Improved absorption of itraconazole tablet by co-administration with lemon beverages in a lung transplant recipient: A case report

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ICMJE statement

All authors contributed to the writing of the manuscript and met the ICMJE authorship criteria.

Authorship statement

KU, YK, MS, and KM conceptualized and designed the study. KU and YK drafted the manuscript. MN provided feedbacks as an expert of clinical microbiology. SN, AY, and TT critically reviewed the manuscript. AO and HD are the primary doctors, and supervised the treatment. All authors contribute to the writing of the final manuscript.

Abstract

After lung transplantation, itraconazole (ITCZ) is used as a prophylaxis for aspergillosis. ITCZ is a weak base with high lipophilicity, and the dissolution and absorption of ITCZ tablets and capsules are pH dependent. Therefore, ITCZ may not achieve sufficient serum concentrations in patients with higher gastric pH because of its poor bioavailability. We report a case of a woman in fifties with post-COVID-19 respiratory failure who successfully underwent lung transplantation, followed by improved bioavailability of ITCZ tablets when given with acidic lemon beverages. The patient was initially administered ITCZ oral solution; this was discontinued because of its unpleasant taste, nausea, and vomiting. The ITCZ oral solution was replaced with ITCZ tablets 78 days after transplantation; however, serum concentrations of ITCZ and hydroxy-ITCZ were below the detection limit (100 ng/mL). We co-administered ITCZ tablets with commercially available lemon beverages. Subsequently, serum concentrations of ITCZ and hydroxy-ITCZ increased to 341 and 673 ng/mL, respectively, on the 125th day after transplantation. Infection with fungi, including *Aspergillus* spp., was not observed in this case. The patient had no adverse events such as gastric ulcer or hyperglycemia. These results suggest that the co-administration of lemon beverages and ITCZ tablets may help achieve better absorption of ITCZ in patients taking acid suppressants.

Keywords (5): itraconazole, lung transplantation, therapeutic drug monitoring, absorption, lemon beverage

Introduction

Invasive fungal infections are a major cause of morbidity and mortality in lung transplant recipients [1]. Therefore, antifungal prophylaxis and treatment are necessary for lung transplantations. Itraconazole (ITCZ), a triazole antifungal agent, is effective against *Aspergillus* species and is used to prevent and treat fungal infections after lung transplantation [2]. The efficacy of ITCZ is related to the systemic exposure of ITCZ and its metabolite, hydroxy-ITCZ (OH-ITCZ). The therapeutic level of trough plasma concentration is above 750 ng/mL combined concentrations of ITCZ and OH-ITCZ [3].

The orally administered ITCZ is formulated as capsules, tablets, and oral solutions. ITCZ is a weak base (pKa = 3.7) with high lipophilicity (log D > 5) [4]. The dissolution and absorption of ITCZ tablets and capsules are pH dependent [5]. ITCZ oral solution containing hydroxypropyl-beta-cyclodextrin has higher bioavailability than tablets and capsules; therefore, ITCZ oral solution is frequently used. However, when ITCZ oral solution cannot be administered due to side effects such as diarrhea, nausea, and vomiting, it should be replaced with ITCZ tablets or capsules. However, it is clinically important to consider the decrease in bioavailability when changing the ITCZ oral solution to tablets or capsules.

ITCZ may not achieve sufficient serum concentrations in patients with higher gastric pH because of its poor bioavailability [6]. Acid suppressants, such as H_2 blockers or proton pump inhibitors (PPIs), are often used in lung transplant recipients because corticosteroids, commonly used immunosuppressive medications, increase gastric acidity and elevate the risk of gastric ulcers. Therefore, in lung transplant recipients who concomitantly use an H_2 blocker or a PPI with ITCZ tablets or capsules, the bioavailability of ITCZ may decrease due to inhibition of gastric acidity. It is ideal for the stomach environment to be acidic only when ITCZ is administered to lower the risk of gastric ulcers and maintain an acceptable bioavailability of ITCZ from tablets or capsules. Acidic solutions to lower stomach pH can improve the bioavailability of ITCZ tablets or capsules, even in the presence of acid suppressants. It was reported previously that co-administration of ITCZ with a cola beverage enhanced the absorption of ITCZ capsules in healthy subjects [7]. Another study showed that co-administration of ITCZ with a cola beverage improved the bioavailability of ITCZ in patients taking H_2 blockers [8]. Vitamin

C beverages are acidic; therefore, they may improve ITCZ absorption. A previous study investigated the effect of a vitamin C beverage on the oral bioavailability of ITCZ [9]. However, its effect in patients taking PPIs or H_2 blockers remains unknown.

Here, we report a case in which the serum concentration of ITCZ was increased by co-administration with commercially available lemon juice and lemon beverage in a lung transplant recipient.

Case Report

A woman in fifties underwent living-donor lobar lung transplantation (LDLLT) for COVID-19-related respiratory failure 104 days after the onset of COVID-19. LDLLT was successfully performed, and immunosuppressive (tacrolimus, mycophenolate mofetil, and corticosteroids) regimens were initiated on a postoperative day (POD) 1. Tacrolimus trough levels were maintained at 10–20 ng/mL during the first 3 months. Antifungal prophylaxis with ITCZ (oral solution [200 mg/day]) was initiated on POD 20. For patients after COVID-19, not only aspergillosis but also other fungal infections such as zygomycosis should be considered [10]. However, we assumed that the risks for other fungal infections related to COVID-19 were low in the present case because 104 days have passed from the onset of COVID-19. ITCZ was temporarily discontinued on POD 23 because of nausea and vomiting. The administration of the ITCZ oral solution (200 mg/day) was restarted on POD 33. The serum concentrations of ITCZ and hydroxy-ITCZ on POD 55 were 240 and 358 ng/mL, respectively, below the target concentration (750 ng/mL as the summation). Thus, ITCZ was discontinued, and voriconazole was started on POD 57 (600 mg/day of voriconazole on POD 57, followed by 400 mg/day on POD 58–63, 500 mg/day on POD 64–70, and 600 mg/day on POD 71–74). The blood concentration of voriconazole was 1.1 μg/mL on POD 75. The serum γ-glutamyl transferase level increased from 327 U/L (POD 54) to 856 U/L (POD 75), and was considered an adverse reaction to voriconazole. Therefore, voriconazole was discontinued, and the ITCZ oral solution was restarted on POD 75. The ITCZ oral solution was then replaced with an ITCZ tablet (300 mg/day) because of nausea and vomiting on POD 78. However, the serum concentrations of ITCZ and hydroxy-ITCZ were below the detection limit (<100 ng/mL) on POD 82. The dose of the ITCZ tablet was increased from 300 to 400 mg/day on POD 82, and vonoprazan (10 mg/day) was changed to famotidine (40 mg/day) on POD 83. Since the bioavailability of ITCZ was poor, we started co-administration of ITCZ tablet on POD 84 with POKKA LEMON® (POKKA SAPPORO Food & Beverage Ltd., Nagoya, Japan) and CHELATE LEMON® (POKKA SAPPORO Food & Beverage Ltd.), commercially available acidic beverages. We selected these lemon beverages to dissolve ITCZ for the following reasons. i) The pH is similar or lower than the pKa of ITCZ (3.7). ii) They consist of naturally derived

ingredients. iii) The total volume is small, making it easy to take daily. The ITCZ tablet was crushed and mixed with 4 mL POKKA LEMON® in a plastic cup. Next, 40 mL of CHELATE LEMON® solution was added. After taking the suspended tablets, the ITCZ remaining in the cup was collected with 10 mL of CHELATE LEMON® and taken again. We confirmed that the pH at room temperature of POKKA LEMON®, CHELATE LEMON®, and their mixtures was 2.3, 3.0, and 3.0, respectively. At 90 days after transplantation, serum concentrations of ITCZ and hydroxy-ITCZ were 196 and 435 ng/mL, respectively, and those on POD 96 were 243 and 518 ng/mL, respectively. On POD 125, the serum concentrations of ITCZ and hydroxy-ITCZ were 341 and 673 ng/mL, respectively. Fig. 1 summarizes the clinical course of the blood concentration of ITCZ plus hydroxy-ITCZ, tacrolimus, and their doses. Improvement in the bioavailability of ITCZ elevated the trough concentration/dose (*C/D*) ratio of tacrolimus, probably due to drug-drug interactions mediated by CYP3A4. The clinical laboratory data and the *C*/*D* ratio of tacrolimus are also shown in Fig. 1. Invasive fungal infections were not observed in the first 4 months after transplantation, although the case was positive for cytomegalovirus on POD 117. Fig. 2 shows the computed tomographic scans of the chest on POD 119. The patient had no adverse events such as gastric ulcer or hyperglycemia. She was transferred to another hospital for rehabilitation on POD 131.

Discussion

Fungal infections following lung transplantation can be fatal. Therefore, prophylactic administration of antifungal agents is required in lung transplant patients. However, the bioavailability of antifungal drugs can be significantly affected by concomitant drugs and comorbidities. Although the present case initially had poor absorption of ITCZ tablets, it improved when the ITCZ tablets were co-administered with lemon beverages. Voriconazole is an alternative for prophylaxis of aspergillosis, but this patient could not continue it due to the elevation of γ-glutamyl transferase. Other alternatives for prophylaxis of fungal infections include liposomal amphotericin B (L-AMB) or posaconazole. However, because L-AMB requires intravenous administration, it is difficult to adapt L-AMB to outpatients. As for posaconazole, there is little evidence regarding prophylaxis of fungal infections after lung transplantation and the drug is expensive. Thus, we considered that ITCZ should be continued in this case as well as to improve the method of administration. The trough levels of serum ITCZ and OH-ITCZ increased by more than 10-fold when combined with lemon beverages. These results suggest that co-administration with lemon beverages would be useful in improving the oral bioavailability of ITCZ in patients taking PPIs or H_2 blockers.

ITCZ is a weak base with a pKa value of 3.7 [4]. Therefore, the solvent used to dissolve the ITCZ tablets should be a strong acid. In fact, the ITCZ tablet (Nichi-Iko Pharmaceutical Co., Ltd.) administered to the present case dissolves well at pH 1.2 but not in pH 3.0 [11~~10~~]. Among the lemon beverages used for mixing with ITCZ, the pH of POKKA LEMON® was less than 3.0, but the pH of CHELATE LEMON® and the mixture was 3.0. Therefore, the POKKA LEMON® may have contributed more to the dissolution of the ITCZ.

Previous studies have reported that cola beverages (pH 2.2) improve the bioavailability of ITCZ tablets and capsules [7,8]. Approximately 300 mL of a cola beverage effectively improves oral bioavailability of ITCZ. However, the use of cola beverages has disadvantages. The major concern is the effects of the components of cola beverages, such as sugar, caffeine, flavors, and additives. Lung transplant patients must use ITCZ for a long time. Taking ITCZ with 300 mL of cola daily for decades might cause an increase in blood glucose levels. Some cola beverages contain artificial sweeteners

such as sucralose and acesulfame potassium, altering the gut microbiome and blood glucose and insulin levels [12,13]. In addition, caffeine may cause psychiatric symptoms and interactions with antidepressants or antipsychotics [14]. Lemon beverages used in the present study have the same pH as cola but contain fewer calories (4 mL of POKKA LEMON® and 50 mL of CHELATE LEMON® contain 35.3 kcal) than cola beverages (300 mL of cola contains 135 kcal). Indeed, the present case showed no increase in serum glucose levels after the administration of lemon beverages. Thus, lemon beverages are appropriate for lung transplant patients.

After lung transplantation, the calcineurin inhibitor tacrolimus is the cornerstone of immunosuppressive therapy [15]. The therapeutic range of tacrolimus trough blood concentrations is 10–20 ng/mL in the first 3 months after lung transplantation [16]. As CYP3A4 mainly metabolizes tacrolimus, the dose of tacrolimus should be adjusted for the concomitant use of potential CYP3A4 inhibitors, including concomitant drugs and foods. In the present case, the *C/D* ratio of tacrolimus increased 6.9-fold (from 1.28 to 8.8 ng/mL/mg) after using ITCZ with lemon beverages, while there was no significant deviation from the target range (10–20 ng/mL). This may have been due to the effects of ITCZ and furanocoumarin of citrus fruits. ITCZ inhibits CYP3A and elevates the *C*/*D* ratio of tacrolimus [17]. A previous report showed that the *C*/*D* ratio of tacrolimus after co-administration of ITCZ was 5.6-fold higher than that before ITCZ initiation [18]. Grapefruit juice interacts with tacrolimus because it contains an inhibitor of CYP3A4, furanocoumarin [19]. The co-administration of grapefruit juice with tacrolimus increased the *C/D* ratio of tacrolimus by an average of 2.2-times [19]. Lemons also contain furanocoumarins, but the amount is lower than that in grapefruit [20]. Given that the effects of ITCZ and furanocoumarins were exerted simultaneously, the *C/D* ratio of tacrolimus was likely to increase more than 10-fold. However, the change in the *C*/*D* ratio of tacrolimus in our case was comparable to ITCZ used alone. These results suggest that ITCZ, and not a lemon beverage, significantly influenced the blood concentration of tacrolimus. Since the trough concentrations of tacrolimus were monitored in this case, the bioavailability of ITCZ and concomitant drug-drug interactions could be estimated. When the bioavailability of ITCZ changes, it is important to consider the efficacy and safety of other co-administered medicines, such as loperamide [21], edoxaban [22], and nifedipine

[23].

This report suggests that lemon beverages can improve the bioavailability of ITCZ tablets. ITCZ oral solution is a useful dosage form to achieve sufficient serum concentration of ITCZ, but in some cases, it is difficult to use because of adverse events. However, the generalization should be done with caution since these results were obtained from one patient. Future studies with larger sample sizes are warranted to evaluate whether the co-administration of lemon beverages with ITCZ tablets achieves better absorption of ITCZ in patients taking PPIs or H_2 blockers.

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Ethical approval

This study was approved by the Kyoto University Institutional Review Board (R2933-1). Written informed consent was obtained from the patient for the publication of this case report.

Declarations of interest

None.

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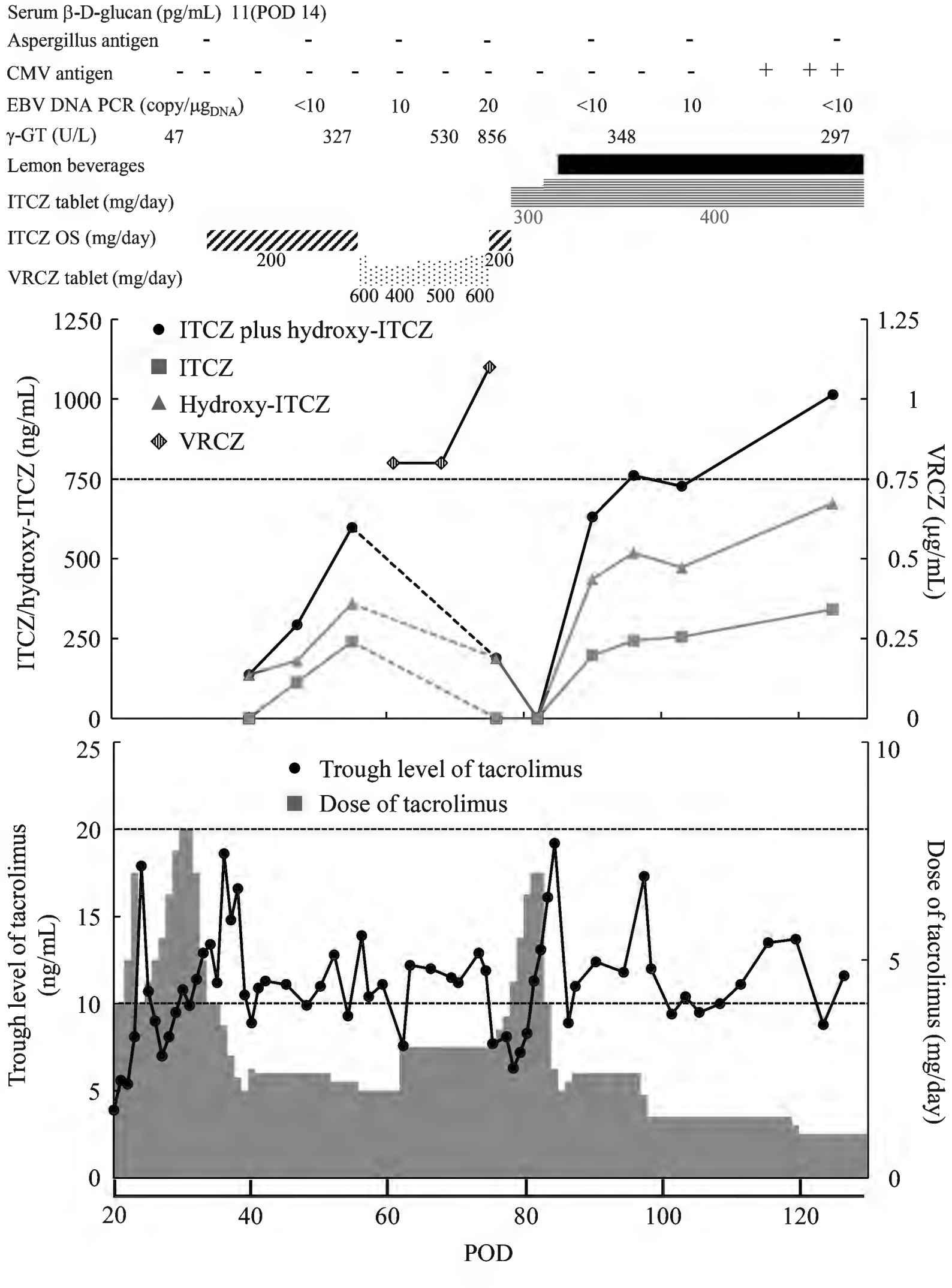
Figure legends

Fig. 1. Clinical course after transplantation.

The doses of itraconazole (ITCZ) or voriconazole, the use of lemon beverages, lab data, the results of infections tests, the concentrations of itraconazole, hydroxyitraconazole, and tacrolimus are shown. The concentrations of ITCZ and hydroxy-ITCZ below the detection limit (<100 ng/mL) were taken to be 0 ng/mL. The target concentration of ITCZ plus hydroxy-ITCZ (750 ng/mL) and tacrolimus (10-20 ng/mL) are also shown. CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; γ-GT, γ-glutamyl transferase; ITCZ, itraconazole; OS, oral solution; VRCZ, voriconazole; POD, postoperative day.

Fig. 2. Chest computed tomography of the patient on POD 119. Horizontal planes of aortic arch, pulmonary trunk, and just above diaphragm are shown.


Serum β-D-glucan (pg/mL) 11(POD 14)
Aspergillus antigen - - - - - -
CMV antigen - - - - - - - - - - - - + + +
EBV DNA PCR (copy/μg$_{DNA}$) <10 10 20 <10 10 <10
γ-GT (U/L) 47 327 530 856 348 297
Lemon beverages
ITCZ tablet (mg/day)
300 400
ITCZ OS (mg/day)
200 200
VRCZ tablet (mg/day)
600 400 500 600
ITCZ plus hydroxy-ITCZ
ITCZ
Hydroxy-ITCZ
VRCZ
ITCZ/hydroxy-ITCZ (ng/mL)
VRCZ (μg/mL)
1250
1000
750
500
250
0
1.25
1
0.75
0.5
0.25
0
Trough level of tacrolimus
Dose of tacrolimus
Trough level of tacrolimus (ng/mL)
Dose of tacrolimus (mg/day)
25
20
15
10
5
0
10
5
0
20 40 60 80 100 120
POD