Establishing a Conversion Factor for Transitioning Tacrolimus from Intravenous to Oral in Allogeneic Stem Cell Transplantation Patients on Concurrent Posaconazole

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Purpose/Background
Calcineurin inhibitors are a mainstay of graft versus host disease (GVHD) prophylaxis following allogeneic stem cell transplant (ASCT). Protocols vary by institution; though, many utilize intravenous (IV) tacrolimus peri-transplant before transitioning to an oral (PO) formulation as mucositis improves and blood counts recover. The historical conversion of IV to PO tacrolimus has utilized a 1:4 ratio based upon previous studies in solid-organ transplant recipients and for patients on concurrent fluconazole. In August of 2017, standard antifungal prophylaxis for ASCT at the University of Virginia Health System (UVA) was changed from fluconazole to posaconazole. Posaconazole is a more potent inhibitor of tacrolimus metabolism via hepatic and gastrointestinal cytochrome P450 (CYP) 3A4. Anecdotal experience with patients concurrently taking posaconazole suggest a more conservative tacrolimus IV to PO conversion factor is necessary to avoid supratherapeutic tacrolimus levels; however, no standard conversion factor exists.

Objective
The purpose of this study was to determine a standard conversion factor for IV to PO tacrolimus in ASCT patients on concurrent posaconazole.

Methods
A single-center, retrospective, cohort study was conducted on patients >18 years of age who received ASCT between January 2016 and December 2018, tacrolimus for GVHD prophylaxis, and either concurrent fluconazole or posaconazole. All ASCT was performed in the inpatient environment. Baseline demographic data were collected via the electronic medical record and patients were separated into two groups: fluconazole versus posaconazole. The PO formulations of antifungal prophylaxis comprised of posaconazole delayed-release tablets or fluconazole tablets. In each group, tacrolimus levels and doses were collected at least twice weekly and dependent upon patient clinical status. Tacrolimus doses were considered stable when linked with 3 or more tacrolimus levels within therapeutic range (5-15 ng/mL). Conversion factor, the primary outcome, was established by the division of the last IV tacrolimus dose and the stable dose of oral tacrolimus. Secondary outcomes were assessed for a historical conversion factor with fluconazole and the incidence of acute kidney injury (AKI) associated with supratherapeutic tacrolimus levels. AKI was determined via the Kidney Disease: Improving Global Outcomes (KDIGO) definition. Descriptive statistics were used to determine primary and secondary outcomes.

Results
Of 98 patients assessed, 59 patients met the criteria for evaluation for conversion of IV to PO tacrolimus with 14 patients on fluconazole and 45 patients on posaconazole. The majority of patients were male (61%) with a median age at transplant of 56 years. The median initial conversion factor from IV to PO tacrolimus on posaconazole was 1.83, which resulted in 38% of patients with a supratherapeutic tacrolimus level after conversion to oral therapy prior to discharge. In addition, AKI was associated with supratherapeutic tacrolimus levels in 36% of patients on posaconazole. However, once patients were stabilized on an oral tacrolimus dose, the median conversion factor was found to be 1.25. The median conversion factor for patients on fluconazole therapy was 3.0. Posaconazole was associated with a median of 3 supratherapeutic tacrolimus levels compared to 1.5 supratherapeutic levels with fluconazole prophylaxis (p=0.003). Of patients on fluconazole, 29% developed an AKI that was associated with supratherapeutic tacrolimus levels.
**Conclusion**

To date, there has been no standardization of tacrolimus conversion factors for patients who transition from IV to PO while on concurrent posaconazole. The conversion factor from IV to a stable PO tacrolimus dose while on posaconazole was found to be much lower than the historically suggested conversion factor at 1.25 and 4.0, respectively. Based on the results of this study, our institution has implemented a new conversion factor for IV to PO tacrolimus in ASCT patients on concurrent posaconazole. Further multicenter studies are warranted to validate our standard conversion factor.