Therapeutic Drug Monitoring of Voriconazole in AIDS Patients

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Research

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Abstract

Background

The safety and efficacy of Voriconazole in Acquired Immune Deficiency Syndrome (AIDS) patients is difficult to guarantee. In this study, Therapeutic Drug Monitoring (TDM) of Voriconazole in AIDS patients was investigated with the aim to further verify the significance of voriconazole TDM in AIDS patients and to explore more strategies to improve individualized medication.

Methods

The data of AIDS patients who underwent voriconazole TDM in our hospital from May 2018 to August 2021 were collected. The basic information of patients, the results of voriconazole TDM, the individualized intervention, the affecting factors of voriconazole concentration were analyzed, as well as the relationship between voriconazole trough concentration and safety.

Results

A total of 46 tests of voriconazole TDM were performed in 28 AIDS patients. Only 57.14% patients reached the therapeutic range at first TDM, and 87.50% patients reached the therapeutic range after intervention based on first TDM. 21.43% patients develop voriconazole-related Adverse Drug Reactions (ADRs), and ADRs were mostly occurred when voriconazole concentration is above 5.0 $\mu\text{g/mL}$. Spearman correlation coefficient r_s was calculated to be 0.729 for voriconazole trough concentration and the incidence of ADRs, exhibiting a significant, positive linear correlation ($P=0.017$). 50% patients had polypharmacy and drug interactions are common. For example, rifampicin can significantly reduce the plasma concentration of voriconazole. Multiple linear regression analysis showed Hypoproteinemia was a significant factor affecting voriconazole trough concentration ($P=0.006$).

Conclusion

AIDS patients usually have a low attainment rate of voriconazole trough concentration after initiation of standard dosing regimen. The affecting factors seem multifactorial and complex, of which hypoproteinemia is of great significance. Meanwhile, we need to be alert to the effects of drug interactions. The incidence of voriconazole related ADRs is high, mostly occurring when voriconazole concentration is above 5.0 $\mu\text{g/mL}$. Therefore, TDM can provide meaningful guidance for dosage optimization of voriconazole, and the dosage adjustment method in Chinese Guideline is applicable for the population of AIDS patients.

Background

Voriconazole, a triazole antifungal agent, has been widely used in clinical practice. Voriconazole exhibits nonlinear pharmacokinetics in vivo, and the therapeutic window is narrow. TDM can improve the safety and efficacy of voriconazole therapy [1, 2]. Due to the special disease status and the polypharmacy in AIDS patients, the individualized dosing of voriconazole is more complicated, and this is an issue that deserves more attention and further research is critical. Unfortunately, researches in this regard are limited, particularly the voriconazole TDM in

AIDS patients. Implementation of TDM may be an important strategy to achieve individualization of voriconazole therapy [3]. This paper retrospectively analyzes the implementation of pharmaceutical care based on voriconazole TDM with the aim to explore more strategies to facilitate individualized dosing of voriconazole used in AIDS patients.

Methods

Case materials collection

The AIDS cases admitted to Quanzhou First Hospital Affiliated to Fujian Medical University from May 2018 to August 2021 were collected. Inclusion criteria: Age ≥ 18 years; Given voriconazole; Underwent voriconazole TDM; TDM-based dosage optimization. The patients' general data, diagnosis of fungal infection, purpose of voriconazole administration, dosage, TDM results and corresponding interventions, voriconazole related ADRs and drug interactions observed with voriconazole were retrospectively analyzed.

Methodology for voriconazole TDM

Plasma concentration of voriconazole was determined by High-performance liquid chromatography (HPLC). According to available literature [4-7], the proposed therapeutic range of voriconazole is 1-5.5 $\mu\text{g/mL}$.

HPLC analytic conditions are as follows: Shim-pack Scepter C18-120 column (250 $\times$ 4.6 mm, 5 μm); carbamazepine as the internal standard; Methanol-water (57:43, V/V) as the mobile phase; column temperature of 40°C; injection volume of 50 μL ; flow rate of 1.0 mL min^{-1} ; isocratic elution; detection wavelength of 255 nm. In these chromatographic conditions, the retention times were approximately 8.8 min for voriconazole, approximately 13.1 min for carbamazepine.

Evaluation of voriconazole related ADRs

The common ADRs noted with voriconazole were monitored, such as visual disturbances, abnormal liver function, rash, hallucinations. According to the causality assessment criteria adopted by the National Centre for ADR Monitoring, the ADR judged to be highly relevant were included in this study.

Evaluation of drug interactions

Referring to the guideline of the voriconazole individualized medication [8], the potentially interacting drugs pre-administration of voriconazole 3 days and administered during all therapy course of voriconazole were all included in the evaluation of drug-drug interactions.

Statistical analyses

Data were statistically analyzed by using SPSS 25.0 software. Continuous variables were compared using t-tests. Categorical variables were compared by chi-square test or Fisher exact test. Correlation between variables were determined by Spearman correlation coefficient. Affecting factors on voriconazole trough concentration were analyzed using multivariate analysis by linear regression. $P < 0.05$ was considered a statistically significant difference.

Results

General clinical information and purpose of voriconazole administration

From May 2018 to August 2021, 28 AIDS patients with TDM-based dosage adjustment of voriconazole were admitted to our hospital, 24 (85.71%) were male and 4 (14.29%) were female, mean age was 39.71 ± 14.14 years (22-75 years), mean weight was 52.25 ± 11.22 kg (33-75 kg), mean serum albumin (ALB) 28.58 ± 5.03 g·L⁻¹ (19.10-44.50 g·L⁻¹), mean glutamate transaminase (ALT) 38.68 ± 40.96 U·L⁻¹ (2.00-163.00 U·L⁻¹), mean glutamic aminotransferase (AST) 70.29 ± 122.20 U·L⁻¹ (9.00-666.00 U·L⁻¹), and all patients presented normal renal function. The purposes of voriconazole administration were shown in Table 1.

Voriconazole TDM results

Of the 28 AIDS patients, 26 were prescribed voriconazole at first-time and given a loading dose of 6 mg·kg⁻¹ q12h followed by a maintenance dose of 4 mg·kg⁻¹ q12h intravenously. 2 patients had taken voriconazole before admission, and they continued take voriconazole orally with a maintenance dose of 4 mg·kg⁻¹ q12h after admission. Blood samples were collected 0.5 h before the 5th dose at the earliest, and the mean sampling time was 4.25 d (2-11 d) after initiation of voriconazole therapy. A total of 46 tests of voriconazole concentration were performed in 28 patients, of which 21 patients had only 1 test of voriconazole concentration and 7 patients had multiple tests of voriconazole concentration, with a mean number of tests 3.6 (2-7). The mean trough concentration at first voriconazole TDM from all the 28 AIDS patients was 4.17 ± 2.70 µg/mL (0.2-9.6 µg/mL). The distribution of voriconazole TDM results were shown in Table 2.

Intervention based on voriconazole TDM

There were 12 patients who did not reach the target range at their first voriconazole TDM, and dosing regimens were intervened according to the therapeutic effect and TDM results. Five patients reached the standard in the second TDM after intervention, among which three patients underwent voriconazole dose reduction, one patient underwent voriconazole dose escalation, and one patient discontinued rifampicin used in combination. No dose adjustments were required in three patients according to guideline recommendation. Voriconazole was replaced by itraconazole in two patients. One patient discontinued voriconazole due to drug fever. Another patient initially treated with voriconazole for empirical treatment was switched to amphotericin B. The results of voriconazole TDM and corresponding interventions were shown in Table 3.

Trough concentration and safety of voriconazole

Among the 28 patients, 6 patients (21.42%) encountered voriconazole related ADRs, including 3 cases of hallucinations, 1 case of visual disturbance, and 1 case of anxiety and insomnia. Of the 6 patients, there were 5 patients that the voriconazole trough concentrations were larger than 5 µg/mL, accounting for 83.33%. The mean voriconazole trough concentration in ADR group (6 cases) and non ADR group (22 cases) was (7.12 ± 2.27) µg/mL and (3.37 ± 2.23) µg/mL, respectively. Statistical difference could be observed between the two groups ($P=0.001$). Correlation between the two groups was examined using Spearman Correlation analysis. Spearman correlation coefficient r_s was calculated to be 0.729 for voriconazole trough concentration and the incidence of ADRs, exhibiting a significant, positive linear correlation ($P=0.017$). The distribution of voriconazole trough concentrations and the occurrence of ADRs were shown in Table 4.

Combination therapy with Voriconazole

Of the 28 AIDS patients, 14 received voriconazole combined medication, 1 patient with Cytochrome P450 (CYP450) enzyme inducer (rifampicin), 12 with CYP450 enzyme inhibitors (esomeprazole in 7 cases, omeprazole in 3 cases, lopinavir/ritonavir in 1 case, and TAF/FTC/EVG/c in 1 case), and 1 with the CYP450 enzyme substrate prednisone. The mean trough concentrations of voriconazole were $(4.32 \pm 2.80) \mu\text{g/mL}$, $(4.32 \pm 2.56) \mu\text{g/mL}$ and $(3.97 \pm 2.60) \mu\text{g/mL}$ in the no-combination group (14 cases), the co-administered with CYP450 enzyme inhibitor group (12 cases), and co-administered with Proton pump inhibitors (PPIs) group (10 cases), respectively. There was no statistical difference in terms of voriconazole concentration between no-combination group and co-administered with CYP450 enzyme inhibitor group ($P=0.99$). Likewise, no significant difference could be observed between no-combination group and co-administered with PPIs group ($P=0.76$).

Affecting factors on voriconazole trough concentration

Multiple linear regression using stepwise procedure were conducted to investigate the relationship between the voriconazole trough concentration and the affecting factors including gender, age, body weight, drug interactions, ALB and Child-Pugh classification. The final results of multiple linear regression analyses were summarized in Table 5.

Multiple linear regression analysis showed that gender ($P=0.044$) and ALB ($P=0.006$) had the greatest impact on voriconazole trough concentration. The $R^2=0.406$ indicated that 40.6% variations of voriconazole trough concentration could be explained by drug interaction, ALB, gender, weight, and Child-Pugh classification. Since the majority of the AIDS patients included in this study were male, the impact of gender was not referential.

Discussion

Candida infection and *Cryptococcus* infection are prevalent fungal opportunistic infections in AIDS patients, and in southern China, *Talaromyces marneffe*(*T. marneffe*)-infection is also common [9]. For *Candida* infections, echinocandins and fluconazole are preferred over voriconazole [10]. For *Cryptococcus neoformans* infection, amphotericin B, flucytosine and fluconazole are often the preferred choice [11, 12]. For *T. marneffe*-infection, a fatal systemic mycosis, the recommended medication regimen is induction treatment with amphotericin B followed by a switch to maintenance oral itraconazole [13]. Therefore, voriconazole is not routinely recommended as the first choice for the common opportunistic fungal infections in AIDS patients. Previous studies have indicated that most isolates of *T. marneffe* are susceptible to voriconazole [14, 15]. Series studies evaluating the efficacy and the safety of voriconazole to treat patients with *T. marneffe* infection have demonstrated that voriconazole is an effective, well-tolerated therapeutic option for this kind of disease [15]. Voriconazole is also active against *Candida* and *Cryptococcus*. Therefore, voriconazole is a guideline-recommended alternative in *Candida* infection, *Cryptococcus* infection and *T. marneffii* infection [10–13]. In this study, we collected HIV cases for more than 3 years, voriconazole was frequently used as an alternative treatment for patients who were intolerant to other antifungal drugs. Thus, the number of HIV cases was relatively small in our study. Nevertheless, the rational use of voriconazole in AIDS patients is essential and of importance. 78.57% AIDS patients used voriconazole for targeted therapy and 21.43% for empirical treatment (Table 1). AIDS patients are a special population with special disease status and polypharmacy, so the individualized medicine of voriconazole in a clinical setting become more challenging. Series studies have investigated the application of voriconazole TDM in special populations, including children [16], the elderly [17], patients with cirrhosis [11], patients with tuberculosis [18]. However, no literature has reported the application of voriconazole TDM in AIDS patients, which is the outstanding highlight of this present study. Moreover, the clinical pharmacist was involved in the whole treatment,

for example, took part in selecting appropriate drugs and formulating treatment regimens for AIDS patients, conduct voriconazole TDM, guide the dose adjustment of voriconazole based on TDM and monitoring of ADRs. Therefore, clinical pharmacist can play an important role in the treatment of AIDS. Besides, clinical pharmacist has emerged as an indispensable member of the multidisciplinary diagnosis and treatment team.

The therapeutic range of trough concentration and the applicable population for voriconazole TDM are still controversial [19]. The voriconazole treatment regimens for 26 cases are all given a loading dose and a maintenance dose based on body weight. The maintenance dose was not halved in 2 patients with hepatic function Child-Pugh class B. Blood samples from the 28 cases were collected 0.5 h before the 5th dose at the earliest, and the average sampling time was 4.25 d after initiation of voriconazole therapy, the timing of blood sampling in the 28 cases all met the guideline requirements [4–8], which ruled out the influence of improper sampling on the TDM results. However, the first results of voriconazole TDM showed that the concentration attainment rate is only 57.14%(Table 2). Recently, there have been plenty of researches about the application of voriconazole TDM on patients with invasive fungal infections, but the patients in our study have a lower attainment rate of concentration compared with other research [20]. Dose adjustment based on TDM is an important element of individualized drug monitoring, and domestic and foreign clinical guidelines have different recommendations. Chinese guideline recommend that 20% maintenance dose can be reduced when the concentration reach above the upper limit and below 10.0 µg/mL and no grade 2 or higher adverse events occurred [8]. Moreover, 50% maintenance dose can be increased when the concentration are below the lower limit or when voriconazole treatment shows suboptimal efficacy [8]. In this study, AIDS patients who did not achieve target concentration range were adjusted to individualized regimens based on TDM results, including avoidance of drugs carrying a high risk of drug-drug interactions, appropriate dose increment or reduction, or switching to alternative regimens. There are three patients in this study reduced the dose by 20%(Table 3). Also, the dose was increased by 20% in another patient since a trough concentration of 0.9µg/mL was measured from the first TDM(Table 3). After individualized intervention, the trough concentration of voriconazole in aboved four patients all reached the standard range as second TDM indicated(Table 3), demonstrating that the Chinese dose adjustment guideline is applicable to the population of AIDS patients. Furthermore, more attention should be paid to the patient's compliance and prompt withdrawal of the interacting drugs other than dose adjustment, according to British guideline [5]. After discontinuation of rifampin, the voriconazole concentration of one patient in our study also rise to the lower limit without dose adjustment (Table 3). Consequently, the attainment rate of trough concentration increased significantly after intervention based on first TDM results, from 57.14–87.50%(Table 2). Thus, there is significant need to perform TDM for AIDS patients using voriconazole.

A meta-analysis showed that the risk of developing drug toxicity could be significantly increased when trough concentration of voriconazole exceed 6.0 µg/mL.² During hospitalization, the incidence of voriconazole associated ADRs is 21.43% in our study(Table 4). 83.33% of the patients suffering from ADRs had trough concentrations above 5.0 µg/mL, manifesting as hallucinations, visual disturbances and drug-related hepatitis(Table 4). The mean trough concentration of voriconazole in the ADR group was (7.12±2.27) µg/mL. It is worth mentioning that the incidence of ADR exhibits positive correlation with the trough concentration level of voriconazole ($P=0.017$).

There are many multifactorial and complex affecting factors that can influence the individual differences in clinical application of voriconazole, and the factors that have been confirmed include genotype, age, gastrointestinal absorptions, pathophysiological status and drug interaction, of which Cytochrome P450 2C19(CYP2C19) genetic polymorphisms and drug interaction are the two most important affecting factors [17, 21].

The C_{max} and AUC values of voriconazole in poor CYP2C19 metabolizers are 2-5 times higher than normal CYP2C19 metabolizers [22]. The CYP2C19 genetic polymorphism influences the steady-state level of voriconazole and is a significant affecting factor contributing to the highly variable pharmacokinetics of voriconazole [23]. The detection of CYP2C19 genetic polymorphism is recommended for patients using voriconazole by Clinical Pharmacogenetics Implementation Consortium (CPIC) [24]. It is worth mentioning that the distribution characteristics of CYP2C19 genetic polymorphisms can differ by race and ethnicity. About 20-30% Asian populations are slow metabolizers, while only about 2-3% Caucasians are slow metabolizers [25]. For 32.14% of the AIDS patients in this study, the mean trough concentration of voriconazole skewed toward higher values (Table 2), and the observed phenomenon may be blamed for genotype. Nevertheless, the present study suffered from a drawback that the patients were not subjected to detection of CYP2C19 genetic polymorphisms.

Drug interaction is another important affecting factor on steady-state level of voriconazole. AIDS patients are immune-suppressed and susceptible to opportunistic infections, so polypharmacy is often required. Thus, there is clearly a need to be more alert to the potential drug interactions. Voriconazole is metabolized mainly in liver, both an inhibitor of CYP2C19, CYP2C9, CYP3A and an enzyme substrate. So voriconazole can easily interacts with other CYP enzyme substrates, inhibitors or inducers. The common drugs observed drug-drug interactions with voriconazole include antiretroviral drugs, antiepileptic drugs, PPIs, rifampicin, antibacterial drugs, glucocorticoids, calcium channel antagonists, sedative hypnotics, antiarrhythmic drugs and so on. CYP inducers can reduce systemic exposure to voriconazole and lead to treatment failure when trough concentration of voriconazole are below the therapeutic range [26]. Rifampicin, a CYP3A4 inducer, can dramatically decrease the C_{max} and AUC of voriconazole in vivo [27]. In our study, a patient diagnosed co-infection with *Mycobacterium tuberculosis* and *T. marneffei* was co-administrated with voriconazole during quadruple antituberculosis therapy for pulmonary tuberculosis (isoniazid, rifampin, ethambutol and pyrazinamide). The dosage of voriconazole and the timing of sampling were in accordance with guideline recommendations. Unexpectedly, the voriconazole trough concentration was measured to be 0.2 µg/mL, which was far below the lower limit of the therapeutic range. After discontinuation of rifampicin for 7 days, the voriconazole trough concentration rised to 1.0 µg/mL without dose adjustment, which was within therapeutic range. Our results further confirmed the potent enzyme-inducing effect of rifampicin on the trough concentration of voriconazole. In contrast, co-administration with CYP inhibitors may increase systemic exposure to voriconazole and alter its safety profile [2]. When trough concentration of voriconazole is above the therapeutic range, an increased incidence of ADR may occur during voriconazole therapy [2]. The most common drugs in combination with voriconazole in this study are PPIs. Surprisingly, there were no effects of esomeprazole or omeprazole on voriconazole trough concentration could be significantly observed between the no-combination group and the co-administered with PPIs group ($P=0.76$). Since this study is a retrospective study in a single center, and the number of cases is relatively small, there is an inherent problem in studying drug interactions, especially co-administration of CYP inhibitors including PPIs.

The specific pathophysiological status of AIDS patients is considered another important factor influencing the steady-state level of voriconazole in blood. AIDS patients are prone to develop hypoproteinemia during treatment, which may also bring about alterations in pharmacokinetic and pharmacodynamic properties of voriconazole. It is well known that the bound drug-albumin complex is the storage form of a drug, and the complex can gradually release free drug when the blood concentration decreases. On one hand, only the unbound or free fraction of a drug can cross the biological membrane and exert pharmacological effects within the body. On the other hand, only the unbound or free fraction of a drug can be cleared from the body. Therefore, serum ALB level will have a significant effect on the apparent volume of distribution (V_d) and clearance (CL) of highly albumin-bound drugs.

Some studies have demonstrated that hypoproteinemia is an influential factor affecting trough concentration of voriconazole [28]. On the one hand, hypoproteinemia can result in increased Vd and CL of a drug, potentially resulting in under-dosing and consequent treatment failure. On the other hand, hypoproteinemia can alter the plasma protein-binding rate of voriconazole, potentially resulting in increased concentration of unbound voriconazole and consequent ADRs, even when the trough concentration of voriconazole is within normal range [28]. One patient with a trough concentration within the therapeutic range, mainly manifested as anxiety and insomnia (Table 4), requiring consideration of hypoproteinemia (ALB=28.4g/L). The mean ALB of AIDS patients in this study was $(28.58 \pm 5.03) \text{ g} \cdot \text{L}^{-1}$, and the ALB level appeared to be an important factor affecting steady-state level of voriconazole in blood (Table 5, $P=0.006$). Furthermore, multiple linear regression analysis also indicates that 40.6% variations of voriconazole trough concentration can be attributed to differentiation of gender, age, ALB, drug interactions and AST (Table 5, $R^2=0.406$).

Conclusion

In summary, the present study indicated the difficulty of predicting voriconazole concentration in blood without TDM. AIDS patients usually have low attainment rate of voriconazole concentration after initiation of standard dosing regimen, and the affecting factors seem multifactorial and complex. Hypoproteinemia is a significant affecting factor, as well as drug interactions. The incidence of voriconazole related ADRs in AIDS patients is high, mostly occurring when the concentration of voriconazole is above $5.0 \mu\text{g/mL}$. Accordingly, the implementation of pharmaceutical care based on TDM is vital to enhance the efficacy and safety of voriconazole therapy, which can guide the dosage optimization of voriconazole. Last but not least, dosage adjustment method in Chinese Practice Guideline is applicable for the population of AIDS patients. However, there are some limitations in our study. First of all, the number of cases is small. Second, the detection of CYP2C19 genetic polymorphisms is not performed. Therefore, more efforts should be made to further investigate the clinical implications of voriconazole TDM in AIDS patients, and to explore more strategies to improve individualized medication.

Abbreviations

Acquired Immune Deficiency Syndrome: AIDS; Therapeutic drug monitoring: TDM; Adverse Drug Reactions: ADRs; Albumin: ALB; Proton pump inhibitors: PPIs; High-performance liquid chromatography: HPLC; aminotransferase: AST; Cytochrome P450: CYP; *Talaromyces marneffe*: *T. marneffe*; Cytochrome P450 2C19: CYP2C19; The apparent volume of distribution: Vd; Clearance: CL

Declarations

Authors' contributions

SW, TC, ZL and HZ conceptualised the study. TC, SW, QZ and LH ran the study and ZL, HZ and LH collected/collated the data. SW, TC and HZ analysed the data. TC wrote the original manuscript and all authors read and contributed to each version. All authors had full access to the study data. All authors have approved this final version. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no conflicts of interest

Availability of data and materials

The dataset supporting the conclusions of this article is included with the article. Please contact author for further data requests.

Ethics approval

This study was approved by the ethical committee of Quanzhou First Hospital Affiliated to Fujian Medical University (Ethics number: QZFH.FJMU.2018.212).

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Tables

Table 1 Purposes of voriconazole administration

Classification of treatment	Proportion [number]	Diagnosis	Number	Notes
Targeted therapy	78.57% [22]	<i>T. marneffe</i> i-infection	17	5 of disseminated infection [11 of bloodstream infection [1 of skin infection
		<i>Cryptococcosis</i>	2	1 of pulmonary <i>cryptococcosis</i> , 1 of Cryptococcal meningitis
		<i>Candidiasis</i>	2	1 of <i>Candida glabrata</i> bloodstream infection [1 of Oral candidiasis
		Pulmonary aspergillosis	1	
Empirical therapy	21.43% [6]	Pulmonary fungal infection	6	Patients were initially treated with broad- spectrum antimicrobial drugs. Subsequently, the lesions progressed, and pulmonary fungal infections were then considered. The serum G ((1 – 3)- β -d-glucan) tests resulted positive in 3 of them

Table 2 Distribution of voriconazole TDM results

Trough concentration (µg/mL)	Results of first TDM		Results of TDM after dose adjustments	
	Proportion Number of cases	Mean trough concentration	Proportion Number of cases	Mean trough concentration
≤1.0	10.71% 3	0.60±0.36	4.17% 1	0.70±0.00
1.0~5.5	57.14% 16	3.03±1.37	87.50% 21	2.70±1.36
≥5.5	32.14% 9	7.40±1.39	8.33% 2	5.90±0.28

Table 3 The partial results of voriconazole TDM and corresponding interventions

No	First TDM µg/mL	Intervention	Secondary TDM µg/mL	Note
1	0.2	Discontinuing rifampin	1.0	
2	7.5	Reduce by 20%	2.0	
3	8.7	Reduce by 20%	1.6	
4	6.6	Reduce by 20%	2.5	
5	9.6	Switching to itraconazole		<i>T. marneffe</i> i-infection
6	8.7	Switching to itraconazole		<i>T. marneffe</i> i-infection
7	7.7	Switching to amphotericin B		Empirical treatment
8	6.0	Withdrawal		Drug fever
9	5.7	Unadjusted		No relevant adverse reactions
10	0.7	Unadjusted		Effective No relevant adverse reactions
11	6.1	Unadjusted		
12	0.9	Increase by 20%	1.1	

Table 4 The distribution of voriconazole trough concentrations and the occurrence of ADRs

Trough concentration (µg/mL)	Number of cases	ADR information		
		Number of cases	<i>Incidence (%)</i>	ADR sign description
0.0~1.0	3	0	0	
1.0~2.0	6	0	0	
2.0~3.0	3	0	0	
3.0~4.0	4	1	25.00	Anxiety and insomnia
4.0~5.0	1	0	0	
5.0~6.0	4	1	25.00	Hallucination
6.0~7.0	2	1	50.00	Visual disturbance
7.0~8.0	2	0	0	
8.0~9.0	2	2	100.00	Drug-induced hepatitis; hallucination
9.0~10.0	1	1	100.0	Hallucination
Total	28	6	21.43	

Table 5 The results of parameter estimation in multiple linear regression model

	Unstandardized coefficient		Standardized coefficient	T	<i>P</i> -values
	B	Standard error	Beta		
Parameters	-4.513	5.565		-0.811	0.426
Drug interaction	1.379	0.854	0.293	1.614	0.121
ALB	0.310	0.101	0.577	3.063	0.006
Gender	-3.397	1.591	-0.448	-2.136	0.044
Weight	-0.033	0.051	-0.137	-0.653	0.521
Child-Pugh classification	1.356	0.841	0.289	1.613	0.121

$R^2=0.406$, $F=3.006$, $P=0.032$