Clinical Pharmacology of Maribavir (SHP620): A Comprehensive Overview

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Introduction: Maribavir, a potent and orally bioavailable antiviral, is being evaluated in Phase 3 trials for the treatment of CMV infections in transplant patients and received FDA Breakthrough Therapy designation. A thorough understanding of the clinical pharmacology of maribavir is necessary to guide the appropriate use of the drug in transplant patients who often have multiple comorbidities and require complex concurrent medication regimens.

Objectives: To summarize the clinical pharmacology data of maribavir.

Methods: Pharmacokinetic and pharmacodynamic assessments were performed in sixteen Phase 1 studies and three Phase 2 studies. Data were summarized to characterize maribavir’s disposition (absorption, distribution, metabolism, and excretion) in healthy adult subjects and special populations (HIV-infected, hepatically impaired, renally impaired, and organ transplant recipients). A definitive QT study was conducted to evaluate the cardiac repolarization effect. The drug interaction risks were assessed using both nonclinical and clinical studies.

Results: Maribavir is primarily eliminated through the CYP3A4 pathway and has a half-life of 5–7 hours. Co-administration with food or antacid, or crushing the tablet, had no impact on maribavir’s exposure. Maribavir binds to plasma proteins with unbound fraction estimated at 1.5% and can penetrate the blood–retinal barrier. No pharmacokinetic difference is found among healthy subjects, transplant patients, subjects with severe renal impairment, or moderate hepatic impairment. Maribavir’s exposure is increased by 46% by ketoconazole and decreased by 61% by rifampin. Maribavir increases tacrolimus exposure by 51%, does not affect voriconazole exposure. Maribavir has no effects on most other concurrent medications. Maribavir has no effects on QT intervals.

Conclusions: Extensive clinical pharmacology data have been generated to support the clinical use and dose of maribavir for the treatment of CMV infections in transplant recipients. Maribavir can be taken with or without food. No maribavir dose adjustment is needed in patients with mild-to-moderate hepatic impairment or renal impairment or with concurrent medications, except for CYP3A4 inducers.

Clinical Validation of a Novel ELISPOT-Based in Vitro Diagnostic Assay: Monitoring Cytomegalovirus-Specific Cell-Mediated Immunity and Risk Stratification in Hematopoietic Stem Cell Transplant Recipients

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Increasing evidence suggests that impaired cytomegalovirus (CMV)-specific cell-mediated immunity (CMV-CMI) is a major cause of uncontrolled CMV reactivations and associated complications in hematopoietic stem cell transplantation (HSCT). Reliable test exists to predict patients at risk of primary and/or recurrent CMV reactivations following HSCT. Accurately assessing CMV-CMI might therefore improve the risk stratification of patients and allow optimizing and individualizing patient care. This study aimed to evaluate the suitability of a novel IFN-γ ELISPOT assay (T-TrackTM CMV), based on the stimulation of peripheral blood mononuclear cells with T-activated pp65 and IE-1 CMV proteins, to predict protection from recurrent CMV reactivation following the resolution of a treatment-requiring primary CMV reactivation. A prospective, longitudinal, observational, multicenter study was conducted in 175 intermediate- and high-risk (Donor (D)+/Recipient (R)+, D+/R-, D-/R+) HSCT recipients (ClinicalTrials.gov ID: NCT02156479). Patients underwent preemptive antiviral therapy per institutional guidelines. CMV DNAemia was analyzed by quantitative PCR. CMV-CMI was measured at day 45, 60, 80, 100 and 120 post-transplantation, as well as at onset and following the end of preemptive treatment. Occurrence of recurrent CMV reactivation was monitored up to 7.5 months post-transplantation. 154/175 patients fulfilling the inclusion/exclusion criteria and having at least one valid T-TrackCMV test result were included in the final analysis. Out of 74 patients (24 D+/R+, 3 D+/R-, 47 D-/R+) who experienced a first CMV reactivation and had a valid ELISPOT test result at the end of this primary reactivation, 30 (41%) faced a recurrent CMV reactivation during the observational period. Interestingly, 41/44 patients free of recurrent reactivation had a positive test result (i.e. positive for at least one of pp65- and/or IE-1-specific result) after resolution of the primary CMV reactivation, resulting in a 93% specificity in diagnostic accuracy. Accordingly, a time-to-event analysis indicated a significantly lower incidence of recurrent CMV reactivation in patients with a positive test result.
Altogether, this novel standardized IFN-γ ELISpot assay allows an improved risk stratification of CMV-related clinical complications, and can support clinicians in the identification and management of patients with increased risk of recurrent CMV reactivation following HSCT.

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Clinical Validation of the Definitions of Resistant and Refractory Cytomegalovirus (CMV) Infection and Disease in Hematopoietic Cell Transplant (HCT) Recipients.

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**Introduction:** Resistant or refractory CMV infections are not well defined and are associated with high morbidity and mortality in HCT recipients. Ganciclovir (GCV), Foscarnet (FOS) and valganciclovir (VGC) are available for treatment of CMV infections with successful results, however, toxicities from these drugs are common and associated resistance have been reported. Definitions for “resistant and refractory CMV infections” were published recently for clinical trials use and to provide guidance for clinical practice (Chemaly RF et al, CID, 2018).

**Methods:** We performed a single center retrospective chart review (1/2010 to 9/2018) of HCT recipients who had CMV genotype performed for suspected antiviral resistance. Based on the published definitions, we categorized patients as either having refractory CMV (defined as CMV viremia that fails to decrease after at least 2 weeks of appropriately dosed and delivered antiviral therapy; and in the absence of known genetic mutations to the available antiviral agents) or resistant CMV infection (defined as refractory infection with identification of genetic mutations in the UL97 and/or UL54 genes correlating with *in vitro* antiviral resistance). Primary outcomes were CMV disease and non-relapse mortality (NRM).

**Results:** CMV genotype analysis was performed in 120 patients and 29 (24%) patients had UL 97 and/or UL54 mutations. When compared to refractory CMV infection, patients with resistant CMV infection were more likely to have AML (38% vs 76%), had cord blood transplant (8% vs 24%), were diagnosed with resistant infection later after HCT (59 d vs 120 d), had greater number of prior episodes of CMV infections, had more CMV diseases (34% vs 62%), and specifically more CMV Gl diseases (22% vs 55%); (all, p<0.01). The median CMV viral load (VL) at baseline was higher in patients with resistant CMV infections when compared to refractory (210 UI/mL (range 137-315.695) vs. 137 UI/mL (range: 137-55,419); p<0.001, respectively) (Figure 1). NRM was higher in patients with refractory CMV infections (70% vs. 30%, p=0.283; Figure 2).

**Conclusion:** Our data showed that resistant CMV infections are associated with higher morbidity including CMV disease while refractory CMV infections are associated with higher NRM. Whether this high NRM in patients with refractory CMV infections is a reflection of the host immunosuppression with persistent CMV infection needs to be determined.