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CYP3A5 genotyping may reduce the cost of care and guide dosing in paediatric renal transplant recipients treated with tacrolimus: A report of two paediatric renal transplant cases

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CASE STUDY

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ABSTRACT

Therapeutic tacrolimus blood levels are often difficult to achieve immediately after transplant. Pharmacogenetic testing is an option to predict the metabolism of tacrolimus; however the clinical benefits of this approach have not been extensively studied. We describe two paediatric renal transplant recipients who were initially treated with a standard dosing equation for tacrolimus, but required increased frequency of therapeutic drug monitoring and multiple dose adjustments leading to increased cost of hospitalization. A novel perspective is that pharmacogenetic testing is appropriate to reduce length of hospitalization and the total cost of care.

Key Words
Tacrolimus, therapeutic drug monitoring, cytochrome P450 3A5, pharmacogenetics, paediatric renal transplant

Implications for Practice:

1. What is known about this subject?
There is no consensus on the clinical utility of pharmacogenetics for predicting tacrolimus whole blood concentrations.

2. What new information is offered in this case study?
Pharmacogenetics for tacrolimus dosing may decrease the length of hospitalization and cost of care for paediatric renal transplantation at institutions serving diverse patient populations.

3. What are the implications for research, policy, or practice?
Pharmacogenetics may result in faster attainment of therapeutic levels of tacrolimus and reduced cost burden in paediatric renal transplantation.

Background

Tacrolimus is a commonly used drug for immunosuppression for kidney, liver, lung, and heart transplantation. Tacrolimus inhibits the activation of T-cells and the synthesis of interleukin-2, and has increased efficacy in reducing graft rejection compared to other calcineurin inhibitors such as cyclosporine.[1] Tacrolimus, like other calcineurin inhibitors, has a narrow therapeutic index and inter-individual variability requiring therapeutic drug monitoring (TDM). Several studies demonstrate how polymorphisms in cytochrome P450 3A5 (*CYP3A5*) affect tacrolimus metabolism and suggest tailoring initial doses based on genotyping of the enzyme to reduce time needed to reach therapeutic concentrations.[2-7]

In general, three major *CYP3A5* metabolizer genotypes have been identified:

1. Poor metabolizers (*CYP3A5*3/**3), who have no expression of the enzyme and frequently have elevated trough tacrolimus levels following standard dosing protocols.
2. Intermediate metabolizers (*CYP3A5*1/*3*), who have one functional allele coding for the enzyme and partially metabolize the drug.
3. Extensive metabolizers (*CYP3A5*1/*1*), who have two functional alleles and are commonly observed with sub-therapeutic levels of the drug with standard dosing regimens.[8]

Here we report two paediatric renal transplant cases who would have benefitted from CYP3A5 genotyping to predict tacrolimus dosing and thereby reduce hospitalization time and total cost of care.

Case details

Case 1: A 17-year-old (72kg) Hispanic boy with end-stage renal disease due to obstructive uropathy underwent a deceased donor renal transplant. For induction, the patient received three daily doses of intravenous (IV) rabbit anti-thymocyte globulin starting just before transplant and a single intra-operative dose of IV methylprednisolone (10mg/kg). For maintenance immunosuppression, he was treated with oral mycophenolate mofetil (1200mg/m^2/day) and oral tacrolimus (starting dose 0.2mg/kg/day) divided every 12 hours with the first doses given pre-operatively. Daily whole blood tacrolimus 11.5-hour trough concentrations were used to make dose adjustments to achieve target trough levels 12–14ng/dL for 0-7 days and 10–12ng/dL for 8–14 days post-transplant. The post-operative recovery was unremarkable, but trough tacrolimus concentrations were repeatedly supra-therapeutic until post-operative day 13, with maximum trough concentration 23.3ng/dL (Figure 1). No drug or food interactions contributed to the high tacrolimus trough. Multiple dose adjustments and increased frequency of TDM to twice daily were required. Discharge was delayed until acceptable target trough level was achieved on post-operative day 14, when patient was taking oral tacrolimus 0.04mg/kg/day. Blood was sent for *CYP3A5* genotype testing and showed the patient to be a poor metabolizer of tacrolimus (*CYP3A5*3/*3*). At one year follow up the patient remains on low dose tacrolimus 0.02 mg/kg/day with good graft function and blood tacrolimus trough 5.6ng/dL (Goal 5–7ng/dL).

Case 2: A 16-year-old (71kg) Hispanic boy with end-stage renal disease secondary to Alport syndrome underwent a living unrelated donor renal transplant. He received the same immunosuppression induction and maintenance regimen as described in case 1, and he had an uncomplicated post-transplant course. Trough tacrolimus concentrations observed in the first 11 days following transplant were consistently sub-therapeutic (Figure 1). The patient was discharged on post-op day 7 on oral tacrolimus 0.36mg/kg/day, a dose 9-fold higher than required in case 1. No drug interactions contributed to the high dose requirement. While the patient's discharge was not delayed due to sub-therapeutic tacrolimus concentrations, multiple outpatient blood tests and tacrolimus dose adjustments were required to reach therapeutic levels. The patient was re-admitted on post-operative day 12 for elevated serum creatinine and evaluation for possible acute transplant rejection, but was found to have acute tacrolimus nephrotoxicity, which resolved with tacrolimus dose reduction. Blood was sent for *CYP3A5* testing and revealed the patient to be an extensive metabolizer of tacrolimus (*CYP3A5*1/*1*). At 1 year follow up the patient remains on high dose tacrolimus 0.2mg/kg/day with good graft function and blood tacrolimus trough 6.5ng/dL (Goal 5–7ng/dL).

Discussion

There is no consensus regarding the utility of pharmacogenetic testing for tacrolimus dosing in transplant patients. This is because few studies have investigated whether knowledge of *CYP3A5* genotype affects clinical outcomes such as graft survival, delayed graft function, episodes of graft rejection, or tacrolimus toxicity and none of these have focused on outcomes in paediatric kidney transplant recipients. Those studies that have examined *CYP3A5* testing failed to show improved clinical end-points despite demonstrating faster attainment of therapeutic levels.[9, 10]

Clinical benefits may be unknown, but testing could lower the total cost of hospitalization by reducing metrics such as length of stay, number of dose changes, and TDM measurements. For example, in the first case presented here identified as a *CYP3A5*3/*3* poor metabolizer, the patient required 12 dose changes, 21 tacrolimus TDM measurements, and 14 days of post-operative hospitalization. Based on our hospital's experience, the expected inpatient stay for a paediatric renal transplant patient without complications averages 7–8 days, with 5–7 dose changes, and 8–10 trough TDM labs. The projected expense incurred while titrating dose to therapeutic levels for case 1 was double the expected cost, including tacrolimus dose changes, additional TDM, and routine nursing services for an additional 7 days of hospitalization. The second case, a *CYP3A5* extensive metabolizer, met the

projected averages for length of stay, TDM, and dose changes; however, he consistently had tacrolimus levels below the desired range and required re-hospitalization shortly after discharge.

These cases are not rare occurrences. A study in adults by Thervet et al. indicates that the percentage of patients achieving target levels of tacrolimus after six oral doses was 29.1 per cent for their population.[9] At our institution, which deals with only paediatric cases, the difficulty in adjusting tacrolimus to therapeutic levels is likely related to the use of a standardized starting dose (0.2mg/kg/day) for all patients in a large hospital setting serving a diversity of ethnicities, including Caucasian, Hispanic, African American, Asian, and others, with different *CYP3A5* allele frequencies. To this end, it has previously been established that individuals of African, Asian, and Hispanic descent express *CYP3A5**1 more often than Caucasians and therefore may be better served using pharmacogenetic-guided dosing regimens.[8,11,12] Another factor influencing the pharmacokinetics of tacrolimus is patient age. Previous studies have established that younger children require increased doses of tacrolimus to achieve similar concentrations to those observed in dose-matched children >12 years of age.[13,14] In fact, these reports suggest that the initial tacrolimus dose should account for pharmacokinetic differences between paediatric age groups. In the cases presented here, however, it is unlikely that age contributed to the difficulty in titrating tacrolimus levels because both recipients were >16 years old with an age difference of less than 1.6 years.

In our geographic region, the projected total cost of the *CYP3A5* genotyping at a reference laboratory is about one-ninth of the price of a single day of hospitalization. The estimated turnaround time is around 72 hours if performed in-house, but could take up to 2–4 weeks if ordered as a send-out test. Thus, to maximize cost-reduction and decrease turnaround time, a more prudent approach may be to implement in-house pharmacogenetic testing at large paediatric hospitals.

For diverse patient populations like ours, we suggest implementing the following: if in-house testing or results in 2–3 days are available, paediatric renal transplant patients who have not achieved desirable levels by the third post-operative day should undergo *CYP3A5* genotyping. We believe this approach will lower the cost of care by minimizing the number of dose changes, reducing additional TDM measurements needed, and decreasing the length of hospitalization. For high-risk patients (Hispanic, Asian and African-American), pre-operative pharmacogenetic testing and individualized therapy should be beneficial for reducing transplant costs. Of note, The Clinical Pharmacogenetics Implementation Consortium (CPIC) has recently published guidelines for *CYP3A5* genotype-specific tacrolimus dosing. This publication provides detailed information on pharmacogenetic dosing algorithms and acknowledges this approach for rapid achievement of therapeutic levels.[8]

Finally, we acknowledge that other factors influence tacrolimus pharmacokinetics, including patient age, weight, food and drug interactions, and cytochrome *CYP3A4* and *ABCB1* genotype.[8,13,14] However, substantial evidence indicates that knowledge of *CYP3A5* genotype and appropriate dose modification leads to faster attainment of therapeutic levels, which has the potential to directly decrease cost of care. Had the genotype of these two patients been known, personalized dosing of tacrolimus may have helped reach therapeutic drug levels more quickly and decreased hospital charges.[15,16]

In addition to *CYP3A5* and tacrolimus, studies in adult kidney transplant recipients suggest that genetic variation in UDP-glucuronyltransferases impact mycophenolic acid metabolism.[17-19] This immunosuppressant is commonly used in conjunction with tacrolimus and it has been reported that co-administration of the two drugs may alter the initial levels of mycophenolic acid.[20] Therefore, future algorithms may need to be set forth to guide dosing of additional immunosuppressants for paediatric patients, however the current clinical utility of pharmacogenetics for other drugs such as mycophenolic acid remain unclear.[5,21]

Conclusion

The estimated cost of extra TDM and additional days in the hospital greatly exceeds the one-time expense of blood *CYP3A5* testing. Pharmacogenetic testing of high-risk paediatric renal transplant patients should be considered to reduce time to achieve therapeutic blood tacrolimus concentrations, prevent prolonged hospitalization, and decrease transplantation costs.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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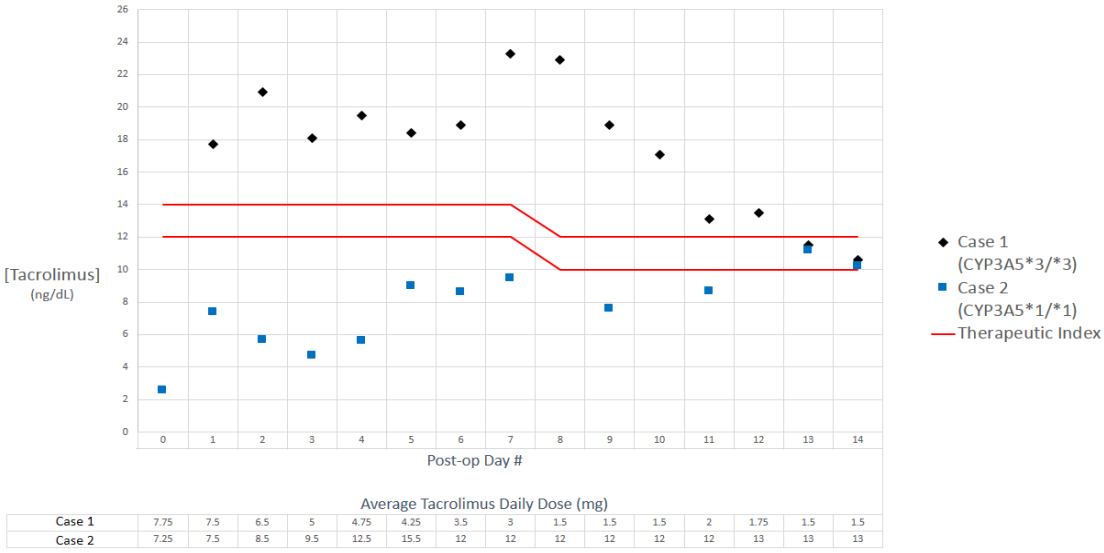
PATIENT CONSENT

The authors, *Roper S, Michael M, Brewer E, Lee J, Orjuela A, Akbas N, and Devaraj S*, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.

2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

Figure 1: Case 1 and case 2 tacrolimus therapeutic drug monitoring and average daily tacrolimus dose: Tacrolimus daily dose is provided in the table for each of the post-op days on the X-axis and tacrolimus levels on the Y-axis. All measurements were made using Abbott Architect immunoassay and are expressed in ng/dL



Average Tacrolimus Daily Dose (mg)

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Case 1	7.75	7.5	6.5	5	4.75	4.25	3.5	3	1.5	1.5	1.5	2	1.75	1.5	1.5
Case 2	7.25	7.5	8.5	9.5	12.5	15.5	12	12	12	12	12	12	13	13	13