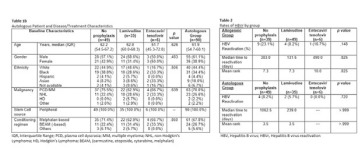

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The Clinical Significance of the Drug-Drug Interaction between Letermovir and Voriconazole in Stem Cell Transplantation

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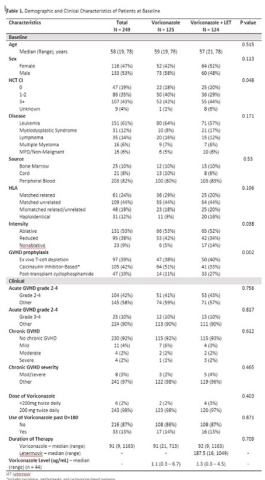
Patients undergoing allogeneic hematopoetic stem cell transplantation (alloHCT) are at an increased risk of developing opportunistic infections due to prolonged durations of neutropenia and utilization of immunosuppression. Prophylactic antimicrobials are utilized in this high-risk patient population to prevent morbidity and mortality. Pharmacokinetic analyses have shown that co-administration of voriconazole and letermovir potentially causing a 30-40% decrease in voriconazole concentrations. The clinical impact of this interaction is poorly described.

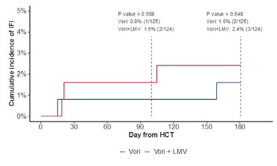
The objective of this study is to characterize the clinical significance of the interaction between letermovir and voriconazole in alloHCT recipients. The primary endpoint is the incidence of proven or probable invasive fungal infections (IFI), defined by the 2020 IDSA updates and revisions in redefining invasive fungal infections, at day +100 and day +180 from transplant. Secondary endpoints aim to characterize the extent of the interaction through assessment of voriconazole trough concentrations and analysis of therapeutic changes made in response to fungal infections.

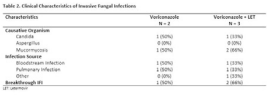
This is a single-center, retrospective, IRB approved study of CMV seropositive adult alloHCT recipients transplanted between January 2015 and June 2021. All patients received voriconazole prophylaxis. Patients who received concomitant letermovir and voriconazole were compared to those that only received voriconazole (historical control). Patients whose duration of prophylaxis with voriconazole and letermovir did not overlap for at least 7 days were excluded. Descriptive statistics and multivariate analyses were utilized for analysis.

A total of 249 patients met inclusion criteria of this study (table 1). 124 patients received combination voriconazole and letermovir (V/L) and 125 patients received voriconazole alone (V). At D+180, a total of 2 (1.6%) patients in the V arm and 3 (2.4%) patients in the V/L arm had experienced a documented IFI (figure 1). The cumulative incidence of IFI at D+180 was similar between arms (p = 0.648). Three infections that occurred in the V/L arm. 2 were proven IFIs and 1 was considered a probable IFI. Both infections in the V arm were proven IFIs (table 2). The cumulative incidence of IFI at D+100 was similar between arms (p = 0.568). There were no differences in the median voriconazole troughs between arms.

The concomitant use of voriconazole and letermovir in patients undergoing hematopoietic allogeneic stem cell transplant does not result in an increased risk of developing IFIs when compared to patients that received voriconazole alone as prophylaxis. Employing therapeutic drug monitoring of voriconazole levels may still be of clinical utility when approaching the management of suspected or proven IFIs when patients are on concurrent letermovir.







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Assessment of the Cytolytic Potential of a Multivirus-Targeted T Cell Therapy Using a Vital Dye-Based, Flow Cytometric Assay

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Introduction: Reliable and specific characterization assays are a pre-requisite for the successful clinical translation of immunotherapies. To measure cytolytic potential, the ^{51}chromium (^{51}Cr) release assay has been the gold standard for testing effector cells. However, attaining the approvals for radioactive work is complex, while technical aspects [i.e. sensitivity, short (4-6hr) assay duration] may lead to suboptimal results. This has been the case with our ex vivo expanded, polyclonal (CD4+ and CD8+) multivirus-specific T cell (multiVST) lines, which are potent against 5 clinically problematic viruses (EBV, CMV, BKV, HHV6, and AdV) when administered to allogeneic HCT recipients. However, evaluating the in vitro cytolytic potential of these VSTs has proven difficult in a standard ^{51}Cr release assay.

Objectives: We, therefore, wanted to explore the utility of an alternate vital dye (CFSE)-based cytotoxicity assay.

Methods: We generated multiVST lines by exposing PBMCs from healthy donors to pepmixes (overlapping peptide libraries) spanning 12 immunodominant antigens from the aforementioned viruses, followed by culture in a G-Rex device in cytokine-supplemented medium for 2 weeks. Subsequently, we assessed the in vitro cytotoxicity of these once-stimulated VSTs against viral antigen-loaded autologous PHA blasts in a standard 5-hour ^{51}Cr-release assay and an optimized 16-hour CFSE-based flow cytometric assay.

Results: The results from the 5-hour ^{51}Cr release assay varied from line to line, with detection of specific lysis against none (0/5) of the target viruses and no more than three (3/5) [mean±sem: AdV: 8.9±1.9%, BKV: 5.4±3.1%, CMV: 9.9±4.1%,