Assessing the Feasibility of Evaluating Tacrolimus Use After Solid Organ Transplantation in the Sentinel Distributed Database

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Background

Tacrolimus is an immunosuppressive drug indicated for prophylaxis of organ rejection in patients receiving allogeneic kidney, liver or heart transplants. Concerns exist among healthcare providers about the therapeutic equivalence of brand and generic tacrolimus. However, the majority of evidence is from bioequivalence studies, and there are limited data on therapeutic equivalence using clinical outcomes. *

* Reference: Johnston A. Equivalence and interchangeability of narrow therapeutic index drugs in organ transplantation. *Eur J Hosp Pharm Sci Pract.* 2013 Oct; 20(5): 302–307.

Objectives

To identify transplant patients and describe their use of brand and generic tacrolimus in the Sentinel Distributed Database (SDD) in order to determine the feasibility of future studies of therapeutic equivalence.

Methods

Data source - 17 Data Partners contributing to the Sentinel Distributed Database

Study period - August 10, 2009 to October 31, 2017

Study population - Kidney, heart, and liver transplant recipients identified by inpatient CPT-4, ICD-9-CM and ICD-10-PCS codes

Eligibility

Inclusion criteria: Have continuous health plan enrollment for at least 12 months prior to inpatient admission

Exclusion criteria: Multiple transplants, prior transplant or tacrolimus dispensing

Exposure - First dispensing of branded or generic oral tacrolimus from outpatient pharmacy following kidney, heart, and liver transplantation identified by NDC codes (by manufacturer)

Feasibility measurements

1. Follow-up time in the SDD for transplant recipients from hospital discharge until disenrollment, death, or the end of data availability, whichever came first.

2. Time to first tacrolimus dispensing (in days, identified using National Drug Codes [NDCs]) since hospital discharge.

3. For patients with the first dispensing ≤60 days after discharge, the duration of continuous use of oral tacrolimus and the length of gaps between episodes.

Study design

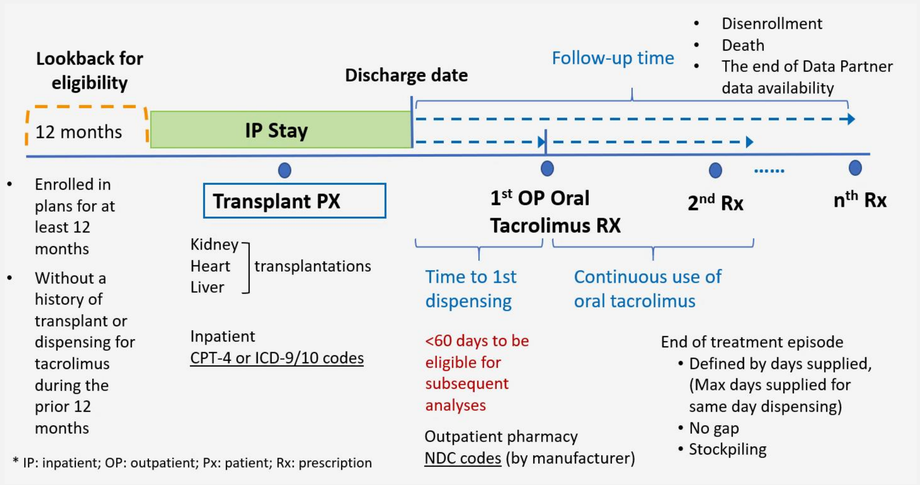

Figure 1. Study design diagram

Results

We identified 3,655 liver transplants, 27,353 kidney transplants, and 1,586 heart transplants in the SDD, with median follow-up times of 557, 714 and 565 days, respectively (Table 1).

We captured dispensing of individual oral tacrolimus products in most transplant patients when restricted to non-Medicare population (Table 2). The median gap between discharge and the first dispensing ranged 2-8 days for all patients and 1-3 days for non-Medicare patients.

Table 1. Aggregated Baseline Table for Liver, Kidney, and Heart Transplant and their follow-up time in the Sentinel Distributed Database*

	Liver		Kidney		Heart	
Number of unique patients (non-Medicare)	**3,655 (1,699)**		**27,353 (5,083)**		**1,586 (596)**	
Demographics	N/Mean	%/Std Dev**	N/Mean	%/Std Dev**	N/Mean	%/Std Dev**
Mean Age (years)	58.3	11.3	51.8	14.7	56.1	13.8
Age: 00-17	65	1.8%	481	1.8%	53	3.3%
Age: 18-64	2,456	67.2%	20,898	76.4%	1,010	63.7%
Age: 65+	1,134	31.0%	5,974	21.8%	523	33.0%
Gender						
Female (N)	1,402	38.4%	10,836	39.6%	427	26.9%
	Median	(Q1, Q3)	Median	(Q1, Q3)	Median	(Q1, Q3)
Follow-Up Time (days)	557	(196, 1,099)	714	(308, 1,149)	565	(182, 1,125)

* Including the Medicare population
** Value represents standard deviation where no % follows the value

Table 2. Oral tacrolimus use following Liver, Kidney, and Heart Transplant in all study population and non-Medicare population*

	Liver (All)		Kidney (All)		Heart (All)		Liver (non-Medicare)		Kidney (non-Medicare)		Heart (non-Medicare)	
Oral Tacrolimus	N	%	N	%	N	%	N	%	N	%	N	%
Any**	1,388	**38.0%**	5,882	**21.5%**	446	**28.1%**	1,205	**70.9%**	3,729	**73.4%**	379	**63.6%**
Brand - Astellas	263	7.2%	677	2.5%	70	4.4%	259	15.2%	647	12.7%	70	11.7%
Generic - Sandoz	632	17.3%	1,887	6.9%	165	10.4%	616	36.3%	1,737	34.2%	160	26.8%
Generic - Dr.Reddys	181	5.0%	521	1.9%	79	5.0%	173	10.2%	424	8.3%	73	12.2%
Generic - Accord	178	4.9%	418	1.5%	73	4.6%	164	9.7%	294	5.8%	66	11.1%
Generic - Mylan	60	1.6%	165	0.6%	17	1.1%	55	3.2%	84	1.7%	16	2.7%
Generic - Panacea	12	0.3%	27	0.1%	1	0.1%	6	0.4%	13	0.3%	1	0.2%
Generic - Strides	4	0.1%	7	0.0%	2	0.1%	4	0.2%	3	0.1%	2	0.3%
Generic - Watson	0	0.0%	2	0.0%	0	0.0%	0	0.0%	1	0.0%	0	0.0%
Extended Release	0	0.0%	39	0.1%	0	0.0%	0	0.0%	27	0.5%	0	0.0%
Procedure ***	299	8.2%	2,793	10.2%	118	7.4%	159	9.4%	1,062	20.9%	70	11.7%

* Dispensed 60 days post transplant discharge, by manufacturer
** Groups are not mutually exclusive, so the sum of subgroups might be greater than the percentage of any tacrolimus
*** Identified by HCPCS code J7507

Among patients who had at least one gap between tacrolimus treatment episodes, the median gaps between the first and second episodes were 15, 20 and 14 days for liver, kidney and heart transplants, respectively (Table 3).

Table 3: Descriptive Statistics for Length of Gaps between Distinct Treatment Episodes*

		Length of gaps (Days)													
		Liver					Kidney					Heart				
		N	Q1	Median	Q3	Mean (SD)	N	Q1	Median	Q3	Mean (SD)	N	Q1	Median	Q3	Mean (SD)
At least 2 episodes	**Gap 1**	853	6	15	31	44.2 (125.8)	2375	7	20	48	61.9 (159.4)	188	5	14	40	46.9 (110.6)
At least 3 episodes	**Gap 2**	684	6	17	39	36.6 (87.5)	1866	6	18	43	48.4 (138.6)	135	4	12	29	53.1 (145.3)
At least 4 episodes	**Gap 3**	563	7	19	46	40.0 (68.7)	1514	6	16	37	41.5 (109.0)	101	4	10	32	27.6 (66.8)

* Grouped all brand and generic oral tacrolimus

Conclusions

- We captured liver, kidney and heart transplant patients in the SDD. Most patients had less than 2 years of follow-up, which might impact the feasibility of evaluating long-term outcomes.
- We captured dispensing of individual oral tacrolimus products using NDC codes in non-Medicare data.
- The lower dispensing among the Medicare population requires further investigation. It may be due to coverage of transplant drugs under Part B instead of Part D, thus not observed in the Medicare fee-for-service (FFS) data.
- Future studies should consider whether the Medicare FFS data is appropriate for studies of tacrolimus.

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