Evaluation of Clinical and Safety Outcomes Following Uncontrolled Tacrolimus Conversion in Adult Renal Transplant Recipients

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Background

Tacrolimus is also categorized as a narrow therapeutic index (NTI) drug. Differences in NTI drug bioequivalence standards creates challenges in both properly comparing and interpreting studies. The use of generic tacrolimus has remained controversial despite numerous studies. In previous evaluations, conversion from innovator to generic was often accomplished in a highly-controlled environment, including prompt trough level follow-up and stringent prospective monitoring. Despite similar allograft function and tacrolimus trough levels in these studies, dose changes were observed in up to 21% of transplant recipients after conversion, with authors suggesting a role for closer tacrolimus level monitoring after switching between manufacturer tacrolimus products. However, none of these conversion studies included control arms in which patients remained solely on either innovator or generic tacrolimus throughout the study period to serve as comparator groups.

The purpose of this retrospective study was to compare clinical and safety outcomes of transplant recipients who were converted between different tacrolimus products to those who were not converted between different formulations in an uncontrolled environment with no pre-defined monitoring protocols.

Methods

- A retrospective, non-randomized single center study of transplant recipients at the University of Cincinnati Medical Center with pharmacy refill data from August 2009 to May 2016. This study was a component of the FDA Solicitation 13-223-SOL-00102 to review tacrolimus conversion in an immunologic high-risk population (i.e. African American, panel-reactive antibody [PRA] > 25%, repeat transplant)
- Patient population:
  - Inclusion: adult (> 18 years), 2 years of pharmacy refill data, > 6 months post-transplant, had tacrolimus conversion at least > 1.5 years from transplantation (for those in the conversion groups)
  - Exclusion: pregnant during the study period, were converted to a non-tacrolimus immediate release product, or had less than two tacrolimus trough levels during the defined observation periods
- Patients were divided into four separate groups: Group A) innovator tacrolimus (no conversion), Group B) single generic tacrolimus formulation (no conversion), Group C) single tacrolimus conversion (from innovator to generic or from generic to innovator), and Group D) multiple tacrolimus conversions between formulations
- Patients in the control arms of the study (i.e. Groups A and B) were assigned an index date for evaluation, which was selected to match time to conversion post-transplantation in the conversion arms (i.e. Groups C and D). Index dates in the conversion arms were defined as the date of first tacrolimus conversion
- Patient data was collected 420 days before and after the index date. To balance the data for statistical analysis, laboratory information was grouped into the following time intervals before and after the index date: 0 – 60 days, 61 – 180 days, 181 – 300 days, and 301 – 420 days. For each time interval, if there were multiple laboratory levels for a patient, the most time-centric set of values and clinical information was selected.
- Groups were compared using the Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Linear trend was estimated for dose-normalized tacrolimus levels, eGFR, and serum creatinine using regression models with terms allowing for differing slopes within each period and within each group. SAS software (version 9.4, SAS Institute, Cary, NC) was utilized for all statistical analysis.

Results

TABLE 1. Patient demographics and baseline immunosuppression

Variable	Group A (n=29)	Group B (n=19)	Group C (n=26)	Group D (n=26)	p-value
Age (years) at transplant, median (IQR)	48.4 (42.0, 58.7)	49.9 (38.6, 60.2)	50.5 (42.2, 60.6)	49.3 (44.5, 56.5)	0.97
Male, n (%)	19 (65.5)	8 (42.1)	15 (57.7)	21 (80.7)	0.06
African American, n (%)	9 (31.0)	7 (36.8)	11 (42.3)	11 (42.3)	0.78
DM (at index date), n (%)	12 (41.4)	6 (31.6)	12 (46.2)	9 (34.6)	0.75
HTN (at index date), n (%)	20 (71.4)	15 (78.9)	23 (88.5)	23 (88.5)	0.22
High immunologic risk, n (%)	13 (44.8)	10 (52.6)	11 (42.3)	12 (46)	0.92
Hemoglobin A1c, median (%)	5.9 (5.3,7.2) n=25	5.3 (5.0,6.0) n=19	5.8 (5.4,6.9) n=26	5.8 (5.3,6.2) n=25	0.23
Reason for transplant, n (%)					
Diabetes Mellitus	8 (27.6)	4 (21.1)	8 (30.7)	5 (19.2)	
Hypertension	2 (6.9)	4 (21.1)	3 (11.5)	5 (19.2)	
FSGS	2 (6.9)	1 (5.3)	2 (7.7)	3 (11.5)	-
Alcoholic Cirrhosis	2 (6.9)	1 (5.3)	1 (3.8)	1 (3.8)	
Hepatitis C virus	3 (10.3)	1 (5.3)	3 (11.5)	1 (3.8)	
Other	12 (41.4)	8 (42.1)	9 (34.6)	11 (42.3)	
Transplant Type, n (%)					
Living kidney	6 (20.7)	9 (47.4)	6 (23.1)	8 (30.7)	
Deceased kidney	6 (20.7)	5 (26.3)	5 (19.2)	14 (53.8)	
Liver	10 (34.5)	4 (21.1)	7 (26.9)	2 (7.7)	
Heart	2 (6.9)	0 (0)	2 (7.7)	0 (0)	0.025
Pancreas	2 (6.9)	1 (5.3)	0 (0)	0 (0)	
Kidney/heart	0 (0)	0 (0)	1 (3.8)	0 (0)	
Kidney/Pancreas	3 (10.3)	0 (0)	4 (15.4)	2 (7.7)	
Liver/ Kidney	0 (0)	0 (0)	1 (3.8)	0 (0)	
HLA mismatches, (IQR)	3 (2, 4) n=13	3.5 (2, 5) n=12	5 (4, 5) n=14	4 (3, 5) n=23	0.12
Peak PRA > 25%, n (%)	2 (13.3) n=15	0 (0) n=12	0 (0) n=15	1 (4) n=23	-
Current PRA > 25%, n (%)	3 (20) n=15	0 (0) n=12	1 (6) n=15	1 (4) n=23	-
Repeat Transplant, n (%)	6 (20.7)	3 (15.8)	2 (7.7)	1 (3.8)	0.23
Time post-transplant (years), median (IQR)	3.7 (2.6, 7.5)	5.0 (2.1, 7.2)	7.6 (3.4, 9.1)	5.2 (3.0, 8.8)	0.31
Median tacrolimus dose, mg/day (IQR)	4.0 (3.0, 8.0)	6.0 (3.0, 8.0)	3.75 (2.0, 6.0)	3.0 (2.0, 6.0)	0.13
Median tacrolimus level, ng/mL (IQR)	7.4 (5.3, 8.2)	6.7 (4.3, 7.9)	5.9 (4.1, 7.6)	5.7 (4.2, 8.0)	0.47
Mycophenolic Acid, n (%)	26 (89.7)	15 (78.9)	23 (88.5)	26 (100)	0.09
Prednisone, n (%)	5 (17.2)	5 (26.3)	0 (0)	6 (31.6)	0.02

TABLE 2. Tacrolimus dose adjustments by patient group post-index date

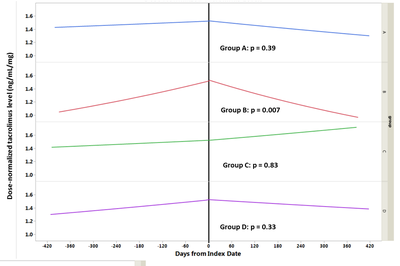
Dose changes after conversion/ index date	Group A (n=29)	Group B (n=19)	Group C (n=26)	Group D (n = 26)	p-value
Decrease tacrolimus only, n (%)	8 (28)	3 (16)	3 (12)	4 (15)	0.32
Increase tacrolimus only, n (%)	1 (3)	2 (11)	4 (15)	6 (23)	
Both Increase and decreases in tacrolimus, n (%)	1 (3)	3 (16)	5 (19)	3 (12)	
No tacrolimus dose change, n (%)	19 (66)	11 (58)	14 (54)	13 (50)	

TABLE 3. Tacrolimus dose changes pre- versus post-index date

Variables	Pre-index date	Post-index date	p-value
Group A (n = 29)			
Percent of patients with dose change, n (%)	13 (45)	10 (34)	0.37
Number of dose changes per patient, median (range)	0 (0, 12)	0 (0, 4)	0.03
Absolute value of the maximum dose change, median mg (IQR)	0 (0, 2)	0 (0,1)	0.34
Percent of patients with tacrolimus dose changes within 30 days of conversion/ index date	-	0 (0)	-
Group B (n = 19)			
Percent of patients with dose change, n (%)	10 (53)	8 (42)	0.48
Number of dose changes per patient, median (range)	1 (0, 7)	0 (0, 5)	0.45
Absolute value of the maximum dose change, median (IQR)	1 (0, 5)	0 (0, 2)	0.13
Percent of patients with tacrolimus dose changes within 30 days of conversion/ index date	-	0 (0)	-
Group C (n = 26)			
Percent of patients with dose change, n (%)	10 (38)	12 (46)	0.41
Number of dose changes per patient, median (range)	1 (0, 4)	0 (0, 3)	0.89
Absolute value of the maximum dose change, median (IQR)	0 (0, 2)	0 (0, 1.5)	0.69
Percent of patients with tacrolimus dose changes within 30 days of conversion/ index date	-	0 (0)	-
Group D (n = 26)			
Percent of patients with dose change, n (%)	12 (46)	13 (50)	0.78
Number of dose changes per patient, median (range)	0 (0, 10)	0 (0, 7)	0.66
Absolute value of the maximum dose change, median (IQR)	0 (0, 2)	0.25 (0, 2)	0.76
Percent of patients with tacrolimus dose changes within 30 days of conversion/ index date	-	1 (4)	-

FIGURE 1.

Changes in dose-normalized tacrolimus trough levels by patient group pre- and post-index date



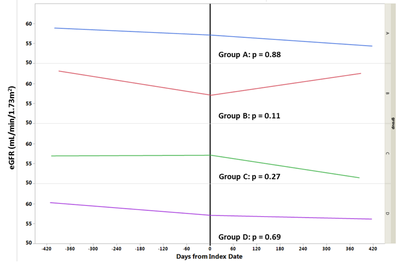


FIGURE 2.

Changes in estimated glomerular filtration rate by patient group pre- and post-index date

TABLE 4. Patient biopsies and rejection episodes pre- versus post-index date

Variables	Pre- index date	Post- index date
Group A (n = 29)		
Number of patients who underwent biopsy, n (%)	7 (24)	3 (10)
Biopsies with rejection, n (%)	11/19 (56)	2/3 (67)
Group B (n = 19)		
Number of patients who underwent biopsy, n (%)	6 (32)	2 (11)
Biopsies with rejection, n (%)	6/10 (60)	3/4 (75)
Group C (n = 26)		
Number of patients who underwent biopsy, n (%)	3 (12)	4 (15)
Biopsies with rejection, n (%)	0/3 (0)	2/4 (50)
Group D (n = 26)		
Number of patients who underwent biopsy, n (%)	4 (15)	1 (4)
Biopsies with rejection, n (%)	2/5 (40)	0/1 (0)

TABLE 5. Patient hospitalizations pre- versus post-index date

Variables	Pre-index date	Post-index date	p-value
Group A (n = 29)			
Patients with hospitalizations, n (%)	13 (45)	10 (35)	0.26
Patients with multiple hospitalizations, n (%)	4 (14)	5 (17)	0.56
Group B (n = 19)			
Patients with hospitalizations, n (%)	8 (42)	6 (32)	0.41
Patients with multiple hospitalizations, n (%)	3 (16)	2 (11)	0.56
Group C (n = 26)			
Patients with hospitalizations, n (%)	8 (31)	6 (23)	0.48
Patients with multiple hospitalizations, n (%)	4 (15)	2 (8)	0.32
Group D (n = 26)			
Patients with hospitalizations, n (%)	7 (27)	6 (23)	0.66
Patients with multiple hospitalizations, n (%)	3 (12)	4 (15)	0.32

Conclusion

Overall, this study demonstrated that conversion of tacrolimus to an alternative product did not result in statistically significant differences in dose-normalized tacrolimus trough concentrations, tacrolimus dose adjustments, or renal function. Additionally, other surrogate markers for immunosuppression (i.e. hospitalizations and rejection episodes) were similar across the pre- and post-index date study periods.

Limitations:

- Patients who transferred their tacrolimus prescriptions outside of the closed pharmacy system were excluded. This could have resulted in underestimating the number of patients with allograft function decline, rejection, or loss.
- Patients had variable laboratory follow-up due to individual allograft and time-post transplantation differences across patients.

References

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