COADMINISTRATION OF REZAFUNGIN DOES NOT IMPACT CYCLOSPORINE OR MYCOPHENOLATE MOFETIL PHARMACOKINETICS

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BACKGROUND

Rezafungin is a novel echinocandin antifungal being developed for treatment of candidemia and invasive candidiasis and for prevention of invasive fungal diseases caused by *Candida*, *Aspergillus*, and *Pneumocystis* species among allogeneic blood and marrow transplantation recipients. Antifungal prophylaxis is often needed with immunosuppressive agents. However, drug-drug interactions (DDIs) with antifungal agents most often used for prophylaxis (eg, azoles) can alter the pharmacokinetics (PK) of immunosuppressive agents, requiring a dose reduction of the primary treatment, or avoiding antifungal prophylaxis altogether. Risks of complications due to such modifications are high and include overdose or ineffective treatment, therefore, therapeutic drug monitoring is often required. Rezafungin, previously shown to have negligible potential for metabolic or transporter DDIs, was studied for its effects on the pharmacokinetics of cyclosporine or mycophenolate mofetil in healthy individuals in support of its future use in patients.

METHODS

This open-label study of approximately 16 male and 16 female healthy inpatients (replacements were allowed during the active screening phase of the study) assessed DDIs between rezafungin (as perpetrator) and cyclosporine or mycophenolate mofetil (males only). Other study drugs (ibrutinib and venetoclax) were also evaluated in this study and their lack of DDI with rezafungin has previously been reported. Cyclosporine (200 mg orally) or mycophenolate mofetil (500 mg orally) were each given alone and with IV rezafungin (400 mg followed by once-weekly 200 mg) with suitable washout periods between dosing. Blood or plasma concentrations of cyclosporine or mycophenolic acid, respectively, were determined using validated LC-MS/MS methodologies.

RESULTS

A total of 35 subjects received any study drug, with 31 receiving cyclosporine alone and with rezafungin, and 16 receiving mycophenolate mofetil alone and with rezafungin.

The plasma concentration versus time curves shown in Figures 1 and 2 for cyclosporine or mycophenolic acid were similar with and without rezafungin. The PK parameter results of the two immunosuppressive agents given alone or with rezafungin (as shown in Tables 1 and 2) were comparable with exposure (AUC and C_{max}) values within ~ 15%.

Figure 1: Cyclosporine Blood Concentration Versus Time When Administered Alone or with Rezafungin

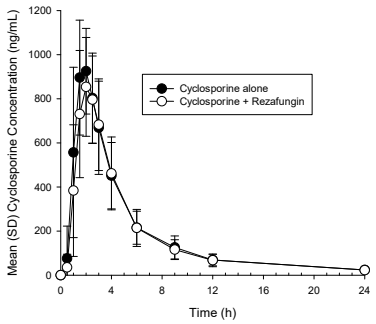

Figure 2: Mycophenolate Plasma Concentration Versus Time When Administered Alone or with Rezafungin

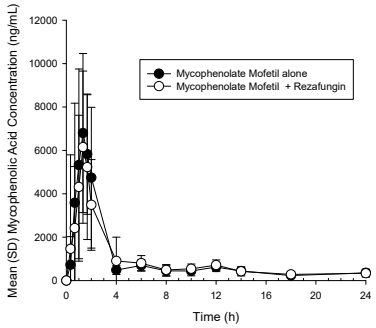

Table 1: Plasma Cyclosporine PK Parameter Estimates Following Administration of 200 mg Cyclosporine Alone or in Combination with 400 mg Rezafungin

	200 mg Cyclosporine Administered Alone				200 mg Cyclosporine Administered in Combination with 400 mg Rezafungin			
Parameter (unit)	N	Mean	SD	CV%	N	Mean	SD	CV%
$AUC_{0\text{-}t}$ (ng*h/mL)	33	4956.33	1295.91	26.1	31	4683.80	1265.77	27.0
$AUC_{0\text{-}\infty}$(ng*h/mL)	33	5193.75	1374.03	26.5	31	4893.58	1324.25	27.1
C_{max} (ng/mL)	33	1023.13	238.08	23.3	31	942.93	214.04	22.7
$t_{1/2}$ (h)	33	22.70	9.98	44.0	31	23.25	7.13	30.7
	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	33	2.00	1.00	4.00	31	1.98	1.48	2.98

AUC=, Area under the plasma concentration time curve from 0 to time of last sample (0-t) or extrapolated to time infinity (0-∞), C_{max}= maximum plasma concentration; CV% = coefficient of variation expressed as a percentage; Max = maximum; Min = minimum, N = number; t1/2= apparent half-life of elimination; T_{max}= time of observed C_{max}.

Table 2. Plasma Mycophenolic Acid PK Parameter Estimates Following Administration of 500 mg Mycophenolate Mofetil Alone or in Combination with 400 mg Rezafungin

	500 mg Mycophenolate Mofetil Administered Alone				500 mg Mycophenolate Mofetil Administered in Combination with 200 mg Rezafungin			
Parameter (unit)	N	Mean	SD	CV%	N	Mean	SD	CV%
$AUC_{0\text{-}t}$ (ng•h/mL)	16	26051.5	6901.7	26.5	16	25643.4	5637.1	22.0
$AUC_{0\text{-}\infty}$(ng•h/mL)	13	29094.5	7528.8	25.9	13	29071.8	5246.6	18.0
C_{max} (ng/mL)	16	10010.2	3263.8	33.8	16	8568.7	3553.2	41.5
$t_{1/2}$ (h)	13	12.98	5.12	39.5	13	15.56	10.04	64.5
	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	16	1.33	0.67	2.00	16	1.32	0.32	3.98

AUC=, Area under the plasma concentration time curve from 0 to time of last sample (0-t) or extrapolated to time infinity (0-∞), C_{max}= maximum plasma concentration; CV% = coefficient of variation expressed as a percentage; Max = maximum; Min = minimum, N = number; t1/2= apparent half-life of elimination; T_{max}= time of observed C_{max}.

There were a total of 10 subjects with at least one adverse event (AE) when the study drugs (cyclosporine or mycophenolate mofetil) were given alone and 15 subjects with at least one AE when rezafungin was given together with either cyclosporine or mycophenolate mofetil. One subject each was withdrawn from the study due to AEs considered to be related to either cyclosporine (esophagitis) or rezafungin (infusion reaction during first infusion of rezafungin). Most AEs were mild or moderate in severity; one subject had an AE of esophagitis rated as severe that was considered related to cyclosporine. The most common AEs were headache, nausea, and infusion site reaction. Overall, no safety trends were seen.

CONCLUSIONS

No dose adjustments are expected for either cyclosporine or mycophenolate mofetil when given in combination with rezafungin.

Rezafungin was well tolerated in most subjects, although one subject discontinued due to an infusion reaction known to be associated with echinocandin infusions, which elicits a 'histamine-like' response. Signs and symptoms of these infusion reactions are associated with the speed of drug administration and typically disappear with slowing or interruption of infusion.

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