JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2022; 6: 325-334
https://doi.org/10.30621/jbachs.1051669
REVIEW

VORICONAZOLE-INDUCED HEPATOTOXICITY CONCISE UP-TO-DATE REVİEW

Ozge Ertem[1], Mukaddes Gumustekin[2]

[1] University of Health Sciences, Izmir Bozyaka Education and Research Hospital, Izmir, Turkey
[2] Dokuz Eylul University, Faculty of Medicine, Department of Medical Pharmacology, Izmir, Turkey.

Address for Correspondence: Mukaddes Gumustekin, **E-mail:** gumustekinm@gmail.com
Received: 31.12.2021; **Accepted:** 09.01.2022; **Available Online Date:** 27.01.2022

Cite this article as: Ertem O, Gumustekin M. Voriconazole-Induced Hepatotoxicity Concise up-to-date review. J Basic Clin Health Sci 2022; 6: 325-334.

ABSTRACT

Voriconazole is a wide spectrum antifungal used primarily for invasive aspergillosis, an invasive mold infection occurs mostly in immunocompromised patients. Hepatotoxicity is the most common voriconazole-related adverse reaction that leads to treatment discontinuation. Even though reported incidence of hepatic adverse reactions during phase 2 and 3 clinical trials were less than 10%, observational studies in post marketing phase revealed much higher incidence reaching up to 69%. Therefore, the burden caused by hepatotoxicity and interruption of antifungal therapy put immunocompromised patients at serious risk.

Currently, there is no biomarker in routine clinical use that can clearly predict susceptibility to voriconazole-induced hepatotoxicity. In effort to identify a predictor, plasma concentrations of voriconazole and cytochrome (CYP) 2C19 genotype/phenotype, which is responsible from substantial inter-individual changes in voriconazole pharmacokinetics, are the most studied subjects. Hepatotoxicity tends to occur at higher concentrations (>4 mg/L), but so far, no significant association has identified in this matter. Although CYP2C19 genotype is strongly associated with voriconazole plasma concentration, current data is insufficient to define a causal relationship between CYP2C19 genotype and voriconazole-induced hepatotoxicity.

This article reviews the epidemiology, mechanism, laboratory features of voriconazole-induced hepatotoxicity and current literature investigating the influence of voriconazole plasma concentration and CYP2C19 genetics on voriconazole-induced hepatotoxicity.

Keywords: Voriconazole, Hepatotoxicity, Drug induced liver injury, plasma voriconazole concentration, CYP2C19 genotype

INTRODUCTION

Drug-induced liver injury (DILI) is a term to describe the damage to hepatocytes or other liver cells caused by medications or any other xenobiotics (1). Estimated annual incidence of DILI caused by prescription medications varies between 0.015% to 0.01% (2). But it is difficult to determine real incidence due to differences in patient-care systems, pharmacovigilance reporting and hepatotoxicity definitions across countries and regions.

DILI is the leading cause of hepatic failure in the United States (2). Post marketing hepatic safety concerns are the leading reason of market withdrawal of licensed medications. However, only 0.1% of the DILI cases caused by licensed medication leads to death or liver failure requiring transplantation.

Considering that new compounds are tested in limited population (roughly 1000 to 3000 people) prior to drug approval, it is quite difficult to fully establish liver safety of a new drug in pre-marketing phase. Complete determination of the hepatotoxicity profile of a given drug requires long term pharmacovigilance data of hundreds of thousands of exposures (1). Therefore, a guidance document intended to assist the pharmaceutical industry and investigators in assessing the potential severe liver injury, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, is released in 2009 by Food and Drug Administration (FDA) (3).

Etiology of DILI varies substantially by cultures, socioeconomic status and health-care systems across countries. Paracetamol is the most common cause of DILI in the United States, whereas anti-tuberculosis medications are the leading cause in China and India (4–6). In Asia, traditional remedies and herbal medicines are held responsible for great majority of DILI cases by being the most common cause in South Korea and the second most common cause in China. (5,7). In European countries such as France, Switzerland, Spain and Iceland, antibiotics are the most common drug class causing DILI with amoxicillin–clavulanate being the most common single agent (1). On the other hand, Antifungals are responsible of 3% of DILI cases (8).

Pharmacology of Voriconazole

Voriconazole is a wide-spectrum second generation antifungal agent licensed in 2002. It inhibits fungal cytochrome P450-dependent, 14-alpha-sterol demethylase-mediated synthesis of ergosterol. This inhibition results in generation and accumulation of toxic methyl sterols within fungal cell and eventually hinders DNA replication and cell proliferation (9,10).

Voriconazole is fungistatic against yeast and fungicidal against mold. It has antifungal activity against Candida *species (spp.)* (including fluconazole-resistant *Candida krusei* and *Candida glabrata), Aspergillus spp*. (including amphotericin B- resistant *Aspergillus terraus*), dematiaceous funguses like *Scedosporium* spp. and *Fusarium spp.* and endemic fungi such as *Histoplasma capsulatum* and *Coccoioides immitis* (10).

Following oral intake, voriconazole is absorbed rapidly independent of gastric pH and reaches to maximum plasma concentration within 1 to 2 hours. Its bioavailability is higher than 90% in adults, but high-fat meal reduces it by 22% (9).

The major proportion of voriconazole undergoes hepatic metabolism via cytochrome (CYP) enzymes with only 2% of the dose being excreted unchanged in the urine. The hepatic enzymes that is mainly involved in the metabolism of voriconazole are CYP2C19, and to a lesser extent CYP2C9 and CYP3A4. Its major metabolite, voriconazole-N-oxide, has no antifungal activity. Following glucuronidation via UDP-glucuronosyltransferase (UGT) 1A4, 80% of voriconazole N-oxide and the other hydroxy-voriconazole metabolites are excreted into urine and 20% of them into feces (9,11).

Epidemiology of Voriconazole- Induced Hepatotoxicity

Hepatic adverse reactions are quite often with voriconazole. The reported incidence of hepatic adverse reactions during phase 2 and phase 3 clinical trials were less than 10%, whereas post marketing phase 4 studies and observational clinical trials revealed an increased frequency of voriconazole-induced hepatic injury (12). Current product label includes a warning of liver function tests (LFTs) monitoring and reports that more than 3 fold elevation in liver transaminases is observed 17.7% of the adult and 27.2% of the pediatric patients receiving voriconazole (9,13).

Clinical experience during the post marketing phase have revealed that incidence of hepatotoxicity attributed to voriconazole use could vary greatly (6.3% to 69%) depending on comorbidities of studied population or inconsistencies in hepatotoxicity definition (14,15). The differences between study populations and hepatotoxicity definitions across studies and hepatotoxicity incidences detected according to these criteria are summarized in Table 1.

For instance, Solís-Muñoz *et al*. detected at least one voriconazole-related severe LFT elevation in 69% of the patients who had been treated in Liver Intensive Therapy Unit with a prior end stage liver disease diagnosis. But clinical signs of hepatotoxicity were reported in only 41.4% of the study population (15). In another study conducted in patients with hematologic malignancy, Den Hollander *et al.* reported that voriconazole-related LFT elevation

Table 1. Populations and hepatotoxicity criteria in the studies evaluating safety of voriconazole and hepatotoxicity incidences detected according to these criteria

Reference	Population	Hepatotoxicity criteria	Hepatotoxicity incidence
(15)	29 patients treated in liver intensive therapy unit with a prior end stage liver disease diagnosis Caucasian: 86.2% Black or African-American: 3.5% Asian: 10.3%	**ALT/AST/ALP** >5 x ULN **Bilirubin** >3 x ULN	69%
		Clinical hepatotoxicity	41.4%
(16)	46 patients with hematological malignancy *	**LFT elevation** >3 x ULN	68%
		LFT elevation >5 x ULN	32%
		Clinical hepatotoxicity	6.5%
(17)	71 patients with chronic aspergillosis *	**LFT elevation** *Not specified*	16.9%
		Severe hepatotoxicity *Not specified*	2.8%
(18)	105 lung transplant patients Caucasian: 93% Asian: 1.9% Indian: 2.9% Middle Eastern: 0.9% Aboriginal: 0.9%	**LFT elevation** >ULN - ≤3 x ULN	51%
		Clinical hepatotoxicity necessitating treatment termination	34%
(19)	200 hematopoietic stem cell recipients Asian: 4% Not defined: 96%	**Hepatotoxicity (total)**	34%
		LFT elevation alone If baseline value is normal: > 3x ULN If baseline value is abnormal: >3x Bazal	8.5%
		Clinical hepatotoxicity necessitating treatment termination plus LFT elevation If baseline value is normal: >1.5- 2.9 x ULN If baseline value is abnormal: >1.5- 2.9 x Basal	25.5%
(20)	93 lung transplant patients in perioperative phase Caucasian: 91% Black or African-American: 8% Middle Eastern: 1%	**LFT elevation** *Not specified*	56%
		LFT elevation >5 - ≤20 x ULN	5%
		Clinical hepatotoxicity necessitating treatment termination	11%
(25)	137 immunocompromised patients *	**LFT elevation** ALT/ AST : >5 x ULN Bilirubin/ ALP: >3 x ULN	15%
(13)	1053 patients participated in phase 2 or phase 3 clinical trials in premarketing phase Caucasian: 81.8% Black or African-American: 9.8% Asian and other: 8.5%	**ALT/ AST/ ALP** If baseline values is < 2 x ULN: ≥5 x Basal If baseline values is ≥2 - <5 x ULN: ≥3 x Basal If baseline values is ≥5- <10 x ULN: ≥2 x Basal If baseline values is ≥10 x ULN: ≥1.5x Basal **Bilirubin** ≥3mg/dL	<10%
(33)	108 immunocompromised patients Caucasian: 78.7% Asian:6.5% Black or African-American: 4.6%	**AST/ ALT** > 5 x ULN **ALP/ Bilirubin** >3 x ULN	13.9%
(14)	95 patients receiving voriconazole Caucasian: 59% Latin: 22% Black or African-American: 16% Asian: 3%	**Clinical hepatotoxicity necessitating treatment termination**	6.3%
(46)	86 immunocompromised patients with hematological malignancy Caucasian:100%	**≥ Grade 3 LFT elevation (CTCAE 2.0)**	10-48% (Bilirubin rise 19%, ALP rise 10%, GGT rise 48%, AST rise 17%, ALT rise 22%)
(35)	29 patients with invasive aspergillosis Asian: 100%	**LFT elevation at any grade (CTCAE v3.0)**	34%
(45)	38 patients receiving voriconazole Asian: 100%	**LFT elevation at any grade (CTCAE v4.0)**	26.3%

LFT: Liver function test, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase
ULN: Upper limit of normal, CTCAE: Common Terminology Criteria for Adverse Events
**** Race or ethnicity is not clearly defined.***

fold of ULN were observed in 68% and 32% of the patients, respectively. Even though the incidence of hepatotoxicity defined by biochemical parameters is reported as high as 68%, a smaller proportion, 6.5% , of the study population manifested clinical signs of liver injury (16).

Saito *et al.,* on the other hand, reported voriconazole-associated LFT elevation incidence as 16.9% among chronic aspergillosis patients, with only 2.8% of the study population developing serious hepatic adverse event. But hepatotoxicity criteria were not clearly defined in this study (17).

Fifty one percent of lung transplant patients receiving voriconazole developed hepatotoxicity defined by 3 fold LFT elevation above the ULN (18). In a retrospective study evaluating the data of hematopoietic stem cell recipients receiving voriconazole, Amigues *et al.* reported that 34% of the patients developed either clinical manifestations or biochemical signs of hepatotoxicity defined by LFT elevation. In this study, the investigators pointed out that 32% of the patients who developed hepatotoxicity contemporaneously had a primary disease-related diagnosis (such as graft versus host disease and veno-oclusive disease) that might be associated with LFT elevation, but the contribution of voriconazole could not be excluded (19).

High frequency of voriconazole-related hepatic adverse events are seriously troublesome considering the fact that this drug is mainly used in immunocompromised patients who are already in critical condition and receiving polypharmacy (1). Furthermore, hepatotoxicity is the most common adverse reaction requiring voriconazole treatment termination (9).

While voriconazole-induced hepatic adverse events lead to voriconazole discontinuation in only 2.8% of immunocompetent patients with chronic aspergillosis, this rate is much more higher in immunocompromised patients with multidrug use (17). Mitsani *et al*. reported a treatment discontinuation rate of 11% among lung transplant patient in perioperative phase due to suspected voriconazole-induced hepatotoxicity, whereas Luong *et al*. reported this incidence as 34% among similar population who had been receiving the treatment for the indication. It is noticeable that therapeutic drug monitoring of voriconazole was part of routine clinical care and in the first study, whereas it was not the case in the latter where decision making was solely based on adverse drug reaction monitoring (18,20).

Mechanism of Voriconazole- Induced Hepatotoxicity

Mechanism behind voriconazole-related liver injury remains elusive. Metabolomics findings in both preclinical and clinical studies indicate oxidative stress driven cellular dysfunction in liver (21,22). In an *in vitro* study, targeted metabolomics analysis of human plasma samples revealed that glutamine to glutamate ratio was significantly lower and β-N-acetyl glucosamine level was significantly higher in voriconazole- induced hepatotoxicity group compared to control group. This finding was interpreted as oxidative stress being the major driver in voriconazole-induced liver injury by the investigators (22). Interestingly, an *in vitro* study evaluating the cytotoxic effects of antifungal agents on the human hepatocellular carcinoma cell line HepG2/ C3A, demonstrated that toxic potential of voriconazole on hepatocytes was not dose-dependent (23).

Laboratory features of voriconazole- induced hepatotoxicity

Hepatotoxicity potentials are comparable between intravenous and per oral application of voriconazole (16). A self-limiting transaminase elevation usually occurs within the first month of the treatment. Clinical patterns of voriconazole-induced liver injury can be cholestatic, hepatocellular or a mixture of these two patterns. In majority of the cases, elevated LFT usually recovers upon stopping therapy (24).

Solís-Muñoz P *et al*. reported different clinical patterns of hepatotoxicity in 20 patients who developed LFT elevation out of 29 patients, with 35% being elevated transaminases, 15% being cholestatic pattern and 45% being combination of both. A late rise in transaminases following dissociated cholestasis was reported in majority of the patients with mixed pattern of hepatotoxicity, except one patient with isolated conjugated hyperbilirubinemia manifested by >10 fold elevation of ULN. In this study, median time to reach a peak following the start of voriconazole therapy was reported as 5 days for bilirubin and alkaline phosphatase (ALP), and 7 days for aspartate aminotransferase (AST). These parameters reported to be normalized at a median of

8 days following termination of voriconazole therapy (15). In a study conducted by Den Hollander *et al*. on 46 patients with hematological malignancy, median time to reach peak was reported as 4 days for bilirubin, 6 days for AST, 7 days for alanine aminotransferase (ALT) and 9 days for ALP. It was indicated that 82% of bilirubin, 54% of AST and 33% of ALT and ALP elevations decreased to baseline values within the follow-up period of the study (4 weeks) among the patients who continued to voriconazole treatment (16).

Denning *et al*. reported that the majority of liver function test abnormalities started within the first 10 days of treatment and ALP was the most commonly elevated parameter, while elevation in transaminases and/or hyperbilirubinemia was also detected (25). In a retrospective study conducted by Amigues *et al*., the median time to hepatotoxicity was reported as 26 days (minimum 0, maximum 341 days). This study also demonstrated that AST, ALT and ALP values were not different than the baseline after 2 to 4 weeks following voriconazole discontinuation, but elevated bilirubin levels persisted. As this study evaluated the laboratory findings for only 2-4 weeks upon treatment termination, the duration or continuation of hyperbilirubinemia was not clearly defined (19).

Luong *et al.* reported that the median time to hepatotoxicity was 14 days (minimum 7, maximum 84 days) in lung transplant patients receiving voriconazole, with 87% of the cases being developed within first 30 days of the treatment. It was also indicated that 94% of the patients who discontinued voriconazole due to hepatotoxicity had >10% improvement in LFT abnormalities within 1 month following treatment termination (18). Zonios *et al.* reported that LFT abnormalities requiring treatment discontinuation commonly developed starting from the first week (between the days 2 and 15) of voriconazole therapy and ALT reached its peak value after 4 days of the first detected rise and recovered rapidly to normal value after drug discontinuation (14). ALP levels of the patient who developed severe hepatotoxicity improved within one week of termination of therapy, but returned to baseline value approximately 7 weeks later in Mitsani *et al*.' s study (20).

Influence of voriconazole plasma concentration on hepatotoxicity

Voriconazole has a narrow therapeutic range. Owing to nonlinearity of its pharmacokinetic, 1.7 fold increase (from 3 to 5 mg/kg twice daily) in intravenous dose, leads to 2.4 increase (from 3 to 7.2 mg/L) in maximum plasma concentration and 3.1 fold increase (from 13.9 to 43.4 mg.h/L) in area under the curve on steady state (AUC_T). Similarly, 2 fold increase (from 200 to 400 mg twice daily) in oral dose leads to 2.8 fold increase (from 1.9 to 5.3 mg/L) in maximum plasma concentration and 3.9 fold increase (from 9.8 to 37.5 mg.h/L) in AUC_T (26). Thus, therapeutic drug monitoring is recommended in voriconazole therapy (27).

Even though the data regarding optimal trough plasma concentration for effective treatment and prophylaxis of invasive fungal infections are mainly obtained from retrospective studies, the guidelines recommends that the trough plasma concentration should be maintained within the range of 1-5.5 mg/L (27–29). However, in patients with severe infections (such as multifocal or disseminated disease and infection of central nervous system), a concentration of 2-6 mg/L is recommended (27). Subtherapeutic concentrations cause decreased efficacy, while supratherapeutic concentrations predispose to voriconazole-related adverse drug reactions such as neurotoxicity (27).

The association between voriconazole-related hepatotoxicity and the plasma trough drug concentration is elusive. Tan *et al.* retrospectively had evaluated the safety data from phase 2/3 clinical trials of voriconazole (10 studies in total) and reported that plasma trough voriconazole concentrations were associated with AST, ALP and bilirubin elevations but not with ALT rise. Individual measurements of plasma voriconazole concentrations at any cut off value were not good predictor for liver function test abnormalities (13). Yuan *et al*. reported that voriconazole peak plasma concentration measured 2 hours after voriconazole administration was significantly associated with AST elevation, but this association was not observed between plasma trough concentrations and AST elevation. There was no clear association between ALT levels and peak or trough concentrations (30).

A study conducted on hematopoietic stem cell recipients by Trifilio *et al*. revealed that plasma trough voriconazole concentrations have a moderate positive correlation with AST levels, and a weak but still statistically significant positive correlation with ALP levels. No statistically significant correlation was reported between bilirubin or ALT levels and trough plasma voriconazole concentrations (31). On the

other hand, Mitsani *et al*.' s study indicated that trough voriconazole concentrations correlated with AST values, but not with ALT, alkaline phosphatase, or total bilirubin values (20).

Pascaul *et. al*. reported an increase in frequency of voriconazole-related severe adverse reactions, mainly neurotoxicity, in patients with a trough concentration of >5.5 mg/L compared to the ones with ≤5.5 mg/L. But no significant difference was found in terms of severe hepatotoxicity frequencies between the two groups (32). Chu el at. reported that having a plasma voriconazole concentration greater than 5.5 mg/L at any time of the treatment did not increase either the frequency of adverse reactions in general or hepatotoxicity (33).

In contrary to the studies where no clear association was seen between voriconazole concentration and hepatotoxicity, meta-analysis of 21 studies conducted by Jin *et al.* reported an association between the plasma voriconazole concentrations higher than 3.0 mg/L and hepatotoxicity in Asian population. As this concentration is within the therapeutic range (1.0-5.5 mg/L), this finding has raised concern about safety of guideline recommended target concentrations for Asian population (34).

Matsumoto *et al* reported that estimated probability of hepatotoxicity at voriconazole trough concentrations of 2 mg/L was 1.6%, whereas this probability disproportionally increased to 21.6% at trough concentration of 4mg/L (35). Similarly, Wang *et al* estimated frequency of severe hepatotoxicity as 12.3% and 35% at a trough voriconazole concentration of 1.5-4 mg/L and >4.0 mg/L, respectively (36). Furthermore, Denning *et al*. observed that 30% of the patients who developed LFT abnormalities had a plasma trough voriconazole concentration of >6 mg/L (25).

Even though a consistent clear association could not be established, hepatotoxicity tends to occur at higher trough voriconazole concentrations. Thus, for a safer treatment, maintaining a trough concentration of <4 mg/L with therapeutic drug monitoring and dose reduction, if necessary, is recommended for the patients with LFT abnormalities (37,38).

Influence of Common CYP2C19 Polymorphisms on Hepatotoxicity

CYP2C19, the gene that encodes the hepatic enzyme that is mainly responsible from voriconazole metabolism is highly polymorphic (11). The most frequent genetic variations are on *2, *3 and *17 alleles. Allele *2 and *3 are nonfunctional, whereas allele *17 is associated with an increased function. Including these, so far 38 variant alleles with known or unknown function have been defined (39). Distribution of these alleles varies across races and ethnicities. As phenotypic reflection of these variations, substantial inter-individual differences in CYP2C19 activity have been described (11,27,40). Carriers of two functionally deficient *CYP2C19* alleles (e.g. *2/*2, *2/*3, *3/*3) are classified as poor metabolizers. The frequency of CYP2C19 poor metabolizers among the population is reported to be 1.5-13%. Individuals carrying two sets of increased CYP2C19 function alleles (*17/*17) are categorized as ultra-rapid metabolizers, with an estimated frequency of 0.7-4.7% among world population. It is also known that only 29.6- 62.8% of world population are normal metabolizers homozygous for the wild type allele (*1/*1) (39). Racial distribution of CYP2C19 phenotype is summarized in Table 2.

Majority (approximately 50%) of inter-individual pharmacokinetic differences creating susceptibility to toxicity or treatment inefficacy stem from *CYP2C19* polymorphisms (11). Ultra-rapid metabolizers cannot reach the steady state concentration until day 18-25 (28). Hamadeh *et al*. observed that ultra-rapid metabolizers carrying *17 allele have significantly lower voriconazole concentration at steady state compared to other phenotypes and have 5.6 fold increased risk of remaining in subtherapeutic zone (41). This situation poses a serious problem in terms of providing desired treatment efficacy.

On the other side of the spectrum, poor metabolizers have approximately 6 times slower voriconazole clearance than ultra-rapid metabolizers. According to pharmacokinetic studies, exposure to voriconazole is 3 times greater in poor metabolizers compared to normal metabolizers (6). Thus, when given the standard doses, poor metabolizers have significantly higher risk of having supratherapeutic voriconazole concentration rendering them being at higher risk of concentration-related adverse drug reactions (39). *CYP2C19* genotype is strongly associated with voriconazole plasma concentration and existing body of evidence regarding the association between voriconazole concentration and hepatotoxicity is controversial. Although with some limitations, there are studies evaluating the association between *CYP2C19* genotype and hepatotoxicity.

Matsumoto *et al.* could not detect a significant relationship between *CYP2C19* genotype and

hepatotoxicity, even though they estimated an increased risk of hepatotoxicity at higher drug concentration. The authors discussed that sample size being limited to 29 patients might have prevented reaching a statistically significance. Furthermore, the maintenance doses for wild-type patients were unintentionally greater than those for non-wild-type patients in this study (35). In another study conducted with a larger sample size of 86 patients, Levin *et al.* also reported that there was no significant relationship between *CYP2C19* polymorphism and voriconazole-induced hepatotoxicity monitored by ALP, gamma glutamyl transferase (GGT), AST and ALT elevation (42). Similarly, Berge *et al.* observed the influence of *CYP2C19* genotype on voriconazole-induced adverse drug reactions and maintenance dose in lung transplant patients and reported no significant relationship between *CYP2C19* genotype and adverse drug reactions in general. Due to the limited sample size of 24 patient (7 patients with *1/*1, 10 patients with *1/*2, 6 patients *1/17 and 1 patient with 17/*17 genotype) no evaluation was made for each specific adverse reaction and the authors discussed that routinely applied therapeutic drug monitoring to all patients and not having any poor metabolizer in study population might have blunted the inter-individual variability related to genetic factors (43).

In a study of 19 patients including normal, intermediate and rapid metabolizers, Trubiano *et al*. demonstrated that 60% of the patients who experienced photopsia or hepatotoxicity were intermediate metabolizer. Due to the limited sample size, no statistical analysis was conducted in this study (44). In a case control-study of 38 patients evaluating the association between *CYP2C19* polymorphisms and voriconazole-related hepatotoxicity, Song *et al.* observed that frequency of *CYP2C19*3* allele was not significantly different between the hepatotoxicity group and the control group. The authors concluded that there was no clear association between CYP2C19 phenotype and risk for hepatotoxicity. The hepatotoxicity group consisted of 10 patients with 50% of them having *1/*2, 30% of them having *1/*3 and %20 of them having *1/*1 genotype (45).

CONCLUSION

Hepatotoxicity is the most common adverse reaction that necessitates voriconazole discontinuation. Both the burden caused by hepatotoxicity itself and interruption of antifungal therapy poses a serious problem for immunocompromised patients who already are in critical condition.

Although the mechanism behind voriconazole-induced hepatotoxicity is not well defined, *in vitro* studies suggests that oxidative stress driven cellular dysfunction is the main problem. Voriconazole-induced hepatotoxicity usually occurs within the first month of therapy and clinical pattern of hepatic injury can be both cholestatic and/or hepatocellular. On the other hand, route of administration does not seem to affect the risk.

So far, no specific biomarker is defined to predict hepatotoxicity in routine clinical use. Limited number of studies report an association between higher plasma voriconazole concentrations and hepatic adverse events and some of them demonstrates a correlation between high drug concentrations and serum ALP, AST or bilirubin levels. But there is no consensus on a specific danger zone value to predict hepatotoxicity. Even the majority of the studies cannot identify a significant association, hepatotoxicity tends to occur at higher trough voriconazole concentrations. Thus, for a safer treatment, maintaining a trough concentration of <4

Table 2. Racial distribution of CYP2C19 phenotype**

CYP2C19 Phenotype	Caucasian	Black or African-American	Asian
Poor Metabolizer	1.5- 2.4%	4.1- 6.3%	1.9- 13.0%
Intermediate Metabolizer	21.4- 26.0%	31.4- 36.2%	40.8- 45.9%
Normal Metabolizer	39.6- 62.8%	30.1- 32.8%	29.6- 38.1%
Rapid Metabolizer	13.6- 27.2%	19.0- 23.7%	2.5-18.6%
Ultra- rapid Metabolizer	0.7- 4.7%	3.0- 4.3%	<2.3%

***Racial distributions are obtained from the allele frequency database in https://www.pharmgkb.org* (47).**

Caucasian: Includes American, European and Near Eastern data

Black or African-American: Includes African-American, African-Caribbean and Sub-Saharan African data

Asian: Includes Middle/South and East Asia data.

mg/L with therapeutic drug monitoring is recommended by the authors. Clinicians should be cautious against hepatotoxicity even at therapeutic concentrations.

On the other hand, *CYP2C19* genotype and phenotype has gross impact on voriconazole pharmacokinetics and plasma trough concentrations of the drug. But current body of knowledge is not sufficient to clearly define an association between *CYP2C19* genotype and voriconazole-induced hepatotoxicity. Studies regarding this subject usually have great limitations. Further studies with much larger sample sizes and with standardized definitions of hepatotoxicity are required to clearly deny or demonstrate the causality.

Author contributions: OE and MG made significant contributions to the main concept and design of the work. All authors contributed to the drafting and critical revision of the paper. All authors reviewed the draft and approved the final version of the manuscript.
Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this article.
Peer-review: Externally peer reviewed.

REFERENCES

1. Andrade RJ, Chalasani N, Björnsson ES, et al. Drug-induced liver injury. Nat Rev Dis Prim 2019;5(1):1–22.
2. Larson A, Lindor K, Robson K. Drug-induced liver injury. UptoDate 2020 [Retrieved: 2020 Oct 15]. Available from: https://www.uptodate.com/contents/drug-induced-liver-injury
3. FDA. Center for Drug Evaluation and Research Center for Biologics Evaluation and Research. Drug-Induced Liver Injury: Premarketing Clinical Evaluation; 2009. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.
4. Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-Center Experience With Drug-Induced Liver Injury From India: Causes, Outcome, Prognosis, and Predictors of Mortality. Am J Gastroenterol 2010;105(11):2396–404.
5. Zhou Y, Yang L, Liao Z, He X, Zhou Y, Guo H. Epidemiology of drug-induced liver injury in China: A systematic analysis of the Chinese literature including 21 789 patients. Eur J Gastroenterol Hepatol 2013;25(7):825–9.
6. Reuben A, Tillman H, Fontana RJ, et al. Outcomes in adults with acute liver failure between 1998 and 2013: An observational cohort study. Ann Intern Med 2016;164(11):724–32.
7. Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in korea. Am J Gastroenterol 2012; 107(9): 1380–7.
8. Raschi E, Poluzzi E, Koci A, Caraceni P, De Ponti F. Assessing liver injury associated with antimycotics: Concise literature review and clues from data mining of the FAERS database. World J Hepatol 2014;6(8):601–12.
9. Pfizer. Vfend ® (voriconazole). Highlights of prescribing information. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=618
10. Cecil JA, Wenzel RP. Voriconazole: A broad-spectrum triazole for the treatment of invasive fungal infections. Expert Rev Hematol 2009;2(3): 237-54.
11. Barbarino JM, Owusu Obeng A, Klein TE, Altman RB. PharmGKB summary: voriconazole pathway, pharmacokinetics. Pharmacogenet Genomics 2017; 27(5): 201–9.
12. FDA. VFEND ® I.V. (voriconazole) for Injection VFEND ® Tablets. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021266s032lbl.pdf
13. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. J Clin Pharmacol 2006; 46(2): 235–43.
14. Zonios D, Yamazaki H, Murayama N, et al. Voriconazole Metabolism, Toxicity, and the Effect of Cytochrome P450 2C19 Genotype. J Infect Dis 2014; 209(12): 1941–8.
15. Solís-Muñoz P, López JC, Bernal W, et al. Voriconazole hepatotoxicity in severe liver dysfunction. J Infect 2013;66(1):80–6.
16. Den Hollander JG, Van Arkel C, Rijnders BJ, Lugtenburg PJ, De Marie S, Levin M-D. Incidence of voriconazole hepatotoxicity during intravenous and oral treatment for invasive fungal infections. J Antimicrob Chemother 2006;57:1248–50.
17. Saito T, Fujiuchi S, Tao Y, et al. Efficacy and safety of voriconazole in the treatment of chronic pulmonary aspergillosis: Experience in Japan. Infection 2012;40(6):661–7.

18. Luong M-L, Hosseini-Moghaddam SM, Singer LG, et al. Risk Factors for Voriconazole Hepatotoxicity at 12 Weeks in Lung Transplant Recipients. Am J Transplant 2012;12(7):1929–35.
19. Amigues I, Cohen N, Chung D, et al. Hepatic Safety of Voriconazole after Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2010;16(1):46–52.
20. Mitsani D, Nguyen MH, Shields RK, et al. Prospective, observational study of voriconazole therapeutic drug monitoring among lung transplant recipients receiving prophylaxis: Factors impacting levels of and associations between serum troughs, efficacy, and toxicity. Antimicrob Agents Chemother 2012;56(5): 2371–7.
21. Wu S-L, Wei T-Y, Lin S-W, Su K-Y, Kuo C-H. Metabolomics Investigation of Voriconazole-Induced Hepatotoxicity in Mice. Chem Res Toxicol 2019;32(9):1840-1849
22. Wu SL, Cheng CN, Wang CC, Lin SW, Kuo CH. Metabolomics analysis of plasma reveals voriconazole-induced hepatotoxicity is associated with oxidative stress. Toxicol Appl Pharmacol 2020;403:115157.
23. Doß S, Potschka H, Doß F, Mitzner S, Sauer M. Hepatotoxicity of antimycotics used for invasive fungal infections: In vitro results. BioMed Research International 2017;3:1-10
24. LiverTox: Clinical and Research Information on Drug- Induced Liver Injury: Voriconazole [Updated 2017 May 17]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547891/
25. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002; 34(5):563–71.
26. Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. Antimicrob Agents Chemother 2002;46(8):2546–53.
27. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect 2018;24:e1–38.
28. Teusink A, Vinks A, Zhang K, et al. Genotype-Directed Dosing Leads to Optimized Voriconazole Levels in Pediatric Patients Receiving Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2016;22(3):482–6.
29. Patterson TF, Thompson GR, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63(4):e1–60.
30. Yuan ZQY, Qiao C, Yang ZC, et al. The Impact of Plasma Protein Binding Characteristics and Unbound Concentration of Voriconazole on Its Adverse Drug Reactions. Front Pharmacol. 2020; 1: 505.
31. Trifilio S, Ortiz R, Pennick G, et al. Voriconazole therapeutic drug monitoring in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant 2005;35(5):509–13.
32. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 2008;46(2):201–11.
33. Chu HY, Jain R, Xie H, Pottinger P, Fredricks DN. Voriconazole therapeutic drug monitoring: Retrospective cohort study of the relationship to clinical outcomes and adverse events. BMC Infect Dis 2013;13(1):105.
34. Jin H, Tiansheng Wang, Falcione BA, et al. Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis. J Antimicrob Chemother 2016;71(7):1772–85.
35. Matsumoto K, Ikawa K, Abematsu K, et al. Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes. Int J Antimicrob Agents 2009;34(1):91–4.
36. Wang T, Zhu H, Sun J, et al. Efficacy and safety of voriconazole and CYP2C19 polymorphism for optimised dosage regimens in patients with invasive fungal infections. Int J Antimicrob Agents 2014;44(5):436–42.
37. Hamada Y, Seto Y, Yago K, Kuroyama M. Investigation and threshold of optimum blood concentration of voriconazole: A descriptive statistical meta-analysis. J Infect Chemother 2012;18(4):501–7.

38. Suzuki Y, Tokimatsu I, Sato Y, et al. Association of sustained high plasma trough concentration of voriconazole with the incidence of hepatotoxicity. Clin Chim Acta 2013;424:119–22.
39. Moriyama B, Obeng AO, Barbarino J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP2C19 and Voriconazole Therapy. Clin Pharmacol Ther 2017;102(1):45–51.
40. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/Pharmacodynamic Profile of Voriconazole. Clin Pharmacokinet 2006;45(7):649–63.
41. Hamadeh IS, Klinker KP, Borgert SJ, Richards AI, Li W, Mangal N, et al. Impact of the CYP2C19 genotype on voriconazole exposure in adults with invasive fungal infections. Pharmacogenet Genomics 2017;27(5):190–6.
42. Levin MD, den Hollander JG, van der Holt B, Rijnders BJ, van Vliet M, Sonneveld P, et al. Hepatotoxicity of oral and intravenous voriconazole in relation to cytochrome P450 polymorphisms. J Antimicrob Chemother 2007;60(5):1104–7.
43. Berge M, Guillemain R, Trégouet DA, et al. Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients. Eur J Clin Pharmacol 2011;67(3):253–60.
44. Trubiano JA, Crowe A, Worth LJ, Thursky KA, Slavin MA. Putting CYP2C19 genotyping to the test: utility of pharmacogenomic evaluation in a voriconazole-treated haematology cohort. J Antimicrob Chemother 2015;70(4):1161–5.
45. Song Y, Jia MX, Yang G, et al. Association of CYP2C19 and UGT1A4 polymorphisms with voriconazole-induced liver injury. Per Med 2019;17(1):15–22.
46. Levin MD, den Hollander JG, van der Holt B, et al. Hepatotoxicity of oral and intravenous voriconazole in relation to cytochrome P450 polymorphisms. J Antimicrob Chemother 2007; 60(5): 1104–7.
47. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther 2012; 92(4): 414–7.