COLUMBIA | VAGELOS COLLEGE OF PHYSICIANS & SURGEONS
PROGRAM FOR EDUCATION IN GLOBAL AND POPULATION HEALTH

Tacrolimus Metabolism and Renal Function Following Renal Transplantation Using Once-Daily Envarsus XR as Compared to Twice-Daily Prograf

Averill Clapp, VP&S Class of 2023
Mentors: Mark A. Hardy, MD and Anette Wu, MD, MPH, PhD

BACKGROUND

Tacrolimus (Tac) is the most commonly used maintenance immunosuppressive calcineurin inhibitor (CNI) in renal transplantation. Tac metabolism is known to vary widely across transplant recipients, particularly among African Americans,[1] and excess exposure to the drug may contribute significantly to CNI nephrotoxicity over the long term. It has previously been shown that faster metabolism of Tac is associated with impaired renal function after transplantation, likely due to CNI nephrotoxicity.[2,3]

OBJECTIVES

In this prospective randomized preliminary study, we sought to investigate the impact of Tac metabolism rate on nephrotoxicity after renal transplantation. We analyzed differences in Tac metabolism and renal outcomes in renal transplant patients receiving a once-daily extended release Tac formulation (Envarsus XR) or a twice-daily immediate release Tac formulation (Prograf). We hypothesized that patients treated with Envarsus XR may achieve more consistent calcineurin exposure with overall lower doses of Tac, decreasing the risk of CNI nephrotoxicity.

We also investigated differences in Tac metabolism and renal function outcomes among African American patients and patients of other races in the hopes of better predicting and avoiding CNI nephrotoxicity.

FIGURES

Table 1. Monthly mean Tac blood trough concentration/total daily Tac dose (ng/mL * 1/mg) following transplantation, showing no significant differences in mean Tac metabolism between Envarsus and Prograf recipients (p=0.757) and African Americans as significantly faster Tac metabolizers than participants of other races (p=0.004).

	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Overall (Months 1-12)	P-Value
Envarsus XR	1.47	1.85	1.95	2.86	2.77	1.97	**1.95**	p=0.757
Prograf	1.68	1.86	2.00	1.92	2.05	1.92	**1.87**	
African American	1.27	1.25	1.54	1.26	1.07	1.33	**1.33**	p=0.004
All Other Races	1.64	1.97	2.05	2.50	2.65	2.12	**1.96**	
Overall	1.58	1.85	1.98	2.30	2.39	1.94	**1.91**	

Figure 1. Monthly mean serum creatinine level (mg/dL) in Envarsus XR and Prograf patients following transplantation.

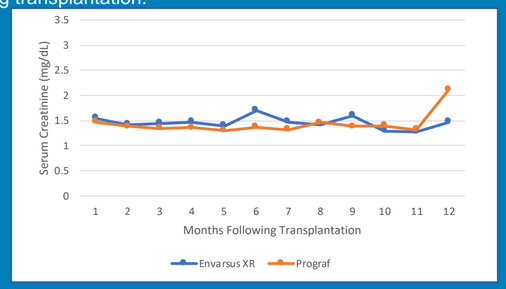
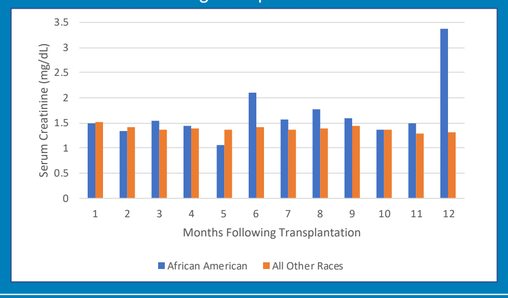


Figure 2. Monthly mean serum creatinine level (mg/dL) in African American recipients and recipients of all other races following transplantation.



METHODS

- 50 renal transplant recipients were randomized to receive Envarsus XR or Prograf, 45 of whom were observed for one year following transplantation
- Tacrolimus metabolism was assessed by calculating the ratio of the Tac blood trough concentration and the total daily Tac dose and was measured at least once every 30 days for 360 days
- CNI nephrotoxicity was assessed by serial collection of serum creatinine levels at least once every 30 days for 360 days

RESULTS

- No significant differences were observed between Prograf and Envarsus XR groups with regards to Tac metabolism rate
- African American recipients demonstrated faster Tac metabolism and higher mean serum creatinine levels than other study participants, suggesting higher risk for CNI nephrotoxicity

DISCUSSION

As the rate of Tac metabolism has previously been shown to impact renal function after transplantation, a sufficiently powered study will be needed to identify the potential benefits of Envarsus XR in reducing CNI nephrotoxicity, particularly in patients with high rates of Tac metabolism, such as African Americans.

REFERENCES

1. Tang JT, Andrew LM, van Gelder T, Shi YY, van Schaik RHN, et al. (2016) Pharmacogenetic aspects of the use of tacrolimus in renal transplantation: Recent developments and ethnic considerations. Expert Opinion on Drug Metabolism & Toxicology 12(5): 555-556.
2. Thölking G, Siats L, Fortmann C, Koch R, Hüsing A, et al. (2016) Tacrolimus concentration/dose ratio is associated with renal function after liver transplantation. Ann Transplant 21: 167-179.
3. Thölking G, Fortmann C, Koch R, Gerth HU, Pabst D, et al. (2014) The tacrolimus metabolism rate influences renal function after kidney transplantation. PLoS ONE 9(10): e111128.

With thanks to mentors Mark A. Hardy, MD, Anette Wu, MD, MPH, PhD, the International Collaboration and Exchange Program, and the Program for Education in Global and Population Health.