



Case report

A case of treatment with voriconazole for chronic progressive pulmonary aspergillosis in a patient receiving tacrolimus for dermatomyositis-associated interstitial lung disease



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ARTICLE INFO

Article history:

Received 30 September 2015

Received in revised form

25 October 2015

Accepted 29 October 2015

Keywords:

Voriconazole

Tacrolimus

Chronic progressive pulmonary aspergillosis

Dermatomyositis-associated interstitial lung disease

CYP2C19

Drug interaction

ABSTRACT

We report a successful treatment with voriconazole (VRCZ) for chronic progressive pulmonary aspergillosis (CPPA) in a patient with dermatomyositis-associated interstitial lung disease (DM-ILD) treated with tacrolimus. A 73-year-old man with DM-ILD, treated with tacrolimus and prednisolone, complained of productive cough and his chest X-ray showed infiltration in the left upper lung field. We diagnosed CPPA and added VRCZ. Although we reduced the dose of tacrolimus for drug interaction, serum VRCZ level increased after the treatment. The patient was found to have cytochrome P450 (CYP) 2C19 *2/*2, a genetic polymorphism in poor metabolizers of VRCZ. We adjusted the doses of both drugs and treated him successfully. We recommend performing individual therapeutic drug monitoring (TDM) in CYP-mediated drug interactions and considering the effect of CYP polymorphisms.

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1. Introduction

Tacrolimus is a calcineurin inhibitor that selectively suppresses T lymphocytes secreting inflammatory cytokines [1]. It has been adopted for the treatment of collagen vascular disease. Recent reports have showed that concomitant use of tacrolimus and prednisolone was beneficial for interstitial lung disease complicated with polymyositis or dermatomyositis [2,3]. However, opportunistic infections frequently occur in patients with polymyositis or dermatomyositis under the use of immunosuppressants. In particular, *Aspergillus* species is one pathogen involved in pulmonary infection [4].

Voriconazole (VRCZ), a triazole antifungal medication, has been shown to be effective as primary or salvage therapy for subacute invasive and chronic pulmonary aspergillosis [5]. This drug is metabolized by cytochrome P450 (CYP) 2C19, 2C9, and 3A4. The

genetic polymorphisms of CYP2C19 in the Japanese have been known higher frequency than that in other races, and poor metabolizers of VRCZ [6–8]. Besides, VRCZ elevates serum levels of tacrolimus, mainly metabolized by CYP3A4 [1], as a result of competitive inhibition of CYP3A4 [9–11]. However, there are a few reports about this drug interaction, and the optimal treatment of tacrolimus and VRCZ with CYP2C19 polymorphism has not yet been determined.

This case report is a valuable report that actually identified the genetic polymorphism of CYP2C19 for successful treatment of chronic progressive pulmonary aspergillosis (CPPA) [12]. We describe a case of CPPA treated with VRCZ in a patient receiving tacrolimus, and discuss the drug interaction between tacrolimus and VRCZ in patients with CYP2C19 polymorphisms.

2. Case report

A 73-year-old man weighting 63 kg had complained of facial flushing, occipital rash, and pain in his shoulder and thigh. He had a medical history of diabetes and autoimmune hemolytic anemia. A

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physical examination revealed the entity of heliotrope rash, myalgia, and arthralgia. Laboratory studies showed elevated serum creatine kinase levels with no autologous antibodies (anti-aminoacyl tRNA synthetase including anti-Jo-1). Myositis was found in muscle biopsy. Chest computed tomography showed interstitial pneumonia. We diagnosed the patient as having dermatomyositis with interstitial lung disease. Treatment with tacrolimus and prednisolone after methylprednisolone pulse therapy was initially commenced. After improvement of disease, the maintenance dose was 4 mg/day of tacrolimus and 12.5 mg/day of prednisolone. He subsequently complained of productive cough and his chest X-ray showed infiltration in the left upper lung field 8 months after the initial treatment (Fig. 1a). The chest computed tomography findings showed wall thickening and infiltrative shadows around the cavity (Fig. 1b) and blood examination revealed slight elevation of white blood cell count (10,370/ μ L) and C-reactive protein (1.39 mg/dL). Liver and kidney function test were within the normal range (aspartate transaminase 13 U/L, alanine transaminase 10 U/L, blood urea nitrogen 15.7 mg/dL, creatinine 0.84 mg/dL). Levels of creatine kinase, Krebs von den Lungen-6, and surfactant protein-D were not elevated. (1,3)- β -D-glucan was <0.6 pg/mL and antigens for *Aspergillus*, *Candida*, and *Cryptococcus* were negative. However, the anti-*Aspergillus* antibody was positive. Furthermore, the percentage of neutrophils in bronchoalveolar lavage was elevated (15.4%), and pathological examination of the transbronchial biopsy revealed alveolitis without fungus. No pathogen was detected in sputum or bronchial lavage fluid culture. We treated the patient with 6 g/day of sulbactam/ampicillin with no symptomatic improvement for 7 days. As a result, we diagnosed clinical CPPA by continuous respiratory symptom over a month, pre-existed cavities and pericavitary progressive infiltrates in the left upper lobe, anti-*Aspergillus* antibody detection, elevation of inflammatory markers, and antibiotics ineffectiveness [12,13]. We began treatment with 600 mg/day of oral VRCZ followed by a 400 mg/day maintenance dose, and also halved the dose of tacrolimus, because the drug interaction with VRCZ had been reported [9–11]. We had performed therapeutic drug monitoring (TDM) during follow-up (Fig. 2). On the 4th day after treatment with VRCZ, we reduced the tacrolimus dose to 1 mg/day because of the high trough tacrolimus level (10.7 ng/mL, optimal trough levels 5–10 ng/mL). On the 14th day, the trough concentration was still elevated (11.8 ng/mL) so we further reduced the dose of tacrolimus to 0.6 mg/day. Although a previous report showed that serum VRCZ concentration was barely affected by tacrolimus [9–11], in our patient the level of VRCZ gradually increased. The serum concentration of VRCZ was 2.21 μ g/mL on the first measurement and

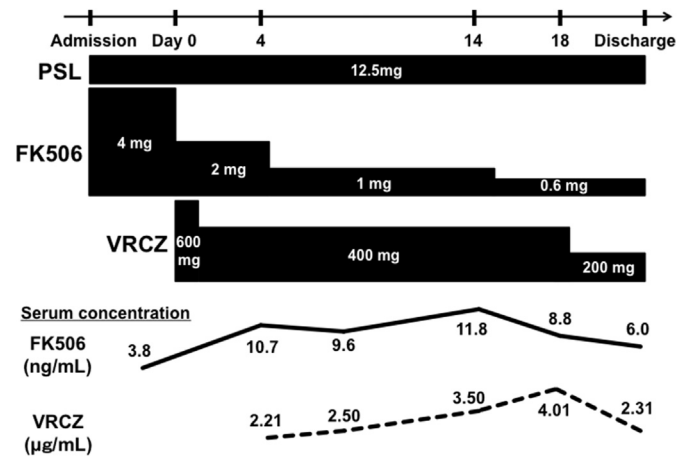


Fig. 2. Clinical course. The abbreviations used are: PSL; prednisolone, FK506; tacrolimus, VRCZ; voriconazole. Solid line indicates serum concentration of FK506. Dotted line indicates serum concentration of VRCZ.

increased maximum 4.01 μ g/mL on the 17th day (appropriate concentration 1–4 μ g/mL). The liver enzymes were elevated simultaneously (aspartate transaminase 118 U/L, alanine transaminase 101 U/L). We examined the genetic polymorphism of CYP2C19 using the GENECUBE[®] (TOYOBO, Fukui, Japan) [14], was a fully automated rapid genetic analyzer, with the informed consent of the patient and the CYP2C19 *2/*2 allele was found. We reduced the dose of VRCZ to 200 mg/day. The serum levels of VRCZ decreased to 2.31 μ g/mL and his liver dysfunction improved (aspartate transaminase 17 U/L, alanine transaminase 16 U/L). The trough concentration of tacrolimus decreased to 6.0 ng/mL on the hospital discharge. The chest X-ray revealed improvement of infiltration around the cyst wall (Fig. 3). His symptoms resolved after treatment with VRCZ, and his dermatomyositis has remained stable.

3. Discussion

VRCZ is mainly metabolized by CYP2C19 in the liver. There are three metabolizer types: extensive metabolizer, heterologous extensive metabolizer, and poor metabolizer (PM) of VRCZ depending on the genetic CYP2C19 polymorphism. The frequency of PM varies among racial groups. For example, the percentage of PM in Japan is about 18–23%, which is higher than that in other

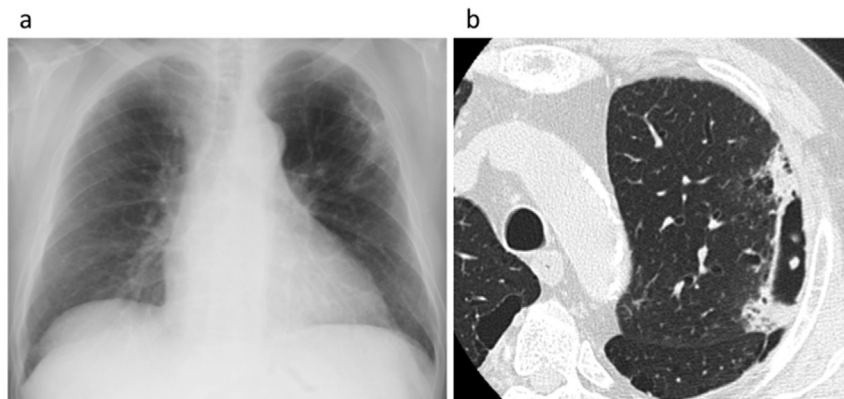


Fig. 1. Chest radiograph showing areas of infiltrative shadows in the left upper lung field (a). Computed tomography scan of the chest showing the wall of the cavity thickening and appearance of infiltration around the cavity (b).



Fig. 3. Chest radiograph showing improvement of infiltration around the cyst wall in the left upper lung field after treatment with voriconazole.

countries (2–8%) [6–8]. In our case, the serum concentration of VRCZ gradually increased. Thus we hypothesized that the patient was a PM of VRCZ by the CYP2C19 polymorphism, and performed gene analysis. We identified the patient as a homozygote of CYP2C19 *2/*2, a PM of VRCZ. Concerning CYP2C19 polymorphisms, two genetic defects are responsible for the majority of the poor metabolizers of this enzyme. These variants are two null alleles, which include a splice defect in exon5 (CYP2C19 *2; trivial name, m1; single base change G→A) and a premature stop codon at position 636 of exon 4 (CYP2C19 *3; trivial name, m2; single base change G→A), while CYP2C19 *1 represents the wild-type allele [8]. We suggest that impaired metabolism of VRCZ leads to an elevation its concentration in serum. Therefore CYP3A4, a common enzyme of VRCZ and tacrolimus, was more strongly inhibited and the serum level of tacrolimus further increased. This supports our hypothesis that the mere reduction of VRCZ dose decreased the tacrolimus concentration after the dose of tacrolimus was fixed.

The drug interaction between VRCZ and tacrolimus has been recognized, with VRCZ increasing serum tacrolimus concentration via competitive inhibition of CYP3A4 [9–11,15]. Other azole antifungals have been known to have the drug interaction involving CYP enzymes. VRCZ has lower inhibitory potency on CYP activity than ketoconazole and itraconazole, and similar to fluconazole [16]. Tacrolimus has a narrow therapeutic window and adverse events such as nephrotoxicity can occur depending on blood concentration. The physician prescribing information for tacrolimus recommends reducing the tacrolimus dose to one-third on initiating VRCZ, followed by TDM [17]. However, this reduction in tacrolimus dose may not be sufficient, and there are limited data about dose reduction of tacrolimus on starting VRCZ. A strategy for adjustment of tacrolimus dose has not yet been determined. In our case, we preemptively halved the dose of tacrolimus and continued TDM of tacrolimus.

Trifilio et al. initially reduced tacrolimus dose by 30% when administered concomitantly with VRCZ. The tacrolimus dose was ultimately reduced between 60 and 80% on a mg/kg basis compared with baseline dosing using a preemptive, two-step dose-reduction strategy for 16 days [10]. Conversely, Mori et al. reported that the concentration/dose (C/D; (ng/mL)/(mg/kg)) ratio was useful for the quantitative evaluation of drug interaction, reflecting both the concentration and dose of tacrolimus [11,15]. They showed that the median C/D ratio of tacrolimus changed from 172.8 with a range of 28.6–1110.7 (ng/mL)/(mg/kg) to 537.5 with a range of 127.8–1933.3

(ng/mL)/(mg/kg) after adding VRCZ. Median increase of the C/D ratio was 138.8% (range –32.0 to 685.7%) [15]. In our case, the final tacrolimus dose reduction was 85%. The C/D ratio changed from 65.3 to 1009.9 (ng/mL)/(mg/kg), an increase of 1546.6%. Both the dose reduction and increase in C/D ratio were higher than in previous reports [10,11,15]. Although serum VRCZ concentration is reportedly unaffected by co-administration of tacrolimus [9–11], we found that a poor metabolizer of VRCZ increased the serum level of VRCZ and resulted in higher concentration of concomitant tacrolimus.

In conclusion, we describe a case of CPPA treated with VRCZ in a patient receiving tacrolimus. The drug interaction and gene polymorphism of CYP enzymes resulted in simultaneous adjustment of the doses of tacrolimus and VRCZ. We should consider performing individual TDM in CYP-mediated drug interactions and take care when reducing doses of co-administered drugs.

Conflict of interest

The authors declare that they have no conflict of interest.

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