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ORIGINAL RESEARCH

Co-Administration with Voriconazole Doubles the Exposure of Ruxolitinib in Patients with Hematological Malignancies

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Background: Ruxolitinib is newly approved for glucocorticoid-refractory acute graft-versus-host disease (GVHD) in patients undergoing allo-geneic hematopoietic stem-cell transplantation (allo-HSCT), and voriconazole is commonly used in allo-HSCT recipients for the prophylaxis or treatment of invasive fungal infections (IFIs). Drug–drug interaction (DDI) may occur between them because their metabolic pathways overlap and can be inhibited by voriconazole, including cytochrome P450 (CYP) isozymes 3A4 and 2C9.

Objective: In the present study, we aimed to investigate the DDI between ruxolitinib and voriconazole in patients with hematological malignancies.

Methods: A total of 12 patients with hematologic malignancies were enrolled in this single-arm, single-center, Phase I/II, fixed sequence self-control study. All subjects received 5 mg ruxolitinib alone, followed by the co-administration of ruxolitinib and voriconazole. The plasma concentrations of the two drugs were determined by two well-validated high-performance liquid chromatography-tandem mass spectrometry methods. Phoenix WinNonlin software was used to compare the differences in maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), terminal elimination half-life ($T_{1/2}$), and apparent plasma clearance (CL/*F*), as well as area under the curve from time zero to last (AUC_{last}) and AUC from time zero to infinity (AUC_{inf}) between the two periods.

Results: After pre-treatment with voriconazole, no significant change existed in T_{max}, while C_{max}, $T_{1/2}$, AUC_{last}, and AUC_{inf} of ruxolitinib were significantly increased by 50.4%, 81.3%, 110.1%, and 118.3%, respectively, and CL/*F* was significantly decreased to 43.6% compared with patients receiving ruxolitinib alone.

Conclusion: Our findings confirmed a moderate inhibitory DDI between ruxolitinib and voriconazole as voriconazole decreased the elimination and increased the exposure of ruxolitinib in patients with hematologic malignancies. We recommended a dose reduction regimen when voriconazole and ruxolitinib were coadministered. Drug monitoring might help determine the ruxolitinib treatment concentration for aGVHD patients, improve efficacy, and reduce toxicity.

Keywords: pharmacokinetics, ruxolitinib, voriconazole, drug–drug interaction, graft-versus-host disease

Introduction

Graft-versus-host disease (GVHD) remains a major challenge after allogeneic hematopoietic stem-cell transplantation (allo-HSCT). Systemic glucocorticoids are the first-line therapy for grade II to IV acute GVHD (aGVHD), while more than 50% of recipients cannot achieve durable response.[1,2] As an orally administered selective Janus Kinase (JAK) 1 and JAK2 inhibitor, ruxolitinib is originally used in patients with myelofibrosis and approved by the US Food and Drug Administration (FDA) in 2019

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for the treatment of steroid-refractory aGVHD (SR-aGVHD) in patients aged over 12 years.[3–5] With the promising outcomes, several other clinical trials are carried out to explore the therapeutic effects of ruxolitinib in other diseases, including chronic GVHD.[6–10] In the multi-centerphase III REACH2 clinical trial, where SR-aGVHD patients are administered 10 mg ruxolitinib twice daily, ruxolitinib is considered as a drug with a narrow therapeutic index in patients undergoing HSCT. The overall response is higher on day 28 (62% vs 39%), while the adverse events are increased either, as the most common severe (grade ≥ 3) adverse events are thrombocytopenia (27% vs 15%), anemia (22% vs 19%), and neutropenia (13% vs 9%) compared with the control group.[3] Unchanged parent molecules are less than 1% in human urine and feces, indicating that almost all the ruxolitinib is eliminated by hepatic metabolism, predominantly catalyzed by cytochrome P450 enzymes (CYPs), mainly by CYP3A4 and to a lesser extent, CYP2C9.[11,12] Although ruxolitinib is also a weak competitive inhibitor of P-glycoprotein (P-gp) with a half-maximal inhibitory concentration (IC_{50}) estimated to be 21.5 μM (6.59 μg/mL), the effect of transporters are not considered in this study since the concentration of 6.59 μg/mL is about 1000 times higher than the C_{max} when 5 mg ruxolitinib was given.[12,13]

As a broad-spectrum triazole antifungal drug, voriconazole is frequently used in patients receiving allo-HSCT for the prevention and treatment of invasive fungal infections (IFIs).[14,15] Voriconazole is metabolized mainly by CYP2C19, and to a lesser extent by CYP3A4 and CYP2C9, and it also acts as a potent CYP3A4 inhibitor, as well as a weak CYP2B6, CYP2C9, and CYP2C19 inhibitor.[16–19] Moreover, it is also a substrate and inhibitor of P-gp, but does not inhibit the breast cancer resistance protein (BCRP).[20] A previous study has reported that the maximum plasma concentration (C_{max}), area under the curve from time zero to last (AUC_{last}), and AUC from time zero to infinity (AUC_{inf}) of plasma concentration-time are increased by 47%, 234%, and 232%, respectively, when coadministered with fluconazole, a strong CYP2C19 and a moderate CYP2C9 and CYP3A4 dual inhibitor, compared with ruxolitinib alone.[12,21] The concomitant administration of rifampin, a potent CYP3A4 inducer, or ketoconazole, a potent and reversible CYP3A4 inhibitor, has also been shown to decrease or increase the exposure as AUC_{inf} of ruxolitinib, respectively.[12] Drug-drug interactions (DDIs), like a competitive inhibition in CYP2C9 and a time-dependent inhibition in CYP3A4, may also occur between voriconazole and ruxolitinib when they are coadministered.[22,23] However, there is still a lack of information on their DDI, especially in hematological patients. Therefore, we conducted a prospective single-center study consisting of 12 patients with hematologic malignancies who were given 5 mg ruxolitinib alone and then coadministered ruxolitinib and voriconazole to reveal the properties of DDIs between the two drugs.

Methods

Study Design

This was a self-controlled study consisting of two fixed-sequence periods to investigate the effects of voriconazole on the pharmacokinetics of ruxolitinib. A total of 12 patients with hematological malignancies who were allo-HSCT candidates before the start of conditioning were enrolled in the Chinese People's Liberation Army (PLA) General Hospital from January 2021 to June 2021 (registered at Chinese Clinical Trial Registry, ChiCTR2100042673). Patients aged over 12 years and weighed more than 40 kg were enrolled in the present study. These patients received a single oral dose of 5 mg ruxolitinib (Novartis, Jakavi, 5-mg tablet, Switzerland) alone on day 1 (period 1) and then orally received voriconazole (Pfizer, Vfend, 200-mg tablet, Italia) and ruxolitinib (period 2). The former four patients were given 200 mg voriconazole per 12 h from day 2 to day 5, and the later eight patients were given a loading dose of 400 mg voriconazole per 12 h on day 2, followed by 200 mg per 12 h from day 3 to day 5. The second single dose of 5 mg ruxolitinib was administered on day 5, 1 h later after voriconazole intake, to reduce the risk of DDIs during the absorption phase.[24,25] This study lasted for 5 days, containing the last blood sampling time point on day 6, and then allo-HSCT was initiated. All the patients were hospitalized and already had a complete physical examination and disease evaluation to ensure they were eligible for allo-HSCT. Patients receiving any drug or food that could interact with voriconazole and ruxolitinib within 14 days and those whose primary disease tended to relapse were excluded before enrolment (Figure 1). Breakfast, lunch, and supper were provided at 7:00 a.m., 11:00 a.m., and 5:00 p.m., respectively. The study was conducted following principles of Good Clinical Practice and the Declaration of Helsinki, and the experimental protocols were approved by the Ethics Committee of PLA General Hospital. Written informed consent was obtained from all participants before undergoing any study-related procedures.

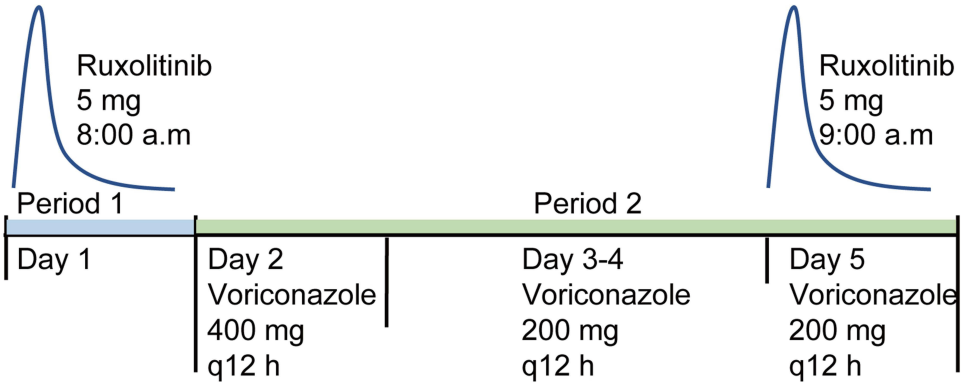

Figure 1 Schematic study design. q12 h, twice a day.

Sample Collection

Blood samples were collected after the administration of ruxolitinib on day 1 and day 5, and after the administration of voriconazole on day 2. The sampling time was scheduled as follows: 5 min pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, and 12 h post-dose, including the last sampling at 24 h post-dose on day 6. Samples of the trough concentration (C_{trough}) of voriconazole on day 4 were also collected to confirm whether the steady-state of voriconazole was achieved before the second dose of ruxolitinib was given. Each blood sample (~ 0.5 mL) was drawn into a 2-mL tube containing ethylene diamine tetra-acetic acid (EDTA). Samples were centrifuged within 1 h after collection, and plasma was stored at −40°C until analysis. All the samples were analyzed within 2 months.

Drug Concentration Detection

The detection of voriconazole was performed according to a well-validated LC-MS/MS method, which has been published by Mei et al.[26] Briefly, 50 μL plasma was added with 50 μL internal standard (IS) and 450 μL methanol to precipitate the protein. After centrifugation, 5 μL supernatant was injected into the LC-MS/MS system. The detection range was 0.01–6 μg/mL, and the intra-day and inter-day precisions were 1.35–7.68% and 3.38–8.97%, respectively. The ruxolitinib detection method was similar to voriconazole, with dasatinib used as the IS. The detection range was 0.4–200 ng/mL, and the intra-day and inter-day precisions for ruxolitinib were 1.78–4.22% and 1.28–4.22%, respectively. The total ion chromatograms of ruxolitinib and voriconazole were presented in Figure 2.

Pharmacokinetic Analysis

The pharmacokinetic parameters of ruxolitinib were analyzed from the plasma concentration-time profiles by using Phoenix WinNonlin software (Certara Inc., WinNonlin version 8.3, Princeton, New Jersey, USA). X-Y graphs with the logarithmic scale of the Y-axis for ruxolitinib concentration-time of two periods were plotted individually, and then the terminal elimination rate (λ_z) was determined automatically using the "Best fit" method built in the software where the fitted lines had the highest R^2. The terminal elimination half-life ($T_{1/2}$) was determined by following the equation: $T_{1/2} = \ln(2)/\lambda_z$. The C_{max} and T_{max} of ruxolitinib were determined according to the real observations, and the apparent plasma clearance (CL/*F*), $T_{1/2}$, AUC_{inf}, and AUC_{last} were determined using the non-compartmental analysis (NCA). The AUC was calculated using the linear trapezoidal linear interpolation method, and λ_z was used to calculate the AUC_{inf}. Two adjacent trough concentrations of voriconazole were used to calculate the value of $(C_{12}-C_0)/C_{12}\times100\%$.[27] Steady-state was defined as achieved if the value was less than 15%.

Statistical Analysis

The normality and lognormality for each variable were evaluated before statistical analysis. Normally distributed pharmacokinetic variables, such as T_{max}, $T_{1/2}$, C_{max}, and CL/*F*, were analyzed using the paired Student's *t*-test, and the results were expressed as mean ± SD. Moreover, log-normally distributed variables, such as AUC_{last} and AUC_{inf},

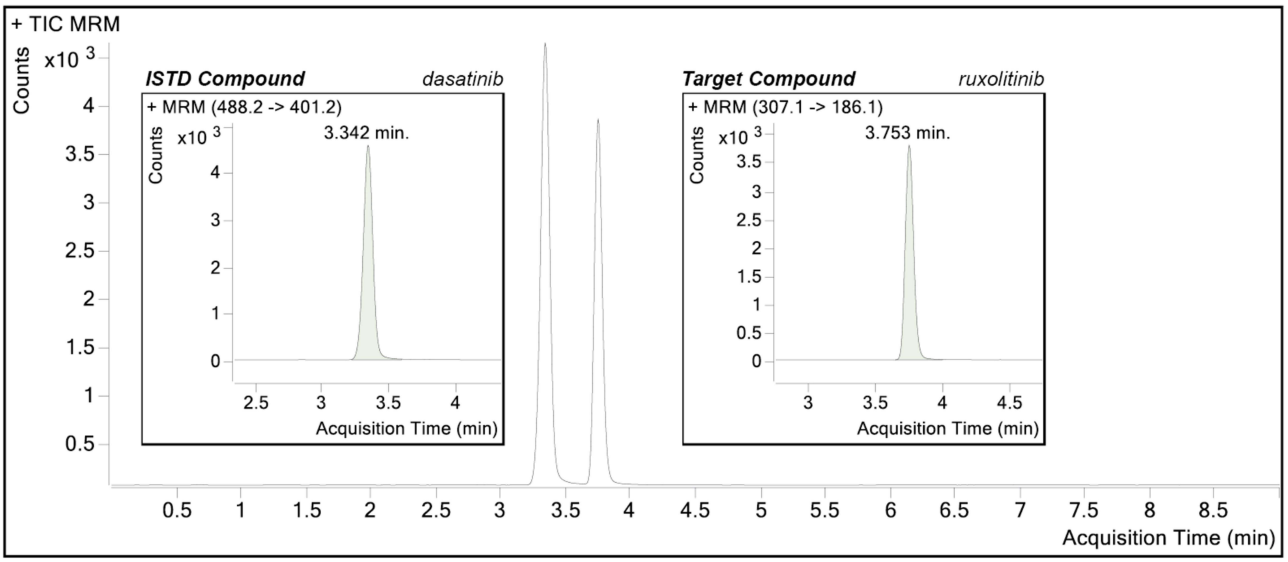

Figure 2 Chromatogram of ruxolitinib and IS.
Notes: Ruxolitinib: 40 ng/mL; IS: 50 ng/mL.
Abbreviations: TIC, total ion chromatogram; IS, internal standard; MRM, multiple reaction monitoring.

were analyzed by the Wilcoxon test, and the data were presented as geometric mean ± geometric SD. $P < 0.05$ was considered statistically significant. All data were analyzed using GraphPad Prism (version 8.4.0).

Results

Patient Characteristics

Table 1 summarizes the demographic characteristics and underlying diseases of the 12 patients. Of the 12 patients, 10 patients already underwent at least three cycles of chemotherapy and were currently in the remission status of the disease, and the remaining two myelodysplastic syndrome with excess of blast (MDS-EB) patients did not undergo chemotherapy. All of them were ready to initiate conditioning for the allo-HSCT and completed the two periods of study.

Table 1 Patient Characteristics and Underlying Diseases

Characteristic	No. (%) of Patients or Mean (± SD)
Demographic	
Gender (female)	12 (4)
Age (yr)	43 (34.8–50.3)
Weight (kg)	65 (58.3–71.8)
Height (cm)	167 (162–171)
BMI (kg/m^2)	23.5 (21.3–25.6)
Underlying disease	
AML	2
MDS	2
CMML	1
ALL	5
NHL	2

Abbreviations: BMI, body mass index; AML, acute myelocytic leukemia; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; ALL, acute lymphoblastic leukemia; NHL, Non-Hodgkin Lymphoma.

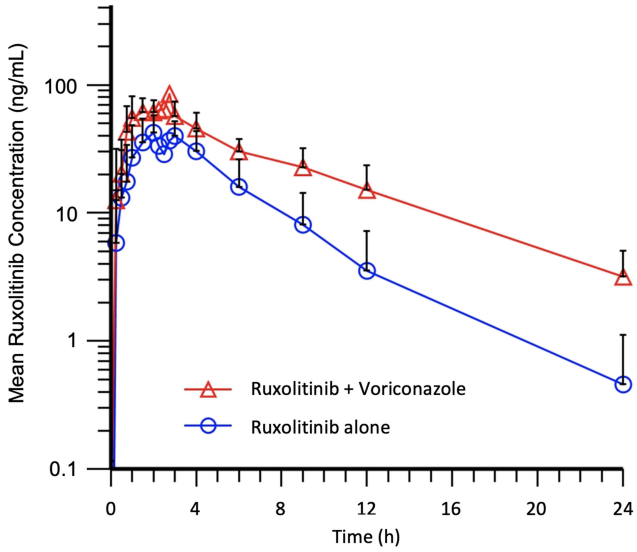

Figure 3 Mean (+SD) ruxolitinib plasma concentrations after an oral dose of 5 mg with (red lines and triangles) or without pre-administered voriconazole (blue lines and circles) in 12 patients with hematological malignancies. Moreover, 200 mg voriconazole was given per 12 h in period 2 with eight patients given 400 mg on day 2 followed by 200 mg per 12 h in day 3–5.

Ruxolitinib

Figure 3 shows the ruxolitinib mean plasma concentration-time profiles of 12 patients with hematological malignancies during two periods of the study. Each pharmacokinetic parameter of ruxolitinib in the absence or presence of voriconazole was compared and analyzed (Table 2 and Figure 4). C_{max}, $T_{1/2}$, AUC_{last}, and AUC_{inf} were increased, CL/*F* was decreased in all patients, and the differences in C_{max}, $T_{1/2}$, AUC_{last}, AUC_{inf}, and CL/*F* but not T_{max} between the two periods had a significant statistical significance. Voriconazole increased the plasma C_{max} of ruxolitinib to 150.4% ($P = 0.0001$), from 48.2 ± 14.5 ng/mL to 72.5 ± 14.7 ng/mL ($P = 0.0001$), and prolonged the terminal elimination $T_{1/2}$ from 3.0 ± 0.8 h to 5.5 ± 2.0 h ($P = 0.0012$). The AUC_{last} and AUC_{inf} of ruxolitinib were increased to approximately 2.1-fold ($P = 0.0005$), and the plasma CL/*F* of ruxolitinib was decreased to 43.6%, from 22.5 ±6.4 L/h to 9.8 ± 2.5 L/h ($P < 0.0001$).

Adverse Effects

No observed adverse effects were reported during the two doses of 5 mg ruxolitinib. Adverse events of voriconazole were reported in five out of eight patients who were given loading doses on day 2. Three patients had slight xanthopsia,

Table 2 Ruxolitinib Pharmacokinetic Parameters After Oral Administration of 5 mg Without Voriconazole (Ruxolitinib) and After Co-Administered with Voriconazole (Ruxolitinib + Voriconazole) in 12 Patients with Hematological Malignancies

Parameter	Ruxolitinib [Mean ± SD]	Ruxolitinib + Voriconazole [Mean ± SD]
$T_{1/2}$ (h)	3.0 ± 0.8	5.5 ± 2.0
% of ruxolitinib alone	100	181.3
C_{max} (ng/mL)	48.2 ± 14.5	72.5 ± 14.7
% of ruxolitinib alone	100	150.4
CL/*F* (L/h)	22.5 ± 6.4	9.8 ± 2.5
% of ruxolitinib alone	100	43.6
AUC_{last} (ng·mL^{-1}·h)	246.5 ± 110.3	518.0 ± 139.8
% of ruxolitinib alone	100	210.1
AUC_{inf} (ng·mL^{-1}·h)	249.7 ± 113.6	545.2 ± 148.3
% of ruxolitinib alone	100	218.3

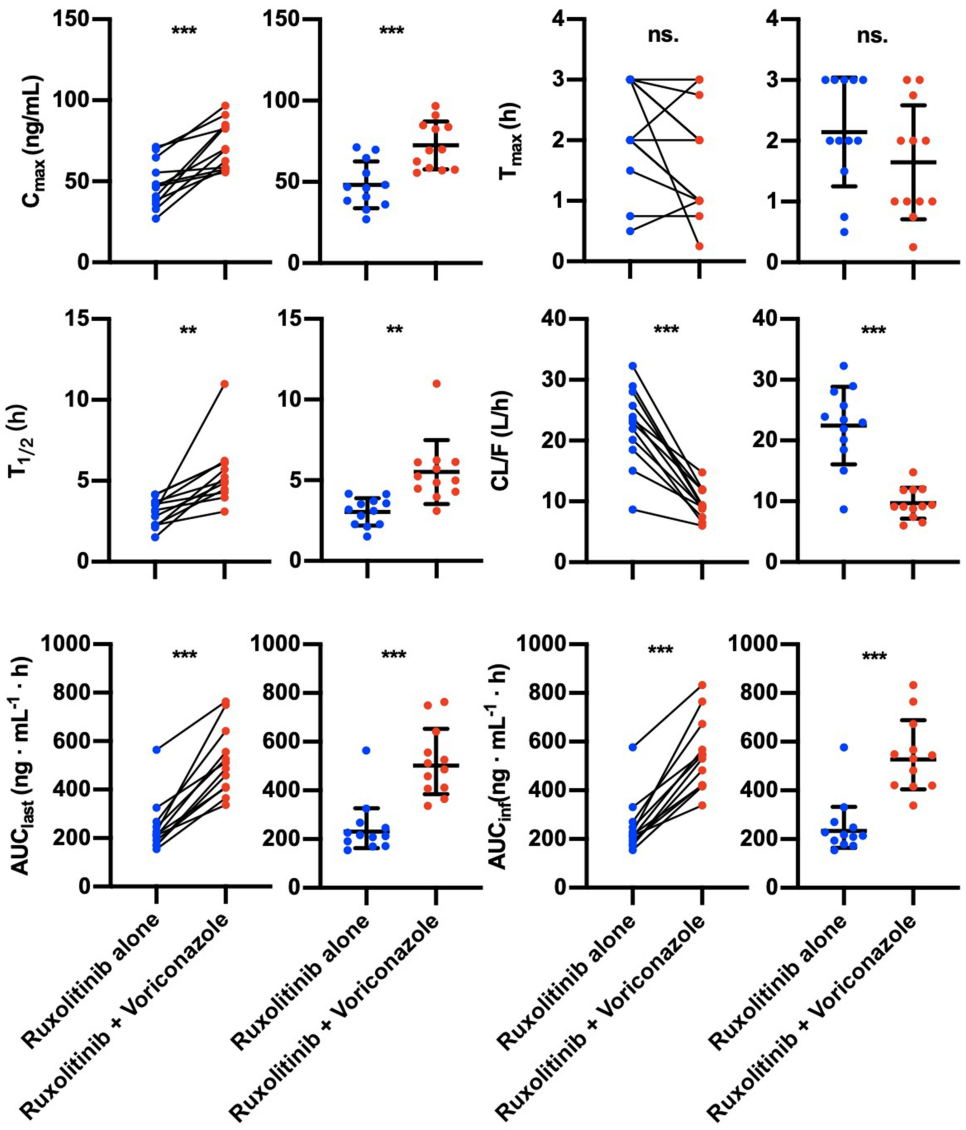

Figure 4 Individual values for the observed time of C_{max}, T_{max}, $T_{1/2}$, CL/F, AUC_{last}, and AUC_{inf} after an oral dose of 5 mg ruxolitinib in the absence (blue dots) or presence of voriconazole (red dots) in 12 patients with hematological malignancies. Data are presented as the mean ± SD or geometric mean ± geometric SD (ns. $P > 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$).

Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time to C_{max}; $T_{1/2}$, terminal elimination half-life; CL/F, apparent plasma clearance; AUC_{last}, area under ruxolitinib plasma concentration-time curve from zero to the last measured sampling time; AUC_{inf}, area under the ruxolitinib plasma concentration-time curve from zero to infinity.

one had oscillopsia, and one had vitreous floaters and syrigmus. All the adverse effects were transient and fully reversible without long-term effects. None of them developed hepatic dysfunction during the study period.

Discussion

Recently, Zeiser et al have reported the increased risk of fungal infection in patients receiving ruxolitinib compared with the control regimen (11.5% vs 5.7%), indicating that antifungal prophylaxis needs to be administered for patients with acute or chronic GVHD treated by ruxolitinib.[28] Posaconazole is the strongly recommended invasive mould disease post-engraftment by the European Conference on Infections in Leukaemia (ECIL), while it was not evaluated in this study because its detection method has not been established. The detection method for voriconazole was established, so voriconazole was chosen to assess the DDI with ruxolitinib. This is one of the limitations of our study. However, quite a few patients are administered voriconazole, either as second-line prophylaxis for an invasive fungal infection or as an

effective treatment for breakthrough fungal infection after failure of the first-line prevention. The tolerance of voriconazole is better than posaconazole, and the bioavailability of voriconazole is higher than posaconazole (96% vs 83%) too. Furthermore, voriconazole tablets are less susceptible to gastrointestinal status, which might be affected by aGVHD, than posaconazole oral suspensions. Even in the meta-analysis of comparison of antifungal prophylaxis drugs in HSCT patients, published in 2020, voriconazole is thought to be the best choice for patients undergoing HSCT.[15] As a result, it is also necessary to evaluate the DDI between voriconazole and ruxolitinib.

Ruxolitinib is mainly metabolized by CYP3A4 (76%) and, to a lesser extent, by CYP2C9 (19%).[12] The pharmacokinetic parameters of ruxolitinib in our present study when it was used alone were consistent with those other studies.[29,30] Voriconazole increased the ruxolitinib plasma exposure as AUC_{inf} to 2.18-fold (range: 1.44–3.35), prolonged $T_{1/2}$ to 1.81-fold, and reduced the mean CL/*F* to 43.6%. This inhibitory effect on ruxolitinib was similar to fluconazole, which causes an increase of ruxolitinib AUC_{inf} by 72–112%.[21,31] However, the variation range of voriconazole was larger than that of fluconazole co-administration. Gene polymorphism and the metabolic characteristics of voriconazole may partly explain this phenomenon.[32–35] Though it has been shown that gender may also play a role in affecting the pharmacokinetics of drugs metabolized by CYP3A4, we did not analyze the effects of gender due to the small sample size.[36]

No adverse effect of ruxolitinib was observed, which might be mainly attributed to the low dose, and the subjects we enrolled did not experience allo-HSCT, thus their hematological tissue was less vulnerable. The adverse events are increased in the REACH2 study compared with the control, where the dose of ruxolitinib is 10 mg twice daily. Other studies have also reported that 75% of patients respond to ruxolitinib at the initial dose of 5 mg twice daily, but 60% develop severe cytopenia, indicating that the patients undergoing HSCT are sensitive to the drug.[37] This is different from the healthy people, in which a regimen of 25 mg twice daily or 100 mg once daily is established as the maximum tolerated dose (MTD).[30] This is also different from the patients with myelofibrosis, in which a regimen of 15 mg twice daily is set as the starting dose, followed by individualized dose titration, and such a regimen is the most effective and safest dosing scheme.[38] Our early Research has found that co-administration of 5 mg ruxolitinib and 1 mg/kg methylprednisolone as the first-line therapy for aGVHD after HSCT can significantly increase the complete response (CR) or partial response (PR) rate on day 28 compared with the historical control group. The dose of ruxolitinib is finally reduced to 2.5 mg for those taking azoles because one of the patients who are coadministered 5 mg daily experiences cytomegalovirus encephalitis, and another one develops post-transplant lymphoproliferative disorders (PTLD).[7] Therefore, we selected 5 mg once daily as the study dose out of safety consideration, and we did not investigate the pharmacokinetics changes of other doses of ruxolitinib.

In our present study, the study period only lasted for 5 days to minimize the trial time and initiate allo-HSCT as soon as possible. Voriconazole was given at a dose of 200 mg per 12 h without a loading dose in the first four patients to avoid toxicity, and indeed no adverse effects were observed. However, a steady-state plasma voriconazole concentration is achieved by day 6 without the loading dose in most subjects.[39,40] Fortunately, steady states were all achieved in the first four patients on day 4 as the difference between two trough concentrations $(C_{12}\text{-}C_0)/C_{12}\times100\%$ was less than 15%. This finding might be attributed to the fact that the genotype proportion representing the ultrarapid and rapid metabolizers was low, a feature of East Asians.[35,41] However, to reduce the possibility that voriconazole did not reach steady-state and avoid the effect of non-steady-state on our results, we revised our study design, and a voriconazole loading dose of 400 mg twice on day 2 was given. Steady states were all achieved in the following eight patients, while five of them developed adverse effects, as shown above.

The subjects we enrolled were patients with hematopoietic malignancies and were transplantation candidates without conditioning but not patients undergoing HSCT, and these subjects could not fully represent those undergoing HSCT. This is one of the limitations in our study. However, it is impossible to change the HSCT therapy to fit our study as patients undergoing HSCT are given many drugs that can interfere with the metabolic pathway of ruxolitinib and face a high threat of death. Although patients who are indicated to have HSCT have similar physical parameters to healthy individuals, they do have more advantages to represent patients undergoing HSCT compared with the healthy subjects as most of them have undergone at least three cycles of chemotherapy and show a relatively low hematocrit.

A study period of 5 days was relatively safe for our subjects. However, we canceled the washout time to narrow down the time between the last chemotherapy and HSCT. However, a lack of washout period for ruxolitinib is acceptable as the previous study has shown that there is no cumulative effect when ruxolitinib is given at a dose of 10 mg, once daily, for 10 days, indicating that ruxolitinib does not cause inhibition or induction of the enzyme involved in its metabolism.[30,31]

Food may interfere with the pharmacokinetics of drugs, and previous results have shown that food decreases the C_{max} of ruxolitinib by 24.3%, while the AUC_{inf} of ruxolitinib in the presence of food is decreased by only 6% compared with that in the absence of food.[30] Therefore, we did not consider food as a major impact factor in ruxolitinib metabolism in our study as the meal schedule was in line with our daily habits.

Conclusions

Collectively, our findings confirmed that voriconazole exhibited a moderate inhibitory DDI effect on ruxolitinib in patients with hematological malignancies. Moreover, a reduction of ruxolitinib dose was recommended to maintain the same amount of ruxolitinib exposure when voriconazole was coadministered in clinical practice.

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Disclosure

The authors declare no competing interests in this work.

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