Hindawi
Journal of Clinical Pharmacy and Therapeutics
Volume 2024, Article ID 6850289, 10 pages
https://doi.org/10.1155/2024/6850289

Research Article

Effects of Triazole Antifungal Agents on the Plasma Concentration and Dosage of Cyclosporin in Patients with Aplastic Anaemia

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Received 8 December 2023; Revised 23 January 2024; Accepted 17 February 2024; Published 27 February 2024

Academic Editor: Peirong Jiao

Objectives. This study aimed to investigate the effects of different triazole antifungal agents on the blood concentration and dosage of cyclosporine (CsA) in patients with aplastic anaemia (AA). *Methods*. This retrospective study enrolled AA patients who received CsA and triazole antifungal agents simultaneously between January 2018 and December 2022. The ratio of CsA blood concentration (ng/mL) to dosage (mg/day) (C/D) co-administration with and without azoles was compared. The effects of different triazole antifungal agents on blood concentrations and dosages of CsA were analysed. *Results*. The mean C/D ratio of CsA increased 1.97 times when co-administered with posaconazole (POS), while the mean C/D ratio of CsA increased 1.76 times when co-administered with fluconazole (FCZ). Compared with CsA monotherapy, there was a significant difference in CsA concentrations among patients with azoles ($P < 0.05$). The mean dose of CsA decreased was 0.26 (−0.25—1.05) mg/kg/day and 0.18 (−0.50—0.69) mg/kg/day when co-administered with POS and FCZ, respectively. There is a wide interindividual variability in the magnitude of drug interaction between azoles and CsA. *Conclusions*. Although azoles increased CsA concentration, a wide individual variability was found in the patients with CsA C/D ratio. Therefore, the CsA dose should be adjusted by closely monitoring the blood levels of CsA co-administered with triazole antifungal agents. In addition, we observed that POS had a greater effect on the blood concentration of CsA than FCZ. When adjusting the dose of CsA in clinical practice, the blood concentration of CsA and the type of co-administered triazole antifungal agents should be considered.

1. Introduction

Aplastic anaemia (AA) is a bone marrow haematopoietic failure syndrome. Its annual incidence is 0.74/100,000 in China, and it can occur in all age groups [1]. Serious aplastic anaemia can cause fatalities, with a mortality rate of 75% [2]. The pathogenesis of AA is unclear; however, T-lymphocyte-mediated immune damage to haematopoietic stem cells is the pathological basis of its development, and abnormally high expression of immune molecules plays a vital role in the pathogenesis of AA. Therefore, immunosuppressive drugs have become the first-line treatment for patients with AA [3]. Cyclosporine (CsA) has been recommended as the treatment of choice for immunosuppressants in patients with AA [1].

Patients with haematological diseases are susceptible to various infections because of their low cellular immunity, especially during immunosuppressive therapy, which further suppresses the immune system and makes them more susceptible to invasive fungal infections (IFIs) [4]. IFIs have

become an important cause of morbidity and mortality in patients undergoing immunosuppressive therapy or haematopoietic stem cell transplantation [5]. According to the Diagnostic Criteria and Therapeutic Principles for Invasive Fungal Disease in Patients with Haematological Diseases/Malignancies (6th Revision), *Candida* and *Aspergillus* are the common causative agents of IFIs in patients with haematological disorders [6], and triazole antifungals are commonly used for the prevention or treatment of invasive fungal infections [5–8]. Therefore, triazole antifungals are often co-administered with CsA in the treatment of patients with AA.

However, triazole antifungals drugs and CsA carry the risk of drug-drug interactions because of their effects on cytochrome P450 (CYP) enzymes and transporter proteins. CsA are substrates of CYP3A4 and p-glycoprotein (P-gp). It interacts with various drugs, including antibiotics, antifungals, and glucocorticoids [9]. Posaconazole (POS), fluconazole (FCZ), and voriconazole (VCZ) inhibit CYP3A4 enzyme activity to varying degrees. POS is both an inhibitor of CYP3A4 and a substrate for P-gp, which affects the blood concentration of CsA via two pathways. POS and VCZ are potent inhibitors of CYP3A4 activity, whereas FCZ is a moderate inhibitor of CYP3A4 [10–15]. It can reduce the metabolism of CsA by inhibiting the activity of hepatic enzymes, resulting in an increase in the blood concentration of CsA, which is prone to cumulative poisoning.

Although the concomitant use of azoles and CsA can result in interactions [16–18], most studies have focused on the interaction between CsA and triazole antifungal drugs in patients undergoing haematopoietic stem cell transplantation (HSCT) [19–25]. There are limited studies on the co-administration of CsA with triazole antifungal agents in patients with AA. HSCT is one of the treatments for AA. AA is a heterogeneous bone marrow failure syndrome and that manifests mainly as red cell aplasia and reduced peripheral pancytopenia numbers. However, 50% to 60% of CsA in whole blood is distributed in red blood cells, and the pathological state of patients with AA will affect the distribution of CsA in the blood, which may be different from patients with HSCT. There are limited research studies on interaction between CsA and azoles in patients with AA. In this study, the effects of triazoles on CsA blood levels in patients with AA were explored. We also compared the effects of different triazole antifungal agents on CsA blood concentration and dosage in patients with AA to provide a basis for developing individualised regimens for administering CsA and triazole antifungal drugs.

2. Methods

2.1. Study Design and Subjects. This study was conducted at the Second Hospital of the Shanxi Medical University between January 2018 and December 2022. Electronic medical records were used to identify patients with AA, severe AA, or very severe AA, and were investigated to identify patients who were treated with CsA soft capsule or CsA injection, co-administered with triazole antifungal agents (e.g., posaconazole oral suspension, fluconazole capsules or fluconazole tablets, voriconazole capsules or voriconazole tablets) to prevent or treat fungal diseases. Each patient's blood concentration of CsA was measured at least once when CsA was monotherapy and at least once when co-administered with triazole antifungal drugs. The exclusion criteria were as follows: (i) use of other drugs that affect CYP3A4 or P-gp during hospitalisation, such as macrolide antibiotics, rifampin, carbamazepine, phenobarbital, phenytoin sodium, and HIV protease inhibitors (e.g., ritonavir and nelfinavir); (ii) age <18 years; (iii) detailed data not available; (iv) immunosuppressive therapy with CsA <3 days; and (v) liver or kidney dysfunction. Hepatic impairment was defined as alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) ≥ five times the upper limit and total bilirubin (TBIL) ≥ two times the upper limit. Renal dysfunction was defined as a serum creatinine level >2.0 mg/dL or glomerular filtration rate <30 mL/min.

This study was approved by the Ethics Committee of the Second Hospital of Shanxi Medical University. The requirement for informed consent was waived as only retrospective data were collected.

2.2. Data Collection. Related clinical data of patients were collected. General biological data of the patients included sex, age, height, and weight. The patients' medication information included the dosage of CsA, dosage form, time of triazole antifungal drug co-administration, and other concomitant medications. The biochemical indicators included ALT, AST, TBIL, total protein (TP), creatinine, urea, white blood cells, red blood cells (RBC), haemoglobin (HGB), haematocrit (HCT), and platelets (PLT). Steady-state trough concentrations were collected for all patients treated with CsA alone and co-administered with triazole antifungal drugs. Data collected for CsA monotherapy included data before the co-administration of a triazole antifungal agent or three days after the discontinuation of the triazole antifungal agent.

2.3. Therapeutic Drug Monitoring. Whole-blood trough CsA concentrations were measured by an enzyme multiplied immunoassay technique (EMIT 2000 TDM; Syva Viva-E drug concentration analyser). The target blood concentration of CsA for AA in adults (C_0 trough concentration) was 150–250 ng/mL [1].

2.4. Statistical Method. All continuous variables were described as mean ± SD or median (interquartile range) based on whether they fitted the normal distribution. Normality was tested using the Shapiro–Wilk test. Statistically significant differences in the concentration/dose (C/D) ratio with and without azole co-medication were assessed using a paired *t* test if the data conformed to a normal distribution; otherwise, the Wilcoxon rank test was applied. Qualitative data are presented as rates and were compared by Fisher's exact test. All analyses were performed using the IBM SPSS Statistics version 25 (IBM, New York, NY, USA). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient Demographics. From January 2018 to December 2022, 5775 CsA concentration samples were monitored at the Second Hospital of Shanxi Medical University. Based on the inclusion and exclusion criteria, 27 hospitalisation records of 25 patients (74 samples of CsA data) were included in this study, as shown in Figure 1. Of the 25 patients, two patients had two hospitalisation records, including one patient who was co-administered with POS and FCZ during two hospitalizations, respectively. The other patient was co-administered with FCZ and VCZ, respectively. The records of 27 hospitalizations were stratified into FCZ ($n = 18$), POS ($n = 7$), and VCZ ($n = 2$) groups based on the different triazole agents. In the FCZ group, there were 18 samples analysed during CsA monotherapy, while 33 samples were analysed during co-administration with FCZ. In the POS group, 7 samples during CsA monotherapy and 11 samples from co-administration with POS were analysed. In the VCZ group, two samples were analysed during CsA monotherapy, and three samples were analysed after co-administration with VCZ. Owing to the small amount of data in the VCZ group, the analysis was restricted to descriptive methods, and no statistical analyses were performed. Detailed information on the patients' characteristics is presented in Table 1. There were no significant differences between the FCZ and POS groups in terms of basic demographic data and clinical examination findings at the time of initial admission ($P > 0.05$).

3.2. Changes in CsA C/D Ratio with Triazole Antifungal Agents Co-Therapy. The concentration/dose (C/D) ratio was evaluated in this study because the dose of CsA was changed in some patients during the study period. To eliminate the effect of the dose on the concentration, conduct a dose correction for the CsA concentration. We compared the change in the mean C/D ratio of CsA between CsA monotherapy and co-administration with triazole antifungal drugs (Figure 2, Table 2). In the FCZ group, the mean C/D ratio of CsA montherapy was 0.54 ± 0.34 (ng/mL)/(mg/day). After co-administration with FCZ, the mean C/D ratio of CsA was 0.95 ± 0.48 (ng/mL)/(mg/day), significantly higher than the ratio of CsA montherapy ($P < 0.05$). The mean C/D ratio of CsA with FCZ co-medication increased by 1.76 times. In the POS group, the mean C/D ratio of CsA increased from CsA monotherapy 0.75 ± 0.25 (ng/mL)/(mg/day) to 1.48 ± 0.73 (ng/mL)/(mg/day) when co-administered with POS ($P < 0.05$). The mean C/D ratio of CsA with POS co-medication increased by 1.97 times. The change in the C/D ratio of CsA after co-administration with azoles increased significantly as shown in Figure 2. There were statistically significant differences in the CsA C/D ratio between CsA monotherapy and co-administration with triazole antifungal agents ($P < 0.05$).

The individual differences of the patients in the CsA C/D ratio were analysed (Figure 3). Compared to the C/D ratio of CsA monotherapy, 88.9% (16/18) of patients had an increased C/D ratio with FCZ co-medication, and the median increase in CsA C/D ratio in the FCZ group was 0.42 (0.04–1.06) (ng/mL)/(mg/day). In addition, 85.7% (6/7) of the patients had an increased C/D ratio with POS co-medication, and the median increased C/D ratio of CsA with POS co-medication was 0.63 (0.076–1.84) (ng/mL)/(mg/day) in the POS group. There was a significant difference in the CsA C/D ratio when co-administered with FCZ or POS ($P < 0.05$).

3.3. Changes in CsA C/D Ratio Over Time after Triazole Antifungal Agents Co-Therapy. These changes were further investigated to determine the influence of the triazole antifungal agent co-administration time on C/D ratio. Based on the co-administration with triazole time, the two groups of patients were also divided into two subgroups: co-medication (1–7 d) and co-medication (8–21 d), respectively (Table 2). During the co-administration with FCZ (1–7 d) and (8–21 d), the mean C/D ratios of CsA were 0.77 ± 0.37 (ng/mL)/(mg/d) and 0.95 ± 0.54 (ng/mL)/(mg/d), respectively. The mean C/D ratio with FCZ co-medication (1–7 d) was approximately 1.43 times greater than CsA alone, and the mean C/D ratio with FCZ co-medication (8–21 d) was approximately 1.76 times greater than CsA alone. The mean C/D ratios for co-administration with POS (1–7 d) and (8–21 d) were 1.30 ± 0.58 (ng/mL)/(mg/d) and 1.87 ± 1.15 (ng/mL)/(mg/d), respectively. The C/D ratio with POS co-medication (1–7 d) was approximately 1.73 times greater than CsA alone. The C/D ratio with co-medication (8–21 d) was approximately 2.49 times greater than CsA alone. These results indicated that the CsA C/D ratio was significantly associated with the co-administration time in the FCZ and POS groups. The C/D ratio of CsA was plotted against the number of days after co-administration with FCZ or POS. The level of CsA increased with the time of co-administration of azoles in the groups. This was a significant difference in the CsA C/D ratio over time when co-administered with FCZ or POS ($P < 0.05$).

3.4. Changes in CsA Dose with Triazole Antifungal Agents Co-Administration. The mean daily dose of CsA decreased after triazole antifungal agent co-administration (Table 3). In the FCZ group, the dose of CsA was decreased from 3.50 ± 1.21 (mg/kg/d) to 3.39 ± 0.94 (mg/kg/day), and the mean daily dose of CsA was decreased by 0.20 (−0.45–0.53) (mg/kg/d) during FCZ co-administration (1–7 d). In addition, the mean daily dose of CsA decreased by 0.40 (−0.81–0.94) (mg/kg/d) during FCZ co-administration (8–21 d). In the POS group, the CsA dose decreased from 3.38 ± 0.96 (mg/kg/d) to 2.99 ± 0.49 (mg/kg/d) during co-administration with POS. The mean daily dose of CsA decreased by 0.31 (−0.20–0.83) (mg/kg/d) during POS co-administration (1–7 d). Furthermore, the mean daily dose of CsA decreased by 0.61 (−1.5–3.74) (mg/kg/d) during POS co-administration (8–21 d).

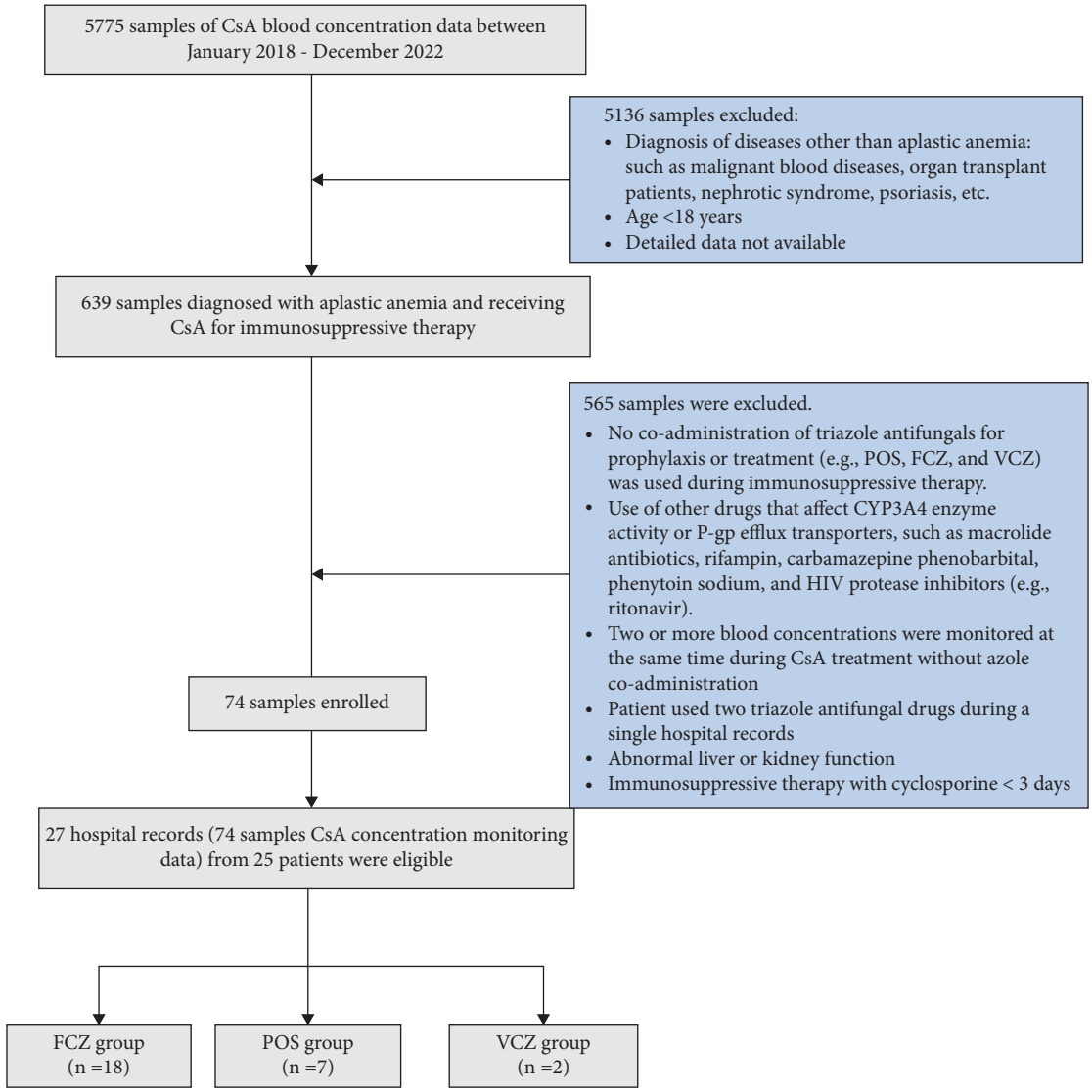

Figure 1: Patient selection flowchart. CsA, ciclosporin; POS, posaconazole; FCZ, fluconazole; VCZ, voriconazole; P-gp, P-glycoprotein.

3.5. Effects of Co-Administration with Triazole Antifungal Agents on Laboratory Data of Patients. Laboratory data of AA patients administered with CsA alone and when co-administered with azole antifungal agents are shown in Table 4. No abnormalities in the biochemical indices were observed. There was no significant difference in the laboratory data of patients during CsA montherapy or the co-administered with triazole antifungal agents ($P > 0.05$).

4. Discussion

It is worth investigating whether there are differences in the degree of interaction between triazole antifungal drugs and CsA in different patient populations. This is because it impacts whether it is necessary to preemptively reduce the dosage of CsA according to the instructions when co-administered with triazole antifungal drugs in patients with different diseases. Hamidreza et al. [26] found that the mean C/D ratio of CsA increased 8.40%–174.10% when co-administered with VCZ in patients received HSCT. POSA increased the mean C/D ratio of CsA to a similar extent in patients with aplastic anaemia in current study (7.60%–184.00%). Studies from Xue et al. [27] and Zhu et al. [28] indicated that the CsA C/D ratio was found to be approximately 1.5-fold higher after POS initiation in patients underwent HSCT. Here, we showed that the CsA C/D ratio increased 1.97 times when co-administered with POSA in aplastic anaemia patients. It is not clear yet if there were differences in the degree of such interactions in these two patient populations. More studies are needed to confirm this.

Furthermore, we compared the effects of different triazole antifungal agents on CsA blood concentration and dosage in patients with AA. We observed that POS had a greater effect on the blood concentration of CsA than FCZ. These findings may be related to and the intensity of azole drugs' inhibition of hepatic drug enzymes. POS is a strong CYP3A4 inhibitor. VCZ is metabolised by CYP3A4 and is

Table 1: Patients' demographic data and clinical characteristics.

Item	FCZ group ($n = 18$)	POS group ($n = 7$)	P value
Sex (male/female)	11/7	1/6	
Age (years)[a]	37.33 ± 11.93	38.78 ± 10.43	0.867
Height (cm)[a]	166.06 ± 9.69	164 ± 5.15	0.306
Weight (kg)[a]	63.19 ± 12.21	60.19 ± 10.88	0.443
Basic disease n (%)			
Hypertension	1 (5.56)	2 (28.57)	0.180
Diabetes	0	1 (14.29)	0.280
RBC (10^{12}/L)	1.92 (1.72–3.07)	1.81 (1.63–2.93)	0.453
HGB (g/L)	59.50 (55–97.75)	68.5 (53.25–90.25)	0.998
HCT (%)	0.17 (0.15–0.27)	0.19 (0.15–0.26)	0.760
PLT (10^9/L)	6 (3.75–20.25)	12 (5.5–22.25)	0.387
WBC (10^9/L)	1.3 (0.80–2.87)	1.56 (0.51–2.40)	0.677
ALT (IU/L)	15.45 (11.75–19.18)	22.5 (11.63–170.03)	0.278
AST (IU/L)	13.35 (11.23–19)	16.35 (14.3–62.80)	0.133
TBIL (μmol/L)	16.4 (10.78–28.03)	18 (11.88–30.43)	0.718
TP (g/L)	63.1 (60.4–67.20)	60.75 (55.4–64.28)	0.130
ALB (g/L)	36.6 (35.45–37.7)	35.65 (30.9–37.08)	0.210
Urea (mmol/L)	5.80 (5.10–6.95)	5.15 (3.9–7.2)	0.382
Creatinine (μmol/L)	60 (48.93–67)	59.5 (47.5–2.75)	0.520

[a]Data are mean ± SD. RBC, red blood cells; HGB, haemoglobin; HCT, haematocrit; PLT, blood platelets; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; TP, total protein; ALB albumin.

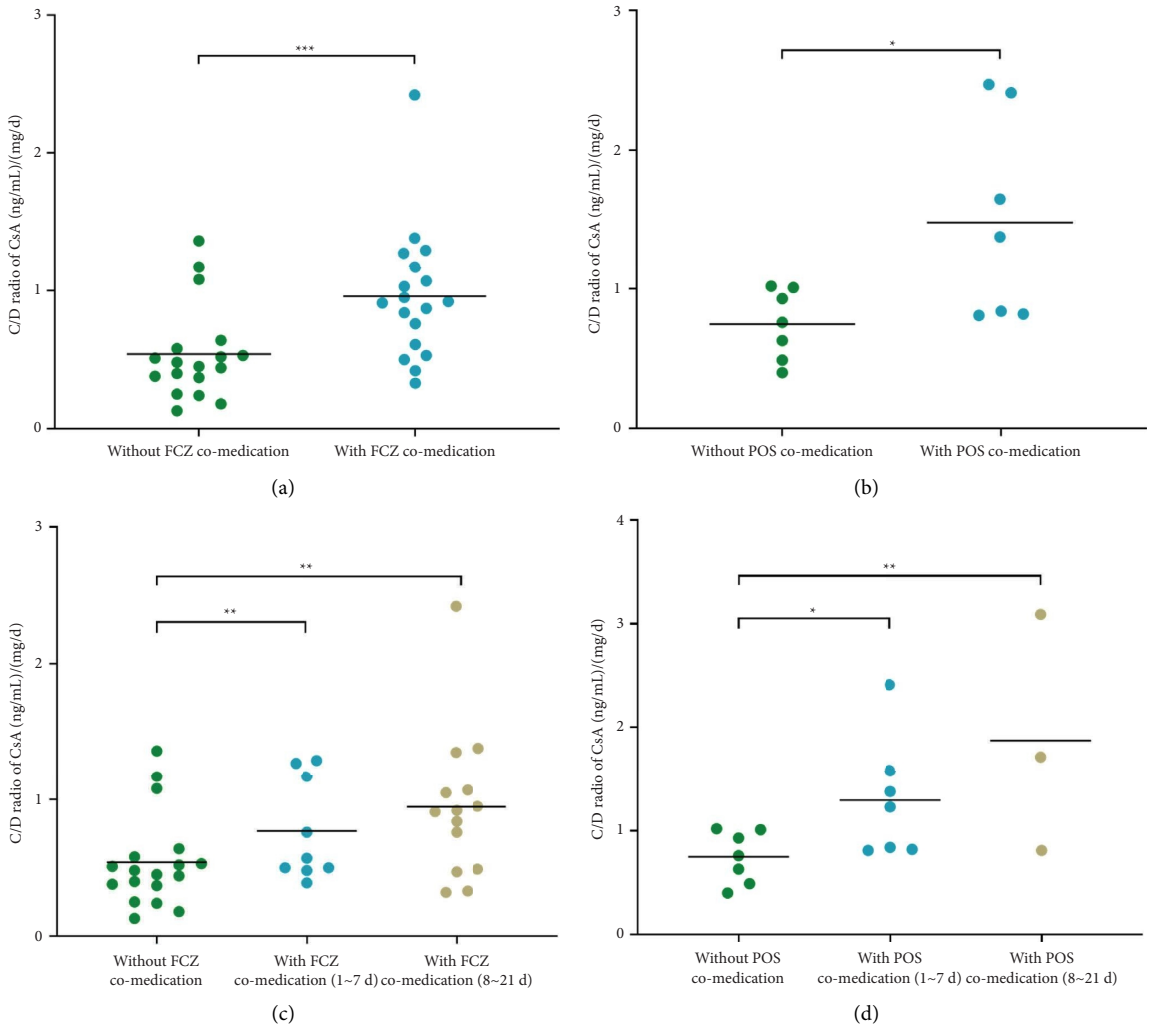

Figure 2: Effect of co-administered use of FCZ (a) or POS (b) on the C/D ratio of CsA, and in the FCZ group (c) and in the POS group (d) combined administration time on C/D of CsA in patients with aplastic anaemia. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Table 2: Effect of POS or FCZ on C/D ratio of CsA in aplastic anaemia patients.

Time	FCZ group			POS group		
	C (ng/mL)	C/D (ng/mL)/(mg/d)	P	C (ng/mL)	C/D (ng/mL)/(mg/d)	P
Without azole co-medication	105.91 ± 56.91	0.54 ± 0.34		152.77 ± 55.67	0.75 ± 0.25	
With azole co-medication	186.35 ± 66.66	0.95 ± 0.48	<0.001[a]	274.18 ± 163.96	1.48 ± 0.73	0.038[a]
With azole co-medication (1~7 d)	159.10 ± 88.84	0.77 ± 0.37	0.007[b]	252.1 ± 160.22	1.30 ± 0.58	0.037[b]
With azole co-medication (8~21 d)	189.12 ± 68.60	0.95 ± 0.54	0.005[c]	293.47 ± 147.78	1.87 ± 1.15	0.006[c]

[a]P values for comparisons between with azole co-medication (total) and without azole co-medication. [b]P values for comparisons between with azole co-medication (1–7 d) and without azole co-medication. [c]P values for comparisons between with azole co-medication (8–21 d) and without azole co-medication.

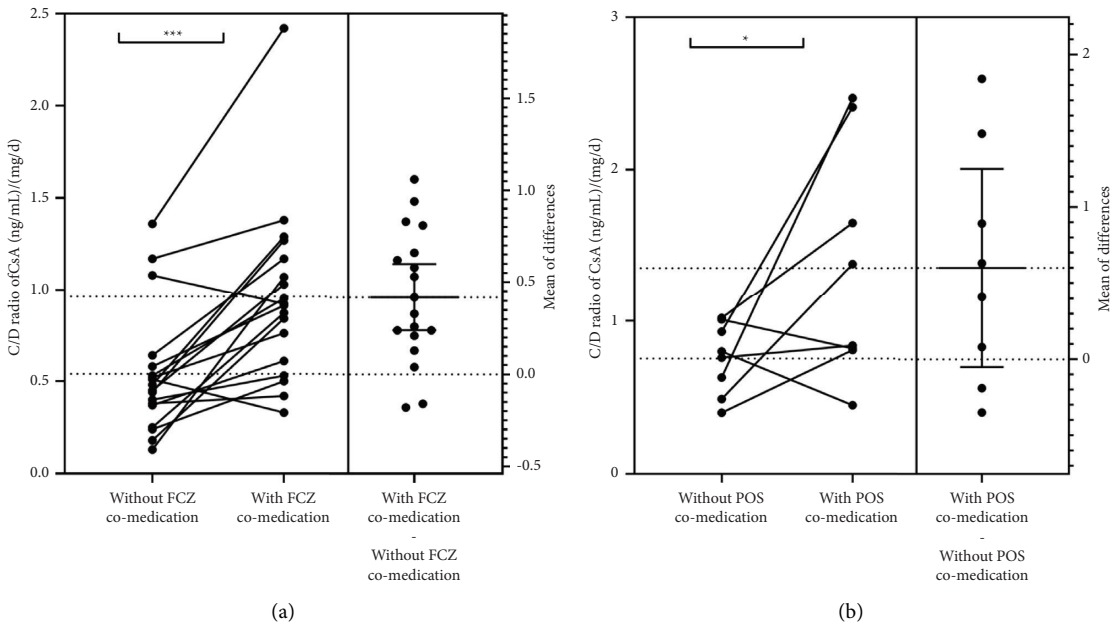

Figure 3: Individual values of the CsA C/D ratio with or without the co-medication of triazole antifungal agents. $^{*}P < 0.05$, $^{***}P < 0.001$.

Table 3: Effect of co-administration with triazole antifungal agent drugs on the dose of CsA.

Time	FCZ group		POS group	
	D (mg/kg/d)	ΔD (mg/kg/d)	D (mg/kg/d)	ΔD (mg/kg/d)
Without azole co-medication	3.50 ± 1.21		3.38 ± 0.96	
With azole co-medication (total)	3.39 ± 0.94	0.09 ± 1.13	2.99 ± 0.49	0.40 ± 0.70
With azole co-medication (1–7 d)	3.19 ± 0.66	0.04 ± 0.53	3.07 ± 0.54	0.32 ± 0.56
With azole co-medication (8–21 d)	3.45 ± 1.13	0.06 ± 1.39	2.87 ± 0.54	1.10 ± 1.06

$\Delta D = D_{\text{CsA monotherapy}} - D_{\text{time of co-administration of triazole antifungal agents}}$.

a moderate CYP3A4 inhibitor. Because the inhibition of CYP3A4 by POS is stronger than that by FCZ, The co-administration with POS in patients with AA may have a greater effect on the CsA than co-administration with FCZ.

Wide interindividual variability in the magnitude of the drug interactions between triazole antifungal drugs and CsA was observed in our study. As shown in Figure 3, compared with the C/D ratio of CsA alone, 85.7% of patients had an increased C/D ratio with POS co-medication, the median increase C/D ratio of CsA during co-administration with POS was 0.63 (range, 0.076–1.84 (ng/mL)/(mg/kg), $P < 0.05$). Further, 88.9% of patients had an increased in C/D ratio with FCZ co-medication, the median increase C/D ratio of CsA was 0.42 (range, 0.04–1.06 (ng/mL)/(mg/kg), $P < 0.001$). Similar to the results reported by previous studies [29–31]. However, the mechanisms underlying the individual variability in the magnitude of the drug interaction between azoles and CsA have yet to be elucidated. In considering the possible mechanisms, we analysed the following: (i) the pharmacokinetic variability of triazole

Table 4: Laboratory safety data in aplastic anaemia patients without triazole antifungal agent co-medication and after triazole antifungal agent co-medication.

	CsA monotherapy	With azole co-medication	*P*
Patients with POS			
ALT (IU/L)	106.67 ± 90.48	92.39 ± 96.74	0.780
AST (IU/L)	58.04 ± 35.19	59.55 ± 55.74	0.953
TBIL (μmol/L)	19.01 ± 10.96	25.63 ± 16.93	0.413
Creatinine (μmol/L)	70.57 ± 39.80	69.59 ± 31.29	0.960
Urea (mmol/L)	7.64 ± 3.99	7.53 ± 3.85	0.957
Patients with FCZ			
ALT (IU/L)	18.74 ± 10.26	17.06 ± 9.78	0.616
AST (IU/L)	14.88 ± 5.93	13.74 ± 4.69	0.527
TBIL (μmol/L)	24.05 ± 17.81	27.60 ± 17.60	0.552
Creatinine (μmol/L)	62.59 ± 22.50	68.75 ± 30.99	0.516
Urea (mmol/L)	6.31 ± 2.82	6.91 ± 2.33	0.525

P is the comparison of biochemical indexes of patients before and after co-administered with triazole antifungal agents.

antifungal agents in the human body is large, and is affected by many factors, such as diet, drug interaction, and the physiological and pathological state of patients and (ii) CYP3A4 gene polymorphism and CYP3A4 enzyme activity. The wide interindividual variability in drug interactions observed in our study highlights the importance of individualised therapy in clinical practice. This interindividual variability strongly suggests that the uniform dose reduction of CsA upon initiating azoles is inappropriate. Therefore, it is suggested that the concentration of CsA should be regularly monitored during the co-administration of the two drugs, and the dose of CsA should be adjusted according to the patient's condition. However, it is yet to be clarified how long it takes for the interaction between CsA and azoles to reach a steady state after co-administration. Our study further investigated the trend of CsA levels over time after triazole antifungal drugs initiation. We divided the patients into two subgroups based on the co-administration time during 1–7 d and 8–21 d. Our research showed that in both the POS and FCZ groups, the CsA C/D ratio was higher during co-administration (8–21 d) than that during co-administration (1–7 d). This may be due to the half-life of these drugs. Previous research has shown that the influence of POS on CsA levels is associated with the steady state of POS, which is considered to be 8 days according to the half-life of POS. POS reaches the steady-state blood concentration in 7–10 d [32]. Sánchez-Ortega et al. [20] results are consistent; the results showed that the allogeneic haematopoietic stem cell transplantation co-administered with POS had an interaction with CsA after 7 days CsA significantly increased blood concentrations. The FCZ prescribing information also indicated that FCZ reached a stable state after 7 days. Hence, we recommend frequent monitoring of CsA concentrations when combined with triazole antifungals. It is particularly crucial to do this after 8 days, preventing excessive concentration from causing adverse reactions.

In keeping with this effect on blood CsA levels and the basis of clinical criteria, the daily dose of CsA was adjusted during co-administration with triazole antifungal drugs. Some studies have recommended an initial empirical reduction in the CsA dose to maintain CsA concentrations within the target range. The POS prescribing information suggests that CsA should be reduced by 29% at the initiation of combined treatment with POS, but these results were from a study of only four cardiac transplant recipients, and whether this is appropriate for AA remains to be investigated. Robinson et al. [24] conducted a retrospective audit of 29 patients who underwent their first allograft, and a prospective review of the subsequent cohort of patients who underwent allogeneic HSCT commenced at a lower dose. They recommended an initial empirical CsA dose reduction of 30%–40%. Another study on drug interactions with azole antifungal agents concluded that, when starting azole therapy, a pre-emptive dosage reduction of immunosuppressive agents (cyclosporine, tacrolimus, or sirolimus) should be strongly considered [17]. This finding is consistent with the results of many studies [33–37]. However, some studies do not recommend prereduction of the CsA dose prior to co-administration. Sanchez-Ortega et al. [20] suggested that reducing the CsA dose may lead to a subtherapeutic CsA concentration, thus affecting the therapeutic effect. Hadjibabaie et al. [26] suggested avoiding uniform reduction in all patients before voriconazole administration, and recommend frequent CsA blood concentration monitoring, once voriconazole antifungal therapy is initiated. In addition, a study also indicated that the dose adjustment of CsA inhibitors for initiating azoles should not be decided uniformly but should be determined individually by closely monitoring their blood concentrations [31]. Our data show that, when co-administered with POS or FCZ, the reduction of the dose of co-administered CsA (8–21 d) was higher than that of co-administered CsA (1–7 d). Moreover, the dose reduction was greater with POS (8–21 d) than with FCZ (8–21 d). None of the patients in our study received a prereduced CsA dose when co-administered with triazole antifungal agents. The CsA dose for most patients was adjusted according to the monitored results, which were within the therapeutic window (150–250) ng/mL. It seems cautious not to automatically reduce the dose in advance [38–41]. Therefore, it is preferable to adjust the CsA dose through therapeutic drug monitoring. We recommend that the dose

of CsA be further adjusted according to the monitored results when co-administered with triazole antifungal agents. To adjust the dose of CsA in clinical practice, the blood concentration of CsA and the type of co-administered azoles should be considered.

In our study, no serious adverse reactions were found in AA patients. On the one hand, it is possible that CsA concentrations were regularly monitored and the dose was adjusted accordingly; on the other hand, although CsA concentrations increased, they did not exceed the reference range. As well as in a few patients, the concentrations exceeded the reference range, but the dose was not significantly reduced. This demonstrated that there is obvious individual variability in the use of CsA in combination with azoles again. Although there were no adverse effects to patients in this study, it is important to be alert to the adverse effects, such as nephrotoxicity, caused by the high concentration of CsA.

There are several potential limitations in our study. Statistical analysis could not be carried out because of the small sample size of the combined voriconazole group. In addition, we considered that the magnitude of drug interaction was correlated with plasma concentration of azoles. Due to the retrospective study, concentration of triazole antifungal drugs was not measured. The influence of the concentration of azole drugs on the concentration of CsA needs further study.

5. Conclusions

There was significant interpatient variability in the magnitude of CsA blood concentration increments after azole co-administration. Therefore, we recommend CsA level monitoring as soon as possible after start of co-administration and dose adjustment on an individual basis. POS had a greater effect on the whole blood concentration of CsA than FCZ in AA patients. When adjusting the dose of CsA in clinical practice, the plasma concentration of CsA and type of co-administered triazole antifungal agents should be considered.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was approved by the Ethics Committee of the Second Hospital of Shanxi Medical University (Reference Number: 2022YX-173).

Consent

The need for informed consent was waived due to the retrospective design of this study.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

The research proposal was written and designed by Yangxiu Tian and Yan Song. The research was performed by Yangxiu Tian, Yan Song, and Qiang Zhao. The data were analysed by Yangxiu Tian, Yan Song, and Li Song. The content of the article was guided by Yanan Qiao, Donghong Yin, and Shuyun Wang. All authors read and approved the final manuscript. Yangxiu Tian and Yan Song contributed equally to this work.

Acknowledgments

The authors wish to thank all patients for their participation and authors for their contribution.

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