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# Hepatic Safety of Voriconazole after Allogeneic Hematopoietic Stem Cell Transplantation

I. Amigues,[1,*] N. Cohen,[3,*] D. Chung,[1] S. K. Seo,[1] C. Plescia,[1] A. Jakubowski,[2] J. Barker,[2] Genovefa A. Papanicolaou[1]

Voriconazole is increasingly used in allogeneic hematopoietic stem cell transplantation (HSCT) for prophylaxis and treatment of fungal infections. Hepatic dysfunction is common in patients undergoing HSCT and may have an impact on the clinical decision to institute voriconazole. We conducted a retrospective review of all adult and pediatric HSCT recipients who received >2 consecutive doses of voriconazole between January 2005 and February 2008. Clinical hepatotoxicity was defined as the subjective attribution of liver enzyme elevation (even a mild one) to hepatotoxicity because of voriconazole by the treating physician and leading to discontinuation of voriconazole. Biochemical hepatotoxicity was defined as an elevation in one or more liver enzymes to >3 times the upper limit of normal or >3 times the baseline value if abnormal at baseline. Liver enzymes assessed included aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin. Simple and multiple logistic regressions were used to define the risks for hepatic dysfunction. The Wilcoxon signed-rank test was used to assess the differences in liver function test values before, during, and after the use of voriconazole. Sixty-eight of 200 patients (34%) developed hepatotoxicity while on voriconazole. The median duration of voriconazole therapy was 72 days (range, 1-804 days). Biochemical hepatotoxicity occurred in 51 patients (75%); clinical hepatotoxicity, in 17 patients (25%). Thirty-five (51%) of the patients with hepatotoxicity required discontinuation of therapy. In simple logistic regression, acute graft-versus-host disease (GVHD) was a risk factor for hepatotoxicity, and receipt of a T-cell depleted allograft was protective. In multiple logistic regression, acute GVHD ($P = .002$) remained significant. There were no cases of liver failure or death attributed to voriconazole. In this cohort of patients undergoing allogeneic HSCT, the rate of hepatotoxicity while on voriconazole was 34%. In general, the hepatic dysfunction was mild and reversible. Voriconazole therapy with monitoring appears to be reasonably safe for use in HSCT recipients at high risk for invasive fungal infections.

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**KEY WORDS:** Voriconazole, Hepatotoxicity, Allogeneic stem cell transplantation, Adverse reaction, Liver function

## INTRODUCTION

Voriconazole is a highly orally bioavailable azole with broad activity against *Candida* and *Aspergillus* [1]. Triazole antifungal agents have been reported to cause both cholestatic and hepatocellular injury [2,3]. Rarely, fulminant hepatitis with hepatic necrosis is reported in patients receiving triazoles. Severe hepatitis can be enhanced on rechallenge and may be fatal [1,4-12]. In clinical trials of voriconazole for the treatment of invasive aspergillosis, a transaminase elevation was observed in up to 19% of patients, with 4% representing a serious hepatic adverse event. In an observational study of patients with hematologic malignancies, up to 69% developed a transaminase elevation; however, only 7% of patients were considered to have clinically significant hepatotoxicity (HT), which necessitated discontinuation of voriconazole [13]. The incidence of liver enzyme elevations and clinically significant HT in recipients of hematopoietic stem cell transplantation (HSCT) treated with voriconazole is not known. Because of its broad antifungal spectrum, relatively low toxicity rate, and convenience of administration, voriconazole is increasingly used for prophylaxis and treatment of invasive fungal infections in HSCT recipients who are already at risk for HT [3,14].

Liver dysfunction in allogeneic HSCT recipients may result from various factors, including toxicity

From the [1]Department of Medicine, Services of Infectious Disease; [2]Bone Marrow Transplantation; and [3]Department of Pharmacy, Memorial Sloan Kettering Cancer Center, New York, New York.
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*These authors contributed equally to this work.
Correspondence and reprint requests: Genovefa A. Papanicolaou, Department of Medicine, Infectious Diseases, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 9, New York, NY 10021 (e-mail: papanicg@mskcc.org).
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from the preparative regimen and other medications, infection, veno-occlusive disease (VOD), and acute and chronic graft-versus-host disease (aGVHD, cGVHD) of the liver. These conditions may increase the risk for HT associated with voriconazole use in HSCT recipients. Over the last 3 years at our institution, voriconazole has been used for prophylaxis and treatment of fungal infections in HSCT. We report our experience on the hepatic safety of voriconazole in this population.

## METHODS

We conducted a retrospective review to determine the frequency of HT in HSCT recipients who received voriconazole and to establish whether any additional transplantation-related factors increased the risk for HT. The study design was approved by the Memorial Sloan-Kettering Cancer Center (MSKCC) Institutional Review Board.

### Study Patients

Adult and pediatric patients who underwent a first allogeneic HSCT at MSKCC between January 2005 and July 2007 were included in the study. Patients who received >2 consecutive doses of voriconazole between January 1, 2005, and February 1, 2008, were identified from pharmacy records. Those with liver enzyme values measured within 2 weeks before and during voriconazole therapy were included in the study.

### Definitions

Biochemical HT (BIO-HT) was defined as elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (Alk Phos), and/or total bilirubin (TBil) to >3 times the upper limit of normal or >3 times baseline if abnormal at baseline, regardless of whether or not the abnormality led to the discontinuation or interruption of voriconazole. Clinical HT (CL-HT) was based on the subjective assessment of the treating physician. CL-HT was defined as mildly elevated liver function test (LFT) values (1.5-2.9 times above the upper limit of normal or above baseline if abnormal) attributed to voriconazole and leading to discontinuation of treatment.

The indication for voriconazole was considered prophylaxis if the drug was initiated before engraftment for the prevention of fungal infections. For this study, all other indications for voriconazole, including secondary prophylaxis while receiving intensive immunosuppression for GVHD and treatment of fungal infection, were defined collectively as "all other indications." These conditions are frequently associated with additional potential reasons for HT. Duration of therapy was defined as the number of days between the first dose and the last dose of voriconazole. If the therapy was interrupted for more than 5 days, resumption of therapy was defined as a second course.

### Standards of Care

Prophylaxis against opportunistic infections was instituted according to the standards of care at MSKCC. To prevent herpes simplex and varicella zoster virus (VZV) reactivation, acyclovir was given from beginning of conditioning until immune reconstitution. Cytomegalovirus (CMV) prophylaxis was not routinely used. Patients at risk for CMV disease were monitored and treated if they showed evidence of CMV reactivation. For *Pneumocystis jiroveci* prophylaxis, trimethoprim/sulfamethoxazole (TMP/SMX) or pentamidine (in cases of sulfa allergy) were given from day -7 to day -3, followed by oral TMP/SMX or inhaled pentamidine from day +30 and continued until immune reconstitution. Penicillin VK or equivalent was used for prophylaxis against invasive disease from *Streptococcus pneumoniae* in patients with cGVHD or splenectomy.

Recipients of conventional grafts received standard prophylaxis for GVHD. All patients on cyclosporine (CsA), tacrolimus, or sirolimus therapy underwent routine therapeutic drug monitoring of the immunosuppressant. An elevated trough level during the administration of voriconazole was defined as > 600 ng/mL for cyclosporine and >15 ng/mL for tacrolimus and sirolimus.

For the prevention of invasive fungal infection, low-risk patients received fluconazole from the day of admission for HSCT until at least day +75 posttransplantation. Patients with any risk factors for invasive mold infection (ie, previous possible, probable, or proven invasive mold infection; GVHD; CMV infection; HLA-mismatched or unrelated donor; previous or current extensive corticosteroid use; or age >50 years) received i.v. voriconazole 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours starting early posttransplantation, followed by oral voriconazole 200 mg every 12 hours until at least day +75 or cessation of intensive immunosuppression. Patients with GVHD or on corticosteroid therapy also received voriconazole until discontinuation of immunosuppression. Patients intolerant to voriconazole received i.v. micafungin. For treatment of mold infections, voriconazole was administered at the same dose as for prophylaxis. There was no routine therapeutic drug monitoring for voriconazole during the study period. Voriconazole levels were checked at the discretion of the treating physician.

### Data Abstraction and Assessment of Hepatic Safety

Patients who received >2 consecutive doses of voriconazole were evaluated for HT. Patient demographics, primary underlying disease, indication for

voriconazole, previous concomitant medications, concurrent medical events, and LFT results were obtained from the electronic medical records. All LFT values measured from 2 weeks before the start of voriconazole therapy, during therapy, and for 2-4 weeks after the end of therapy were recorded. The maximum value for each of the 3 time periods was recorded. Concomitant medications were defined as any drugs taken while on voriconazole therapy. The timing and reasons for discontinuation of voriconazole, as documented in the medical record, were recorded.

### Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and safety outcomes. Simple logistic regression was used for univariate analysis of age, sex, duration of voriconazole therapy (> 30 days or <30 days), underlying disease (leukemia, myelodysplastic syndrome [MDS], non-Hodgkin or Hodgkin lymphoma [NHL, HL], nonmalignant, or other), donor type (matched related, matched unrelated, mismatched related, or mismatched unrelated), stem cell source (peripheral blood [PBSC], bone marrow [BM], or cord blood [CB]), graft manipulation (T-cell depletion or unmodified), conditioning intensity (myeloablative [MA] or nonmyeloablative [NMA]), conditioning regimen (total body irradiation [TBI]–containing, busulfan [Bu]-containing, or other), aGVHD (grade 0-I or grade II-IV), and indication for voriconazole (prophylaxis or all other indications). Fisher's exact test was used to determine the significance of the association between elevated levels of voriconazole or immunosuppressants (CsA, tacrolimus, and sirolimus) and HT. The Wilcoxon signed-rank test was used to assess the difference between maximum LFT values at baseline, during treatment, and posttreatment. A $P$ value $\leq .05$ was considered significant. All analyses were performed using Stata version 8 (StataCorp, College Station, TX).

## RESULTS

### Hepatotoxicity Rate

A total of 334 adult and pediatric patients underwent allogeneic HSCT at MSKCC during the study period. A total of 200 patients who received >2 consecutive doses of voriconazole and had liver enzyme monitoring before and during therapy were included in the study. Of these 200 patients, 117 (58.5%) received voriconazole for posttransplantation prophylaxis and 83 (41.5%) received voriconazole for all other indications. The median overall duration of voriconazole therapy was 72 days (range, 1-804 days). The median duration was 63 days (range, 3-530 days) in patients with HT and 77 days (range, 1-804 days) in those without HT.

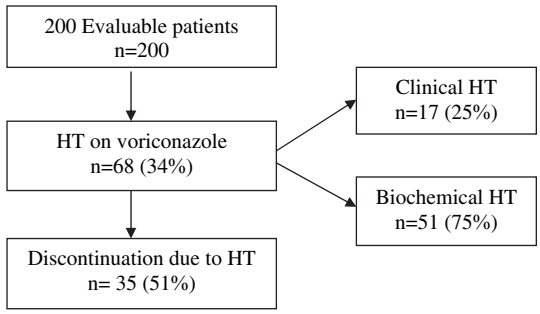


**Figure 1.** Rates of CL-HT and BIO-HT in 200 patients who received voriconazole. Values in parentheses represent the percentages of total.

Overall 68 patients (34%) developed HT while on voriconazole therapy. HT developed after a median of 26 days (range, 0-341 days). Fifty-one patients (75%) met the criteria for BIO-HT. The remaining 17 patients (25%) had CL-HT. Figure 1 shows the rates of HT for the study patients. Voriconazole therapy was discontinued in 35 patients (51%) with HT. Six patients were rechallenged with a second course of voriconazole. Two of these 6 patients discontinued the second course due to recurrent HT. The second course of treatment was not included in any of the subsequent analyses.

In 22 of the 68 patients who developed HT (32%), HT occurred contemporaneously with major diagnoses associated with HT, including GVHD of the liver or gut (n = 11), VOD of the liver (n = 3), sepsis with multisystem organ failure (n = 4), acute infectious hepatitis (n = 1), major bleeding leading to TBil elevation (n = 1), and cholecystitis (n = 2). Although we cannot exclude the contribution of voriconazole to the HT, the presentation and temporal association of HT in these patients was more consistent with alternative causes.

### Assessment of Hepatic Dysfunction

In the patients who experienced BIO-HT, we compared the maximum values of liver enzymes at baseline, during treatment, and after discontinuation of voriconazole to assess the magnitude and reversibility of HT. Figure 2 shows boxplots of LFT values for these 3 time points. For the majority of patients, the maximum elevations in AST, ALT, TBil, and Alk Phos were moderate during treatment. Posttreatment values of AST, ALT, and Alk Phos were significantly lower than the values during treatment and were similar to baseline values. Posttreatment TBil was similar to that during treatment and significantly higher than baseline ($P = .02$). Ten patients had elevated TBil and underwent follow-up monitoring after discontinuation of voriconazole. In 6 of these 10 patients (60%), HT was attributable to other causes; in the other 4 patients, TBil value returned to normal.

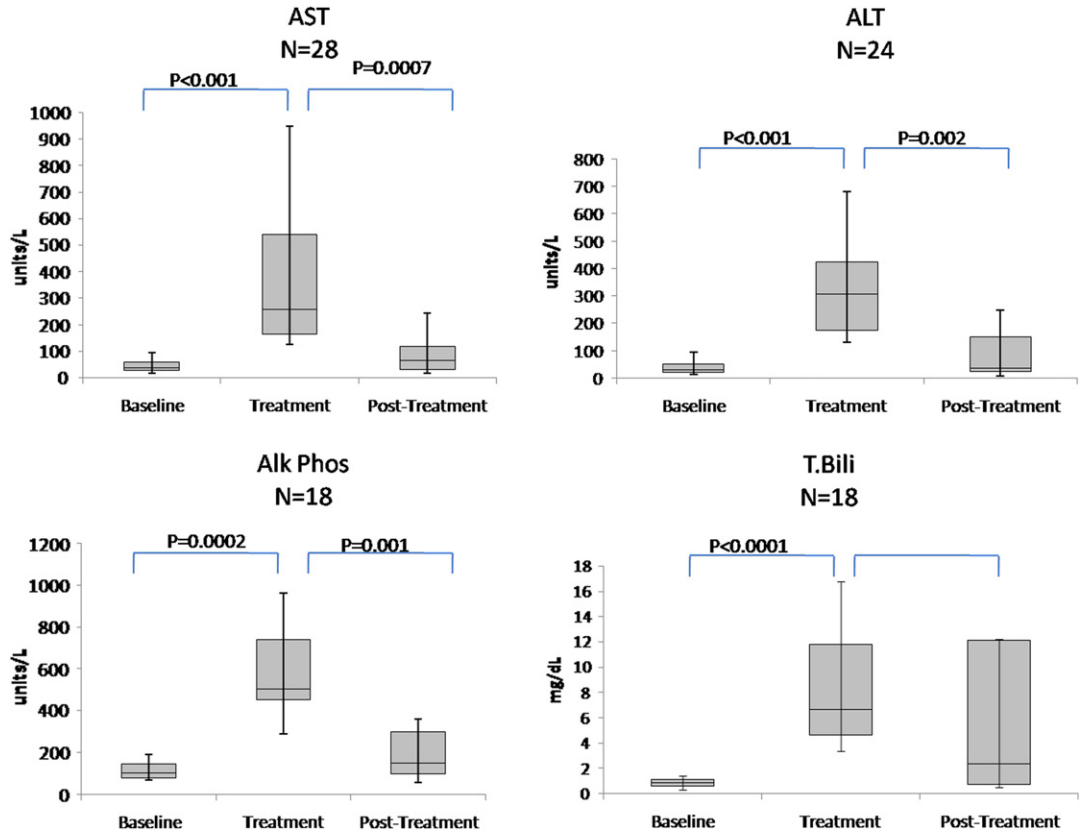


**Figure 2.** Changes in LFT values during and after voriconazole treatment in patients with HT. Twenty-four patients met the criteria for BIO-HT based on ALT, 28 did so based on AST, 18 did so based on Alk Phos, and 20 did so based on TBil. Boxplots were created to illustrate the difference in maximum values for ALT, AST, Alk Phos, and TBil at baseline, during treatment, and posttreatment in patients with BIO-HT. Shaded regions represent the interquartile range (IQR). Capped whiskers represent the upper and lower adjacent values (the highest value within 1.5 times the IQR of the upper or lower bound of the IQR). Outliers are excluded. To assess hepatic dysfunction during voriconazole treatment, we compared LFT values at baseline with those during treatment. The values during treatment were significantly higher than baseline values for all LFTs examined. To assess the reversibility of hepatic dysfunction, we compared the values at the end of treatment with those posttreatment. Posttreatment ALT, AST, and Alk Phos values were significantly lower than during treatment and not different from baseline. The posttreatment TBil value was significantly higher than baseline.

Fifteen patients died before or during week 2 after the discontinuation of voriconazole and did not have posttreatment LFTs. Voriconazole HT was not considered to contribute to death in any of these 15 patients. Causes of death included septic shock with multisystem organ failure (n = 7), relapsed underlying malignancy (n=4), alveolar hemorrhage (n = 2), and VOD (n = 2).

## Risk Factors for Hepatotoxicity

Table 1 compares the characteristics of the 68 patients who developed HT and the 132 patients who did not. We conducted simple logistic regression to identify risk factors for HT. All of the variables listed in Table 1 were included in the analysis as putative risk factors for HT. Table 2 gives significant variables. Acute GVHD was a risk factor for HT (odds ratio [OR]=2.98; 95% confidence interval [CI] = 1.52-5.85; $P$ = .001). This was supported by an association between the receipt of a T-cell depleted graft and less HT (OR = 0.51; 95% CI = 0.28-0.93; $P$ = .027). In multivariate analyses, HT was associated with aGVHD grade II-IV (OR = 3.17; 95% CI = 1.50-6.68; $P$ = .002).

## Concomitant Medications

The majority of patients received multiple medications known to cause HT alone or synergistically with voriconazole. The most commonly used concomitant medications with a potential for HT are listed in Table 3. Overall, there was no substantial difference in the utilization of each major category of concomitant medications between the patients who developed HT while on voriconazole and those who did not. Ten patients (15%) with HT had received concomitant agents that were temporally related and likely contributed to HT, including antifungal agents (n = 5), oral contraceptives (n = 3), deferasirox (n = 1), and anabolic steroids (n = 1).

During the study period, voriconazole levels were monitored at the discretion of the clinician. Steady-state trough levels of voriconazole were checked in 36 patients who developed HT and in 29 patients who did not develop HT. Three patients (8.3%) with

**Table 1. Characteristics of Patients with and without HT Receiving Voriconazole**

| Characteristic | HT (n = 68) | No HT (n = 132) |
|---|---|---|
| Age, years | | |
| Median, years | 41.5 | 47.6 |
| Age <12 years (n = 19), n (%) | 7 (10.3) | 12 (9.1) |
| Age >12 years (n = 181), n (%) | 61 (89.7) | 120 (90.9) |
| Sex, n (%) | | |
| Male | 43 (63.2) | 76 (57.6) |
| Female | 25 (36.8) | 56 (42.4) |
| Voriconazole exposure, n (%) | | |
| 30 days or less | 25 (36.8) | 40 (30.3) |
| More than 30 days | 43 (63.2) | 92 (69.7) |
| Underlying disease, n (%) | | |
| Leukemia | 33 (48.5) | 67 (50.8) |
| Myelodysplastic syndrome | 11 (16.2) | 23 (17.4) |
| Non-Hodgkin lymphoma | 16 (23.5) | 21 (15.9) |
| Hodgkin lymphoma | 4 (5.8) | 7 (5.3) |
| Nonmalignant | 2 (2.9) | 7 (5.3) |
| Other | 2 (2.9) | 7 (5.3) |
| Donor type, n (%) | | |
| Matched-related | 18 (26.5) | 43 (32.6) |
| Matched-unrelated | 21 (30.9) | 42 (31.8) |
| Mismatched-related | 2 (2.9) | 4 (3.0) |
| Mismatched-unrelated | 27 (39.7) | 43 (32.6) |
| Stem cell source, n (%) | | |
| Peripheral blood | 50 (73.5) | 105 (79.6) |
| Bone marrow | 4 (5.9) | 14 (10.6) |
| Cord blood | 14 (20.6) | 13 (9.9) |
| Graft manipulation, n (%) | | |
| Unmodified | 38 (55.9) | 52 (39.4) |
| T-cell depleted | 30 (44.1) | 80 (60.6) |
| Conditioning intensity, n (%) | | |
| Nonablative | 21 (30.9) | 28 (21.2) |
| Ablative | 47 (69.1) | 104 (78.8) |
| Conditioning regimen, n (%) | | |
| Busulfan-containing | 17 (25.0) | 51 (38.6) |
| Total body irradiation–containing | 38 (55.9) | 65 (49.2) |
| Other non–total body irradiation | 13 (19.1) | 16 (12.1) |
| Acute GVHD, n (%) | | |
| Grade 0-I | 37 (59.7) | 106 (81.5) |
| Grade II-IV | 25 (40.3) | 24 (18.5) |
| Not evaluable (n=8) | | |
| Indication for voriconazole, n (%) | | |
| Prophylaxis | 41 (60.3) | 76 (57.6) |
| All other indications | 27 (39.7) | 56 (42.4) |

HT indicates hepatotoxity; GVHD, graft-versus-host disease.

HT and 4 patients (13.8%) without HT had at least one trough level >6 mg/L ($P$ = not significant). All patients receiving CsA, tacrolimus, or sirolimus had routine therapeutic drug monitoring. An elevated trough level was noted in 26 of the 63 patients on cyclosporine, in 21 of the 38 patients on tacrolimus, and in 3 of the 16 patients on sirolimus. The proportion of elevated trough levels was not significantly different between patients with and without HT: cyclosporine, 44% vs 39% ($P$ = .97); tacrolimus, 73% vs 44% ($P$ = .35); sirolimus, 50% vs 14.3% ($P$ = .69).

## DISCUSSION

Evaluating the hepatic safety of medications in HSCT recipients is challenging because of frequent confounding conditions and medications associated with hepatic abnormalities [15-17]. Our observational study is the largest assessment of the hepatic safety of voriconazole in allogeneic HSCT to date outside the context of a randomized, controlled clinical trial. We analyzed HT based on the measurement of serum transaminase level. The assessment of CL-HT was partly subjective.

The exposure to voriconazole was long, with a median of 72 days. HT occurred at a median of 26 days of therapy. Approximately one-third of the

**Table 2. Univariate Analysis of Risk Factors for HT While on Voriconazole***

| | OR | 95% CI | P |
|---|---|---|---|
| T-cell depletion | | | |
| Unmodified | 1.00 | - | - |
| T-cell depleted | 0.51 | 0.28-0.93 | .027 |
| GVHD† | | | |
| Grade 0-I | 1.00 | - | - |
| Grade II-IV | 2.98 | 1.52-5.85 | .001 |
| Stem cell source | | | |
| Peripheral blood | 1.00 | - | - |
| Bone marrow | 0.60 | 0.19-1.92 | .389 |
| Cord blood | 2.26 | 0.99-5.17 | .053 |

HT indicates hepatotoxicity; OR, odds ratio; CI, confidence interval; GVHD, graft-versus-host disease.
*The variables listed in Table 1 were included in the model. Significant variables are shown.
†Eight patients with nonevaluable acute GVHD were excluded from this analysis.

**Table 3. Concomitant Medication Use in Patients with and without HT**

| | HT | No HT |
|---|---|---|
| Agent | (n = 68) | (n = 132) |
| Antiviral, n (%) | | |
| Acyclovir | 50 (73.5%) | 108 (81.8%) |
| Ganciclovir | 4 (5.9%) | 8 (6.1%) |
| Valganciclovir | 17 (25%) | 32 (24.2%) |
| Foscarnet | 6 (8.8%) | 14 (10.6%) |
| Cidofovir | 2 (2.9%) | 5 (3.8%) |
| PCP prophylaxis, n (%) | | |
| Dapsone | 1 (1.5%) | 1 (0.8%) |
| TMP/SMX | 11 (16.2%) | 29 (22.0%) |
| Atovaquone | 14 (20.6%) | 37 (28.0%) |
| Pentamidine | 36 (52.9%) | 67 (50.8%) |
| Antifungals | | |
| Micafungin | 29 (42.7%) | 42 (31.8%) |
| Amphotericin B | 7 (10.29%) | 2 (1.5%) |
| Immunosuppressants | | |
| Cyclosporin A | 27 (39.7%) | 36 (27.2%) |
| Tacrolimus | 15 (22.0%) | 23 (17.4%) |
| Sirolimus | 2 (2.9%) | 14 (10.6%) |
| Mycophenolate mofetil | 25 (36.7%) | 32 (24.2%) |
| Budesonide | 12 (17.7%) | 13 (9.9%) |
| Other immunosuppressants* | 3 (4.4%) | 4 (3.03%) |
| Corticosteroids | 34 (50%) | 46 (34.9%) |
| Calciumchannel blocker | | |
| Amlodipine | 5 (7.4%) | 3 (2.3%) |
| Psychotropics | | |
| Olanzapine | 10 (14.7%) | 24 (18.2%) |
| Lorazapam | 23 (33.8%) | 57 (43.2%) |
| Zolpidem | 12 (17.7%) | 27 (20.5%) |
| Other† | 13 (19.1%) | 33 (25.0%) |

*Includes alemtuzumab and methotrexate.
†Includes escitalopram, citalopram, dronabinol. clonazepam, gabapentin, and alprazolam.

patients (34%) developed HT during voriconazole therapy. This is higher than the rate of 19% reported in previous randomized clinical trials of voriconazole [13]. Determining the causality of HT in relation to voriconazole in our cohort was extremely difficult. Almost half of our patients had other concomitant conditions or medication exposures causing or contributing to HT. Some patients with mild transaminase changes continued voriconazole therapy with their transaminase values improving or remaining only mildly elevated.

Because the majority of the allogeneic HSCT recipients at MSKCC receive voriconazole prophylaxis, identifying a comparator cohort of patients who did not receive voriconazole and had similar characteristics as our study cohort was not feasible. Thus, to identify risk factors for HT, we compared the patients who developed HT while on voriconazole to the patients who did not. In multivariate analyses, only aGVHD grade II-IV remained a significant risk factor for HT.

Our patients' extensive exposure to other potentially hepatotoxic medications posed an additional challenge in the assessment of competing causes for HT. CsA, tacrolimus, warfarin, and calcium channel blockers can cause HT and have a known pharmacokinetic interaction with voriconazole. A comparison of the use of immunosuppressants and other hepatotoxic drugs in patients who developed HT and those who did not revealed no substantial differences between the 2 groups (all $P > .1$). The proportion of patients with an elevated level of a calcineurin inhibitor (cyclosporine and tacrolimus) or an mTOR inhibitor (sirolimus) did not differ significantly between the 2 groups. Interestingly, in univariate analysis, recipients of T-cell depleted grafts, who did not require additional exogenous immunosuppression for GVHD prophylaxis, were less likely to develop HT compared with recipients of unmodified grafts. A lack of exogenous immunosuppression or lower rates of GVHD in the recipients of T-cell depleted grafts may account for this finding.

Voriconazole is extensively metabolized by the liver. Cytochrome CYP2C19, the major enzyme responsible for voriconazole metabolism, exhibits genetic polymorphisms that result in variations in voriconazole metabolism and exposure. Poor metabolizers may experience up to a 4-fold increase in drug exposure; such a phenotype is found in up to 20% of non-Indian Asians, but in only 3%-5% of Caucasians and African Americans [18]. Our population included only 9 Asian patients (4%). The association between HT and elevated voriconazole levels is not well defined. An elevated voriconazole trough level has been associated with HT, which certainly is of concern in HSCT recipients who are already at risk for liver dysfunction [19-23]. Because therapeutic drug monitoring was done at the discretion of clinicians in our study, the possibility of testing bias is plausible. Patients with LFT abnormalities or those requiring a high dose of voriconazole would be more likely to have their levels checked. Nonetheless, we did not observe any significant differences between the 2 groups in the number of patients with a voriconazole trough level >6 mg/L.

Our assessment of the trend of transaminase values with time revealed a significant decrease in all enzymes except TBil after withdrawal of therapy. The TBil elevations could be explained by the presence of other conditions and comorbidities in the majority of patients. Our data strongly suggest that HT was largely reversible after discontinuation of voriconazole. Although there was a temporal association between the increased transaminase values with voriconazole treatment and decreased values with discontinuation of treatment in many patients with HT, a causal relationship is less clear. In a review of the medical records of patients who developed HT and died while on voriconazole therapy, voriconazole was not considered to contribute to death in any of these patients.

In summary, in this large cohort of high-risk HSCT recipients, 34% of the patients experienced mild to moderate elevations in liver enzymes. All of the abnormalities except elevated TBil were reversible after stopping voriconazole. aGVHD was a significant risk factor for HT. Approximately 50% of the patients had concomitant diagnoses or medications associated with HT. In approximately 50% of the patients, LFT abnormalities normalized or remained only mildly elevated and did not necessitate discontinuation of voriconazole therapy. Voriconazole therapy with monitoring appears reasonably safe in HSCT recipients at high risk for invasive fungal infections.

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