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Case report

Rechallenge of voriconazole successfully tolerated after hepatic toxicity

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ABSTRACT

Infections caused by Aspergillus species are often life-threatening. Drugs effective for Aspergillus infection are limited. Voriconazole is one of the most important drugs, however, considerable portion of patients experience liver toxicity and have to stop the drug administration. We frequently experience liver toxicity even though the serum concentration of voriconazole is within the target range. Historically, in some life-threatening situations like tuberculosis, where a suitable alternative is unavailable, rechallenge has been attempted. However, there have been no report on the rechallenge of voriconazole. We report cases of successful re-administration of voriconazole after liver toxicity.

1. Introduction

Infections caused by *Aspergillus species* are often life-threatening. In contrast to bacterial infections where several different classes of antibacterial agents can be considered, the number of antifungal agents for the treatment of infections with *Aspergillus* spp is limited. As a result, we sometimes need to struggle through various adverse effects without switching to other agents. Voriconazole is one of the most important drugs for the treatment of Aspergillus infection. However, around 16.9–50.1% of the patients are reported to experience abnormal liver function tests and 2.8–34% of them had to stop the drug administration [1]. The treatment of aspergillus infection after occurrence of liver toxicity is difficult and controversial. The monitoring of serum concentration is the first thing to do in case of liver toxicity. Guidelines recommend a trough concentration of around 1.5–5.5 mg/l [2]. However, we sometimes experience liver toxicity even though the serum concentration of voriconazole is within the range.

Usually rechallenge of drugs that caused liver toxicity is not recommended. European association for the study of the liver (EASL) guideline states, "Deliberate rechallenge with the causative drug in clinical practice is not advocated, unless the clinical scenario demands such an exposure, as it can cause more severe hepatotoxicity [3].". American college of gastroenterology (ACG) guideline also discourages rechallenge of causative drugs except in cases of life-threatening situations where there is no suitable alternative [4]. Historically, in some life-threatening situations where a suitable alternative is unavailable, rechallenge has been attempted.

Tuberculosis and cancer treatment are two common situations where rechallenge has been attempted. In the treatment of tuberculosis, drugs are often rechallenged after abnormal liver function test, and 70–90% of them are reported to succeed [5]. Aspergillus infection is also life-threatening and there are not so many choices of drugs especially in the outpatient setting. However, we could not find any data on the rechallenge of voriconazole. We supposed rechallenge of voriconazole might be tolerated in a majority of patients who experienced liver injury. We report cases of successful re-administration of voriconazole after liver toxicity.

2. Methods

In order to search the rechallenged cases, we systematically selected patients to whom voriconazole had been administered at a dose of less than 100mg/day among patients who were admitted to the Tokyo National Hospital between April 2006 and January 2020. Seven patients were selected, and medical records were reviewed regarding backgrounds and laboratory data. Patients were excluded when their liver injury was suspected to be caused by other drugs administered at the same time. We selected four patients who were rechallenged with voriconazole for hepatic toxicity from a small dose.

3. Results

The results are summarized in Table 1. As a background, no patient had drinking habits at the time of hospitalization. Only patient 4 had

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Table 1
Characteristics of each patient.

	Patient 1	Patient 2	Patient 3	Patient 4
Age	70	67	66	58
Sex	Male	Male	Female	Male
Body weight (kg)	54.5	54.4	36.4	36
Diagnosis	CPA[a]	CPA	CPA	CPA
Liver disease	None	None	None	HBV
Alcohol intake	None	None	None	None
Max ALT/AST on first exposure to voriconazole(U/l)	293/269	155/80	268/207	268/199
γGTP(IU/l)/ALP (U/l)	796/878	No data	76/455	98/-
Total bilirubin (mg/dl)	0.78	0.3	0.48	0.52
R quotient[b]	2.6	–	4.5	–
Severity of DILI[c]	Grade 3	Grade 2	Grade 3	Grade 3
Periods of taking voriconazole (days)	7	15	50	7
Plasma trough concentrations at the time of liver injury (μg/ml)	4.88	0.55	1.94	2.75
Doses of voriconazole (mg/day)	300	240	200	200
Symptoms at the time of liver injury	None	None	None	rash
Eosinophils at the time of liver injury (% and count/mm^3)	6.3%, 309	1.9%, 122	1.2%, 60	17%, 1260
Rechallenge doses of voriconazole (mg/day)	209	300	200	200
Rechallenge protocol	3–7 days step up from 50mg, 100mg–200mg	3–5 days step up from 50mg 100, 200–300mg	7 days step up from 50mg 100mg–200mg	3days step up from 50mg, 100mg–200mg
Max ALT/AST on second exposure (U/l)	21/16	18/8	15/7	47/22
γGTP(IU/l)/ALP (U/l)	70/251	30/567	69/386	22/91
Total bilirubin (mg/dl)	0.67	0.3	0.3	0.52
Plasma trough concentration after successful rechallenge(μg/ml)	2.09	2.95	2.80	3.48

[a] Chronic pulmonary aspergillosis.
[b] R quotient [7]= (ALT/ULN)/(ALP/ULN); ULN = upper limit of normal) defines whether the pattern of the injury is hepatocellular (R ≥ 5), cholestatic (R ≤ 2), or mixed (2 < R < 5). Calculated from the following value. AST ULN 30 U/l, ALT ULN 42 U/l, ALP ULN 322 U/l, gamma GTP ULN 64 IU/L, Total bilirubin ULN 1.50 mg/dl.
[c] Severity of DILI was determined according to the EASL Clinical Practice Guidelines: Drug-induced liver injury [3].

underlying liver disease of HBV infection, although HBV DNA was not detectable. The serum trough concentration of voriconazole was within the range of 1.5–5.5 mg/l in all patients, when they first experienced liver injury. The grade of liver injury was grade 2 and 3. Rechallenge was started after all data of liver injury returned to normal levels. All patients received ursodeoxycholic acid at doses of 300–600mg/day on rechallenge. Other drugs were not changed for all patients. Regarding clinical symptoms and laboratory data, one patient had elevated eosinophils at the time of liver injury. Same patients experienced rash, but other patients were asymptomatic (no fever, no appetite loss). Rechallenge of voriconazole was attempted from a dose of 50 mg/day and doses were increased every 3–7 days for all patients except “patient 3”. After she failed in the first rechallenge of a full dose, second rechallenge was attempted from a dose of 50 mg/day. Patient 1 had lower dosage of voriconazole at the time of rechallenge, however other three patients were tolerated with same or higher amount of voriconazole on rechallenge. All patients attempted of rechallenge from a small dose succeeded in the re-administration of voriconazole.

4. Discussion

This result is promising to chronic pulmonary aspergillosis patients suffering from liver toxicity of voriconazole despite drug concentrations in the therapeutic range/window.

Although rechallenge of voriconazole does involve the risk, the compelling rationale for doing so exists because aspergillosis is a fatal disease, and we have only a few agents for the treatment of aspergillosis. However, there are some limitations. First, this is a retrospective study with only four patients, and patients with severe liver injury are not included. Second, we are unable to identify the cause for the success of rechallenge.

There is an article reporting successful intravenous administration of voriconazole after the failure of oral administration [6]. They hypothesize high concentration in the portal blood may cause liver enzyme abnormality. However, in our study, final trough concentration of voriconazole was higher in 3 patients, so, drug concentration per se does not explain why the drug was tolerated on rechallenge. Starting from a small dose may have changed immune response to the drug, or ursodeoxycholic acid may have played some role. We need further accumulation of data to specify the reason.

In conclusion, rechallenge of voriconazole can be one of the options after voriconazole-induced moderate liver toxicity.

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Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101191.

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