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Implementation of a Pharmacist-Driven Immunosuppression Drug Monitoring Protocol

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Abstract

For patients with serious hematologic malignancies, hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment option.Majority of HSCT recipients receive tacrolimus as part of their immunosuppressive regimen. Tacrolimus is a calcineurin inhibitor (CNI) that inhibits T-lymphocytes to suppress the transplant recipient's immune response and prevent graft-versus-host disease (GVHD). The purpose of this study is to evaluate the clinical impact of a pharmacist driven immunosuppression drug monitoring protocol for HSCT recipients on tacrolimus.

This was a single-center, pre-post interventional study conducted at the University of Chicago Medical Center.Data collected via chart review includes the immunosuppressive agent used, interacting medications, adverse events, dose adjustments, drug concentrations, time to engraftment, and diagnosis of GVHD. Chi-square tests were conducted to compare nominal objectives and Wilcoxon rank-sum tests were conducted to compare continuous objectives.

Following the incorporation of a therapeutic drug monitoring protocol, the percentage of therapeutic tacrolimus levels was similar to when there was no protocol in place; 68% vs 64%, respectively (p=0.34).There were 18 total adverse events observed in the pre-protocol group versus 10 in the post-protocol group (p=0.03).Nephrotoxicity was the most common adverse event occurring in 23% of patients in the pre-protocol group and 15% of patients in the post-protocol group (p=0.18).In the post-protocol group, there were 20 patients with two or more interacting drugs versus two patients in the pre-protocol group (p<0.05).Additionally, the post-protocol group had 12 instances of an empiric dose adjustment made whereas the pre-protocol group had three instances (p=0.006). Although there was no significant difference in percentage of therapeutic tacrolimus levels, pharmacist involvement resulted in improved safety outcomes such as management of drug interactions and incidence of adverse events.

Keywords: Stem cell; Hepatitis; Dermatitis

Introduction

For patients with serious hematologic malignancies, hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment option. Following an allogeneic HSCT, graft versus host disease (GVHD) is a major cause of morbidity and mortality. This commonly manifests in the skin, liver, and gastrointestinal tract resulting in symptoms such as rash, dermatitis, hepatitis, jaundice, nausea, vomiting, abdominal pain, and diarrhea [1]. GVHD can present acutely (aGVHD), within 100 days following transplant, or chronically (cGVHD), greater than 100 days following transplant. Although the true incidence of GVHD is unknown, it is estimated that aGVHD occurs in 30-70% of patients and cGVHD occurs in up to 50-70% of patients [2] depending on various risk factors including age, HSCT source, donor type, and immunosuppressive regimen.

GVHD prophylaxis serves as a core element of the conditioning regimen and commonly utilizes the immunosuppressant tacrolimus. Tacrolimus is a calcineurin inhibitor (CNI) that inhibits T-lymphocyte activation and proliferation to suppress the immune response and thereby prevent graft rejection and GVHD. Tacrolimus is primarily metabolized hepatically through the CYP3A4 enzyme which is a common metabolizer of many drugs.Common toxicities include nephrotoxicity, hyperkalemia, hypertension, and neurotoxicity [3]. Given this high potential for drug interactions and its narrow therapeutic index, therapeutic drug monitoring (TDM) is utilized to maintain therapeutic levels.

Similarly, sirolimus is an immunosuppressant that inhibits T-lymphocyte activation but also T-cell proliferation via mTOR inhibition. This agent may be used as an alternative in patients unable to tolerate tacrolimus. Common toxicities of sirolimus include gastrointestinal toxicity, hypertriglyceridemia, hyperlipidemia, peripheral edema, and interstitial pneumonitis. Sirolimus is also metabolized via CYP3A4 and has a narrow therapeutic index necessitating TDM [4].

While tacrolimus and sirolimus TDM is widespread, there is a lack of standardization in the management of dosing. The University of Chicago Medicine (UCM) implemented a full-time bone marrow transplant (BMT) clinic pharmacist in 2016. However, on the inpatient side, immunosuppression TDM was being inconsistently managed by rotating pharmacists and the final dose adjustments were left to the discretion of the physician or advanced practice nurse. Therefore, in November 2018, a pharmacist-managed immunosuppression dosing protocol was implemented on both the inpatient and outpatient sides.

Pharmacist management of TDM in the allogeneic hematopoietic stem cell transplant patient population is not well defined. Correa and colleagues conducted a study at a tertiary care facility in Brazil comparing TDM in the outpatient setting for patients who were cared for by a clinical pharmacist and those who were not. Sixty-six patients who underwent an allogeneic HSCT and were receiving tacrolimus or cyclosporine were included in this study. The authors found that pharmacist intervention resulted in 82% of therapeutic levels of

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tacrolimus and cyclosporine as compared to 65% when a pharmacist was not involved (p = 0.004) but clinical outcomes were not evaluated [5]. Our study aims to assess the impact of a pharmacist-driven immunosuppression protocol on clinical outcomes in addition to rates of therapeutic levels for HSCT patients.

Methods

This was a single-center, pre-post interventional study conducted at a large academic medical center. The pre-intervention cohort includes patients who underwent an allogeneic HSCT from January 1, 2016 to October 31, 2018 and the post-intervention cohort includes patients treated after November 1, 2019. The University of Chicago Medicine Bone Marrow Stem Cell Transplantation Section performs over forty allogeneic stem cell transplants annually. This project was formally determined to be quality improvement, not human subject research, and was therefore not overseen by the Institutional Review Board, per institutional policy. The protocol was accepted by the institution's Chief Quality Determination Reviewer.

Eligible patients included those at least 18 years of age that were followed in the inpatient and outpatient setting following an allogeneic stem cell transplant who remained on either tacrolimus or sirolimus through day +30. This was a pre- and post-review of the implementation of a pharmacist-driven immunosuppression TDM protocol which outlined recommended dosing modifications in response to trough levels, organ function, drug-drug interactions, and toxicities. Patients were identified by reviewing the University of Chicago internal electronic hematopoietic transplant patient database. Identified patients were then screened for inclusion by investigators who retrospectively performed a chart review. Patient protected health information was secured in a password protected RedCap database.

At UCM, allogeneic HSCT patients begin oral tacrolimus 5 days prior to their transplant. On day -5, all patients start with an empiric dose of tacrolimus at 0.03 mg/kg/dose twice daily in order to achieve a goal trough of 5-10 ng/mL for matched allogeneic HSCT and 10-15 ng/mL for haplo and haplo-cord allogeneic HSCT (Table 1). Tacrolimus level monitoring is initiated on day -3 with daily troughs prior to the morning dose which are evaluated by the transplant team. Once a patient has achieved tacrolimus therapeutic steady state with troughs within the goal range, frequency of monitoring is decreased to three times weekly at the provider's discretion.

The standardized dosing protocol (Tables 2-5) was created by HSCT pharmacists and providers. This protocol outlines recommended dose adjustments based on trough levels, organ function, drug-drug interactions, and toxicities. Patients in the inpatient and outpatient setting were all managed using this same protocol to ensure uniformity.

The primary endpoint of this study was rate of therapeutic tacrolimus levels from transplant day 0 to day +100. Secondary endpoints include the rate of therapeutic tacrolimus levels from transplant day 0 to day +30, number of empiric dose adjustments made, adverse events, incidence of GVHD, incidence of relapse, time to engraftment, tapering off tacrolimus for falling chimerism, and switches to sirolimus. Adverse events included nephrotoxicity (increase in serum creatinine by ≥ 0.3 mg/dL), hypertension (initiation of a new anti-hypertensive during tacrolimus treatment), and neurotoxicity (patient reported headache, tremors, or vision changes and provider reported confusion or stupor).

Type of HSCT	Transplant day 0 through +14	Transplant day +14 and thereafter
Matched	5-10 mcg/mL	
Haplo	10-15 mcg/mL	5-10 mcg/mL
Haplo-cord	10-15 mcg/mL	

Table 1: Therapeutic Goals.

Trough Concentration (ng/mL)	Recommended Adjustment	Timing of Next Level
>2 below goal	Load with 200% of dose once then increase dose by 50%	2 - 3 days
>0.3 – 2 below goal	Increase dose by 25%	4 - 7 days
<0.3 below goal (twice)		
<0.3 below goal (once)	Continue current dose	4 - 7 days
Therapeutic		1 week
<0.3 above goal (once)		4 - 7 days
<0.3 above goal (twice)	Decrease dose by 25%	4 - 7 days
>0.3 – 2 above goal		
>2 – 5 above goal	Hold one dose then decrease dose by 25-50%	2 – 3 days
>5 above goal	Hold doses until therapeutic then decrease dose by 50%	Daily

Table 2: Dose Adjustments per Level.

	Recommended Monitoring
Mild-moderate impairment (Child-Pugh A or B)	Continue present management
Severe impairment (Child-Pugh C)	Monitor level once or twice weekly

Table 3: Dose Adjustments per Hepatic Function.

Concomitant Medication	Recommended Adjustment	Frequency of Monitoring	
		Inpatient	Outpatient
Strong CYP3A4 Inhibitor • Clarithromycin • Posaconazole • Voriconazole	Decrease dose by 50%	Daily levels	Levels 2 – 3 times weekly
Moderate CYP3A4 Inhibitor • Diltiazem • Fluconazole • Isavuconazole • Letermovir • Verapamil	Continue current dose	Levels Monday, Wednesday, Friday	Levels 1 – 2 times weekly
Strong CYP3A4 Inducer • Carbamazepine • Phenytoin • Rifampin	Increase dose by 25-50%	Daily levels	Levels 2 – 3 times weekly

Table 4: Dose Adjustments per Drug Interactions.

All statistical analysis was evaluated utilizing STATA software, version 15.0 (StataCorp). Non-normally distributed continuous data was analyzed by Wilcoxon rank-sum tests and non-normally distributed nominal data was analyzed by Chi-square tests.

Results

During the study period, 60 patients were identified for study inclusion. In the 30-day analysis there were 30 patients in the pre-intervention group and 30 patients in the post-intervention group.In the 100-day analysis, there were 28 patients in the pre-intervention group and 29 patients in the post-intervention group (Figure 1). Baseline characteristics were well matched between the two groups (Table 6). Majority of patients in both groups underwent a matched HSCT.

The rate of therapeutic levels at day 30 was 64% in the pre-intervention group and 68% in the post-intervention group (p = 0.35). In the 100-day analysis, the rate of therapeutic levels in both groups was 70% (p = 0.84). In both groups, sub-therapeutic levels were more

Adverse Effect	Recommended Adjustment	Recommended Monitoring
SCr of >2.0 or 2x above baseline	Hold until SCr<2.0 or at baseline	Daily SCr
SCr of >1.5 or 1.5x above baseline	Continue current dose	SCr in 2 – 3 days
Grade 3 hypertension (SBP >160 or DBP >100)	Initiate calcium channel blockers	Blood pressure at every visit
Refractory grade 3 hypertension (>2 anti-hypertensives)	Hold tacrolimus until blood pressure is controlled	
Mild neurotoxicity (headache, tremor)	Continue current dose	Symptom assessment at every visit
Moderate neurotoxicity (dysphasia, stupor, visual disturbances)	Hold tacrolimus until symptom resolution	Admission for close monitoring
Severe neurotoxicity (seizures, PRES)	Discontinue tacrolimus permanently	

Table 5: Dose Adjustments per Adverse Effects.

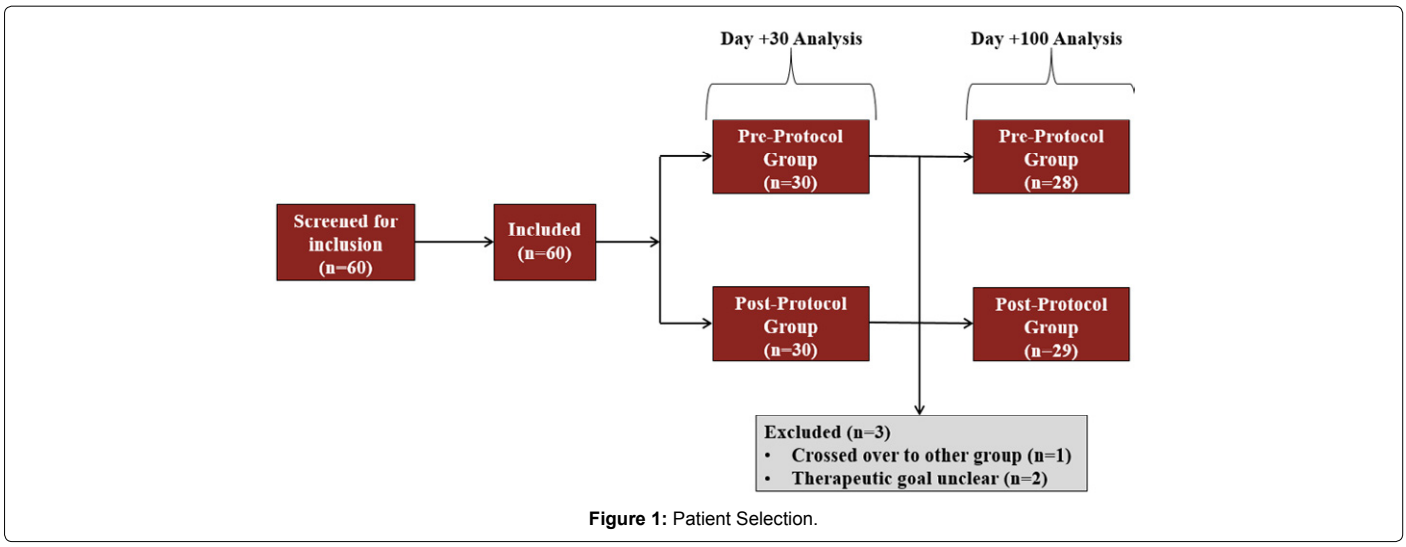

Figure 1: Patient Selection.

Variable	Pre-Intervention Group (n = 30)	Post-Intervention Group (n = 30)	p-value
Age (years)	52	57	0.68
Male	17 (57%)	17 (57%)	1
Baseline SCr (mg/dL)	0.9	0.9	0.5
Type of Transplant			
Matched-Related Donor	14 (47%)	11 (37%)	0.87
Matched-Unrelated Donor	10 (33%)	14 (47%)	
Haplo-Cord	5 (17%)	5 (16%)	
Haplo	1 (3%)	0	

Table 6: Baseline Characteristics.

common than supra-therapeutic levels (Figure 2). Rates of therapeutic sirolimus levels were not collected due to the smaller number of patients who were switched.

There were no significant differences in rates of nephrotoxicity, hypertension, or neurotoxicity between groups in both the 30-day and 100-day analysis (Figure 3). However, in the 30-day analysis, there was a significant difference in number of total adverse events between groups. The pre-intervention group had 20 total adverse events whereas the post-intervention group had 11 total adverse events ($p = 0.03$).This difference was not observed in the day-100 analysis.

At day 100, the post-intervention group had a greater number of drug interactions ($p < 0.0001$) and empiric dose adjustments made ($p = 0.002$) than the pre-intervention group (Figures 4 and 5). Interacting drugs were recognized as clarithromycin, -azole antifungals (posaconazole, voriconazole, fluconazole, isvuconazole), letermovir, diltiazem, verapamil, carbamazepine, phenytoin, and rifampin. There was also a significantly higher proportion of patients with a document empiric dose adjustment in the post-protocol group than in the pre-protocol group. An empiric dose adjustment was one that was made in anticipation of sub-therapeutic or supra-therapeutic tacrolimus levels, not a reactive dose adjustment made based on one tacrolimus level.

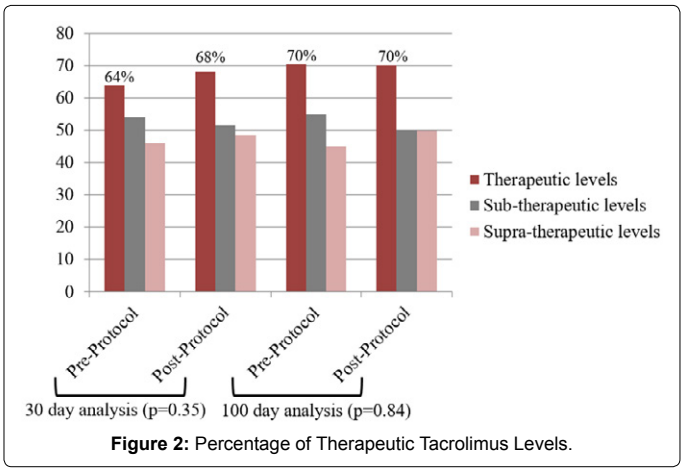

Figure 2: Percentage of Therapeutic Tacrolimus Levels.

There were no significant differences found in other secondary

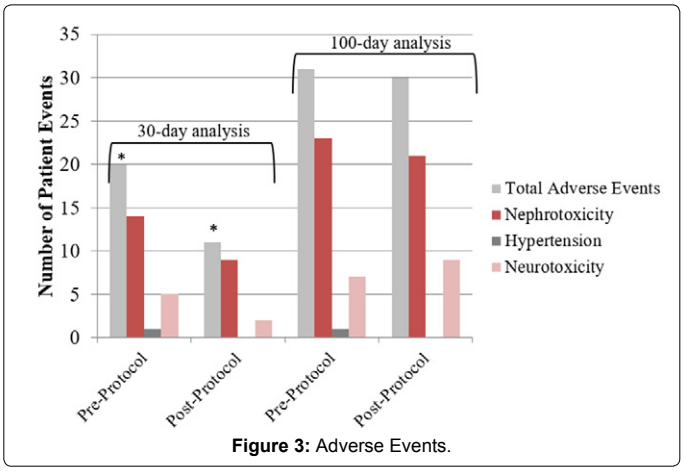

Figure 3: Adverse Events.

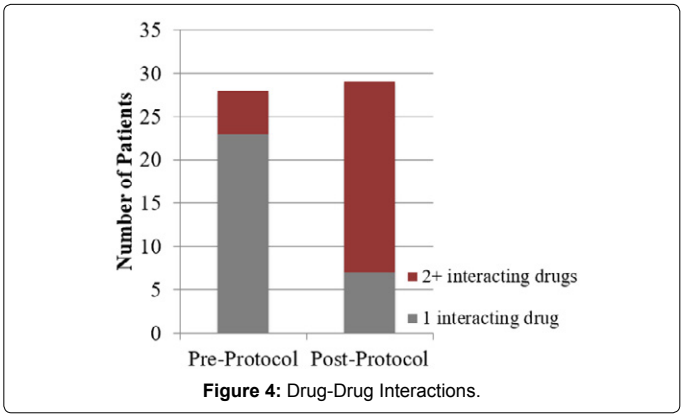

Figure 4: Drug-Drug Interactions.

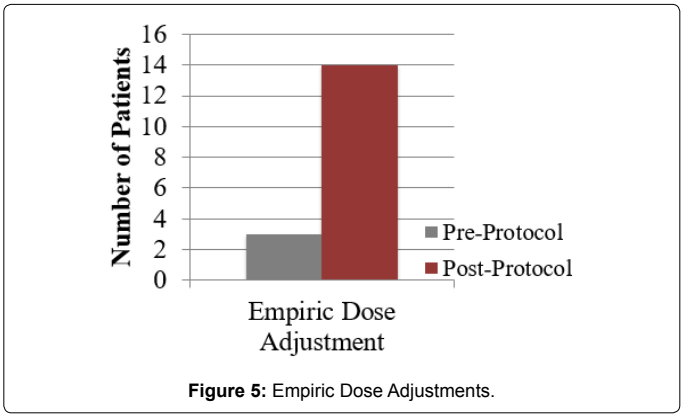

Figure 5: Empiric Dose Adjustments.

outcomes such as time to engraftment, peak SCr, incidence of GVHD, and incidence of relapse, tapering of tacrolimus, and switching to sirolimus (Table 7).

Variable	Pre-Intervention Group (n=28)	Post-Intervention Group (n=29)
Day of engraftment (if >14 days)	21 (n=30)	21 (n=30)
Median peak SCr (mg/dL)	1.7	1.5
Incidence of acute GVHD	7 (25%)	6 (21%)
Incidence of relapse	2 (7%)	5 (17%)
Tapering off tacrolimus for falling chimerism	9 (32%)	7 (24%)
Switch to sirolimus	2 (7%)	2 (7%)

Table 7: Secondary Outcomes.

Discussion

This study evaluated the impact of pharmacist intervention on therapeutic tacrolimus levels in addition to clinical outcomes. Previous studies have examined the relationship between pharmacist involvement and therapeutic drug monitoring in the hematopoietic stem cell transplant population, however, clinical outcomes have not been evaluated. As mentioned previously, Correa and colleagues conducted a study at a tertiary care facility in Brazil comparing TDM in the outpatient setting for HSCT patients who were cared for by a clinical pharmacist and those who were not. It was found that pharmacist intervention resulted in a significantly higher proportion of therapeutic tacrolimus and cyclosporine levels [5].

Although in this study there was no difference in the rate of therapeutic levels of tacrolimus between groups in both the 30-day and 100-day analyses, there was a significant difference in total adverse events between groups in the 30-day analysis. However, because an inpatient pharmacist was also directing tacrolimus management in the pre-protocol group, it cannot be deduced that implementation of a pharmacist-driven protocol had no impact on the rate of therapeutic levels without further investigation.

In addition, when evaluating differences in drug interactions, it was found that the post-protocol group had significantly more concomitant drug interactions with tacrolimus due to increased usage of posaconazole (a strong CYP3A4 inhibitor) and letermovir (a moderate CYP3A4 inhibitor).These interactions required more diligent pre-emptive adjustments to avoid toxicities. Documentation of daily tacrolimus levels, concomitant interacting drugs, and planned dose adjustments was also significantly more transparent and more frequently documented in the post-protocol group as this was done in a standardized format by pharmacists.

Limitations of this study include the retrospective nature of data collection, the small sample size evaluated, and inclusion of a single center which does not fully portray provider-dependent variability in the management of therapeutic drug monitoring. The pre-protocol group included an inpatient pharmacist on the treatment team who drove tacrolimus dosing and therefore influenced the rate of therapeutic levels. Since documentations by pharmacists was standardized in the post-protocol group, this may have led to unidentified interventions, such as empiric dose adjustments, in the pre-protocol group. Following discharge, many patients had afternoon clinic appointments during which tacrolimus troughs were drawn and were therefore not representative of true troughs. Several patients in both groups began tapering tacrolimus due to falling chimerisms prior to day +100 which reduced the total number of levels assessed. Additionally, conditioning regimens varied amongst patients which makes it difficult to compare clinical outcomes such as GVHD and relapse between groups.

Further multi-center studies with larger sample sizes should be done to evaluate differences in percentage of therapeutic drug levels between patients who do and do not have a pharmacist present on their treatment team. It would also be beneficial to include conditioning regimen subgroups in order to assess its true impact on outcomes such as GVHD and relapse. This study found that incorporation of a pharmacist-driven therapeutic drug monitoring protocol for narrow index medications results in more consistent management strategies and improves safety outcomes for patients without increasing the risk of GVHD or relapse.

Conclusion

Pharmacist involvement improves outcomes by increasing the rate of empiric dose adjustments to account for drug interactions, reducing the incidence of adverse events, and providing standard documentation within the electronic health record.

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