doses immediately following a trough concentration.
- Average dose does not increase over dosing-epoch (p =.9411) and concentrations increased over dosing-epochs (p = .0384 Figure 1)

- **Changes in physician prescribing patterns in response to tacrolimus trough concentrations are featured in Table 2.**
  - **Dose change frequencies differed by transplant type- kidney patients were most likely to stay at the same dose.**
  - **Changes occurred frequently even in patients with recommended trough concentrations**

CONCLUSIONS

Tacrolimus doses and concentrations were, on the average consistent with recommended levels. Tacrolimus doses were changed frequently, even among children with trough concentrations within the normal reference range. This finding suggests that other physiological factors may influence tacrolimus prescribing practices.

Differences were also noted between transplant types, which may imply that the exposure requirements needed to achieve immunosuppression vary by transplant type. Further investigation is needed to identify other factors that influence pediatric tacrolimus prescribing practices and to develop transplant-specific trough reference ranges

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