The Effect of Therapeutic Drug Monitoring on Safety and Efficacy of Voriconazole in Invasive Fungal Infections: A Randomized Controlled Trial

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Background. Blood levels of voriconazole, a first line therapy for invasive aspergillosis, may correlate with adverse events and treatment response. However, no randomized controlled studies have been conducted to evaluate the clinical utility of routine therapeutic drug monitoring (TDM) of voriconazole. This study aimed to determine whether routine TDM of voriconazole reduces drug adverse events or improves treatment response in invasive fungal infections.

Methods. This was a randomized, assessor-blinded, controlled, single center trial. One hundred ten adult patients were randomly assigned to TDM or non-TDM groups. In the TDM group, voriconazole dosage was adjusted (target range, 1.0–5.5 mg/L) according to the serum trough level measured on the fourth day after initiation of voriconazole. The non-TDM group received a fixed, standard dosage. Voriconazole-related adverse events were monitored, and treatment response was assessed three months after the initiation of therapy.

Results. Baseline characteristics including the CYP2C19 genotype were comparable between the two groups. While the incidence of adverse events was not different between the TDM group and the non-TDM group (both 42%; $P = .97$), the proportion of voriconazole discontinuation due to adverse events was significantly lower in the TDM group than in the non-TDM group (4% vs 17%; $P = .02$). A complete or partial response was observed in 81% (30 of 37) of patients in the TDM group compared to 57% (20 of 34) in the non-TDM group ($P = .04$).

Conclusions. Routine TDM of voriconazole may reduce drug discontinuation due to adverse events and improve the treatment response in invasive fungal infections.

Clinical Trial Registration. NCT00890708.

Voriconazole is a triazole antifungal agent that is currently a drug of choice for invasive aspergillosis [1]. Voriconazole may be associated with adverse events, including visual disturbance, encephalopathy, rash,

and hepatic enzyme elevation, which may result in drug discontinuation [2, 3]. The steady-state blood concentration of voriconazole has large inter-personal variability because it can be affected by diverse factors including patient age, drug-drug interactions, and cytochrome P450 (CYP) polymorphism (mainly CYP2C19) [4].

Recently, several observational studies demonstrated that the blood trough level is associated with adverse events and treatment response [5–8]. However, there have been no controlled trials that have evaluated the clinical utility of routine voriconazole therapeutic drug monitoring (TDM). In addition, the trough level of voriconazole may be markedly variable over time in

the same patient [9]. This intra-personal variability along with nonlinear saturable pharmacokinetics of voriconazole in adults may raise the concern that the adjustment of the voriconazole dosage based on TDM at a single time point may result in a suboptimal voriconazole blood level at a later time. We conducted this randomized, controlled trial in order to determine whether routine TDM of voriconazole reduces drug-related adverse events and improves the treatment outcome in invasive fungal infections.

METHODS

Patients

This was a prospective, randomized, assessor-blinded, controlled trial conducted from November 2008 through December 2011 at Seoul National University Hospital, a 1600-bed, tertiary-care teaching hospital in South Korea. Patients aged ≥15 years and within 4 days of beginning intravenous or oral voriconazole for invasive fungal infections or for empirical treatment were enrolled. Exclusion criteria were death, discharge, or transfer before the day of blood sampling for TDM, enrollment in another clinical trial, or declined consent. Invasive fungal infection was defined and classified according to the definitions of the Invasive Fungal Infection Group of the European Organization for Research and Treatment of Cancer and Mycoses Study Group of the National Institute of Allergy and Infectious Diseases [10]. Neutropenia was defined by a neutrophil count of <500 per cubic millimeter.

Study Design

Patients were randomly assigned to the TDM group or non-TDM group using computerized 1:1 random selection. Patients in both groups initially received the standard dosage of voriconazole, irrespective of the administration route: 2 loading doses of 6 mg/kg every 12 hours, followed by a maintenance dose of 4 mg/kg twice per day.

In the TDM group, blood sampling was done on the fourth day after the initiation of voriconazole. The voriconazole dosage was adjusted 24–48 hours after blood sampling based on the results of TDM. The timing of the TDM blood collection was calculated based on data from the literature so that it coincided with the target trough concentration range (1.0–5.5 mg/L), and was determined to be the fourth day after the initiation of therapy [5, 11]. The dosage was increased by 100% if the trough level was <1.0 mg/L; it was lowered by 50% if the trough level was >5.5 mg/L and there was no drug-related adverse event. If the trough level was >10.0 mg/L or if an adverse event was suspected in a patient with a level >5.5 mg/L, 1 dose was skipped and subsequent doses were reduced by 50%. If the voriconazole dosage or administration route was altered or if the interacting drug was introduced or halted,

follow-up TDM was repeated on the fourth day. This adjustment was repeated until the trough level was within the target range.

For the future determination of voriconazole levels in the non-TDM group, we collected and stored blood samples in that group on the same day that blood was collected from the TDM group. The standard dosage of voriconazole was maintained in the non-TDM group. In both groups, CYP2C19 typing and extra blood sampling to check intraindividual variation were performed, but these results were not used to adjust drug dosage.

Patients were followed up to 3 months after starting voriconazole. Discontinuation of voriconazole due to adverse events or treatment failure was decided independently by attending physicians who were blinded to treatment groups and any related information such as blood levels or genotype. The Institutional Review Board of Seoul National University Hospital approved the study protocol. All patients or their legal representatives provided written informed consent before study entry.

Measurement of Voriconazole Level and CYP2C19 Genotyping

The measurement of the voriconazole trough level and CYP2C19 genotyping were performed in the study center by the methods described in our previous publication [12]. In brief, quantitative analysis of voriconazole was performed using high-performance liquid chromatography (1200 series, Agilent Technologies) coupled with tandem mass spectrometry (API3200, Applied Biosystems/MDS Sciex). For CYP2C19 genotyping, CYP2C19*2, *3, and *17 allele detection was conducted using TaqMan allelic discrimination assays on an ABI Prism 7500 Sequence Detection System (Applied Biosystems). The CYP2C19 genotype was classified as homozygous extensive metabolizer (*1/*1), heterozygous extensive metabolizer (*1/*2, *1/*3), heterozygous ultra-rapid metabolizer (*1/*17), or poor metabolizer (*2/*2, *2/*3, *3/*3).

Adverse Events and Treatment Response

Adverse events were monitored with a questionnaire for up to 3 months and assessed by investigators blinded to the group allocation and voriconazole level. Adverse events and their relationship with voriconazole were defined according to the criteria of the National Cancer Institute [13]. Grade 3–4 adverse events were considered severe, and a voriconazole-related adverse event was defined as one with a possible or stronger relationship.

Only patients with invasive fungal infection were included in the analysis of the treatment response that occurred 3 months after the initiation of voriconazole; patients treated empirically were excluded [10]. Treatment response was categorized as complete, partial, stable, undetermined, or treatment failure [14]. Complete response indicates resolution of

all clinical signs and symptoms attributable to fungal infection and complete or very nearly complete radiographic resolution. Partial response indicates major improvement or resolution of clinical signs and symptoms attributable to fungal infection and at least a 50% improvement in radiologic findings. A stable response indicates some improvement but <50% radiologic improvement. Undetermined response includes follow-up loss, death for reasons other than fungal infection, and voriconazole discontinuation due to adverse events. Treatment failure includes voriconazole discontinuation due to the progression of fungal infection and death caused by invasive fungal infection. For the analysis of the treatment response, patients with an undetermined response were excluded, and treatment success was defined as complete or partial response.

Statistical Analysis

The primary objective of the study was to determine whether routine TDM of voriconazole reduced the incidence of voriconazole-related adverse events in all patients included in the study. The sample size necessary to detect a 3-fold decrease in the incidence of adverse events in the TDM group was calculated. We assumed that the incidence of voriconazole-related adverse events in the control group would be 35% based on previous literature and our experience [3, 15], which was equal to 53 patients in each group being required in order to detect a difference of this magnitude (power, 0.8; type I error, 5%). Considering dropouts, 55 patients were planned for recruitment in each group.

Secondary objectives were to compare the incidence of voriconazole discontinuation due to adverse events in all analyzed patients and to determine the treatment success rate in patients with invasive fungal infection. Subgroup analyses including only CYP2C19 homozygous or heterozygous extensive metabolizers and only patients with an initial voriconazole level >8.0 mg/L were performed.

The χ^2 test or Fisher's exact test was used to compare categorical variables including adverse events, drug discontinuation, and treatment success or failure. The Student t test was used to compare voriconazole levels, and time-to-event data was compared by the log-rank test using the Kaplan–Meier method. Statistical analyses and randomization were performed using SPSS (Statistical Package for the Social Sciences) software (ver. 19.0; SPSS Inc.). All tests were 2-tailed. A P value <.05 was considered statistically significant.

RESULTS

Baseline Patient Characteristics

Of the 153 patients screened for this study, 43 patients were excluded (Figure 1), which left 110 remaining patients that were randomized into the TDM group (n = 55) or non-TDM group (n = 55). Two patients in the non-TDM group withdrew their consent during the study, and thus, 108 patients were ultimately included in the analyses. The mean age was 56 ± 15 years; 31 (29%) patients were female, and all were Korean (Table 1).

Characteristics of Voriconazole Therapy

There were no distinct differences in overall therapy characteristics between the TDM group and the non-TDM group (Table 2). The initial trough level of voriconazole was within the target range in 52 (51%) patients (Figure 2A). Of 53 patients in the TDM group with an appropriate voriconazole trough level, 26 (49%) patients had initial levels within the target range. Of 27 patients with an inappropriate trough level, 6 (22%) patients were not given a dose adjustment because of drug discontinuation or death before the dose adjustment, and the other 21 (78%) patients received a dose adjustment; the dosage was decreased in 16 (62%) patients, whereas the dosage was increased in 5 (19%). Finally, the voriconazole trough level reached the target range in 41 (77%) patients. When the target range was validated with our own data, a therapeutic range of 2–5.5 mg/L seemed more appropriate (see Supplementary Material).

Phenobarbital was coadministered with voriconazole in 1 patient in the TDM group. Other drugs, including omeprazole, which is known to have substantial interactions with voriconazole, were not administered. To evaluate the intraindividual variation, follow-up blood sampling was performed in 31 patients with voriconazole levels within the therapeutic range. The median intraindividual difference was 1.05 mg/L (range, 0.04–3.45 mg/L).

Adverse Events

There was no significant difference in the incidence of adverse events between the TDM and non-TDM groups (Table 3). Visual disturbance or encephalopathy could be evaluated in only 92 (85%) patients who were communicable.

Voriconazole was discontinued due to adverse events in 2 (4%) patients in the TDM group, which was significantly less than the 9 (17%) in the non-TDM group (P = .02). The most common adverse event causing drug discontinuation was hepatic enzyme elevation (n = 5) followed by arrhythmia (n = 1), rash (n = 1), agitation (n = 1), confusion (n = 1), hyponatremia (n = 1), and visual hallucination (n = 1). The median time from treatment initiation with voriconazole to the development of the adverse event was 5 days (range, 0–16) in the TDM group and 3 days (range, 0–16) in the non-TDM group (P = .86; Figure 3).

Treatment Response

Of 108 patients, overall mortality was 11 (20%) in the TDM group and 18 (34%) in the non-TDM group at 6 weeks after the
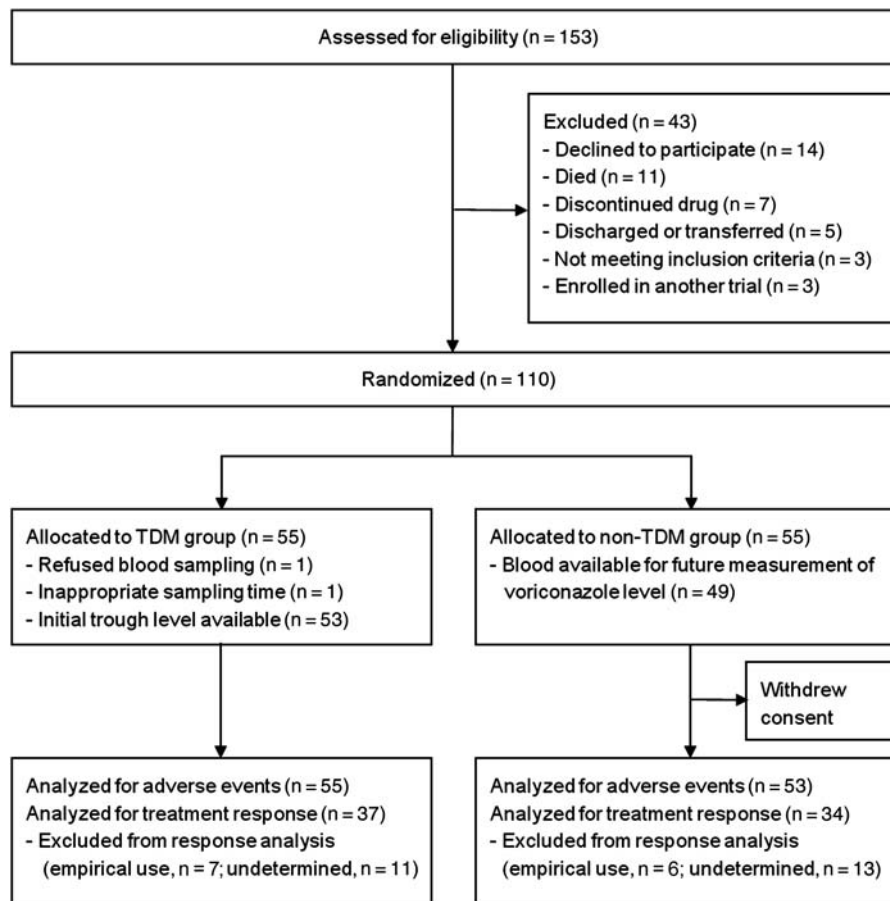
Figure 1. Study flow diagram. Abbreviation: TDM, therapeutic drug monitoring.

initiation of voriconazole therapy and 13 (24%) in the TDM group and 21 (40%) in the non-TDM group at 12 weeks after treatment initiation ($P = .14$). Of 94 patients with invasive fungal infections, 23 (24%) were classified as having undetermined response, 11 (12%) patients discontinued voriconazole due to adverse events, 10 (11%) died due to causes other than fungal infection, and 2 (2%) were lost to follow-up.

Treatment success in the TDM group was significantly greater than in the non-TDM group (Table 4). When only probable or proven fungal infections were included, treatment success was observed in 86% (25 of 29) of patients in the TDM group and in 63% (20 of 32) in the non-TDM group ($P = .04$), and treatment failure was more prevalent in the non-TDM group than in the TDM group (31% vs 10%, respectively; $P = .04$).

Among patients included in treatment response analyses, the final voriconazole level was available in 35 patients in the TDM group and 32 patients in the non-TDM group (Figure 2B). The mean final trough level of voriconazole was 3.2 ± 2.1 mg/L in the TDM group and 4.3 ± 3.1 mg/L in the non-TDM group ($P = .10$). Treatment failure was observed in

3 (60%) of 5 patients who had a final voriconazole trough level that was <1 mg/L and in 8 (57%) of 14 patients who had a level >5.5 mg/L.

Subgroup Analyses

In the subgroup analyses including only CYP2C19 homozygous or heterozygous extensive metabolizers, voriconazole-related adverse events occurred in 47% (20 of 43) of patients in the TDM group and 38% (17 of 45) in the non-TDM group ($P = .41$), and voriconazole was discontinued due to adverse events in 5% (2 of 43) of patients in the TDM group and 18% (8 of 45) in the non-TDM group ($P = .09$). Treatment success occurred in 82% (22 of 27) of the patients in the TDM group and 62% (18 of 29) in the non-TDM group ($P = .11$).

Of 16 patients with an initial voriconazole level >8.0 mg/L, 6 (40%) were heterozygous extensive metabolizers and 4 (27%) were poor metabolizers. In this subgroup, adverse events included severe hepatic enzyme elevation (n = 1), hallucination (n = 2), and confusion (n = 2), and voriconazole treatment was halted in only 1 patient. In the 5 patients who received a dose adjustment, the voriconazole level reached the

Table 1. Baseline Patient Characteristics

	TDM (n = 55)	Non-TDM (n = 53)	Total (N = 108)
Age, years	58 ± 16	53 ± 14	55 ± 15
Sex, female	13 (42)	18 (34)	31 (29)
Ethnicity, Korean	55 (100)	53 (100)	108 (100)
Underlying condition			
Hematologic disease	44 (80)	39 (74)	83 (77)
Steroid use	4 (7)	6 (11)	10 (9)
Others[a]	7 (13)	8 (15)	15 (14)
Neutropenia	22 (40)	22 (42)	44 (41)
CYP 2C19 genotype[b]			
Homozygous extensive metabolizer	23 (44)	21 (42)	44 (43)
Heterozygous extensive metabolizer	20 (39)	24 (48)	44 (43)
Poor metabolizer	9 (17)	5 (10)	14 (14)
Heterozygous ultra-rapid metabolizer	0	0	0
Invasive fungal infection			
Proven	9 (16)	10 (19)	19 (18)
Probable	29 (53)	33 (62)	62 (57)
Possible	9 (16)	4 (8)	13 (12)
Empirical use	8 (15)	6 (11)	14 (13)
Site of infection[c]			
Lung	43 (91)	42 (89)	85 (90)
Brain	1 (2)	1 (2)	2 (2)
Others[d]	3 (6)	4 (9)	7 (7)
Fungal organisms[e]			
Aspergillus	37 (97)	39 (91)	76 (94)
Candida	1 (3)	3 (7)	4 (5)
Phialophora	…	1 (1)	1 (1)

Data are the mean ± SD or No. (%).

Abbreviation: TDM, therapeutic drug monitoring.

[a] Others include lung disease (n = 6), solid tumor (n = 2), esophageal perforation (n = 2), drug-induced cytopenia (n = 1), kidney transplantation (n = 1), and none identified (n = 3).

[b] The CYP 2C19 genotype was available in 52 patients in the TDM group and 50 patients in the non-TDM group.

[c] Data from invasive fungal infections (n = 94).

[d] Others include brain (n = 2), sinus (n = 2), liver (n = 2), kidney (n = 1), leg (n = 1), and blood (n = 1).

[e] Data from proven or probable fungal infections (n = 81).

Table 2. Voriconazole Use Between Therapeutic Drug Monitoring (TDM) and Non-TDM Groups

	TDM (n = 55)	Non-TDM (n = 53)	Total (N = 108)
Reason for voriconazole use			
First-line use	29 (53)	27 (51)	56 (52)
Failure of other antifungal agent	18 (33)	17 (32)	35 (32)
For oral administration	6 (11)	4 (8)	10 (9)
Intolerance to other antifungal agent	2 (4)	5 (9)	7 (7)
Administration route			
Intravenous followed by PO	28 (51)	27 (51)	55 (51)
Intravenous only	16 (29)	19 (36)	35 (32)
PO only	11 (20)	7 (13)	18 (17)
Loading dose, mg/kg/day	11.3 ± 1.6	11.8 ± 0.9	11.5 ± 1.3
Maintenance dose, mg/kg/day	7.6 ± 0.7	7.8 ± 0.7	7.7 ± 0.7
Initial voriconazole trough level, mg/L	4.7 ± 3.0	4.7 ± 3.0	4.7 ± 3.0
>5.5 mg/L	21 (40)	18 (37)	39 (38)
<1.0 mg/L	5 (9)	6 (12)	11 (11)
Duration of voriconazole use, days	41 ± 31	37 ± 30	39 ± 30

Data are the mean ± standard deviation or No. (%).

Abbreviations: PO, per oral; TDM, therapeutic drug monitoring.

target range in 3 patients after a 50% dose reduction and in 2 patients after a 75% dose reduction. Of 11 patients (excluding 5 who underwent a voriconazole level adjustment), 6 (55%) died; the median time from a toxic level to death was 7.5 days (range, 6–13 days).

DISCUSSION

In this randomized, controlled trial, routine TDM of voriconazole did not decrease the overall incidence of voriconazole-related adverse events. However, it did significantly reduce the incidence of voriconazole discontinuation due to adverse events and improve the success rate in the treatment of invasive fungal infections. To the best of our knowledge, this is the first randomized, controlled study to evaluate the utility of routine TDM of voriconazole in the clinical setting. Although previous studies either did not use TDM for intervention or did not have a control group [5–8, 16, 17], our randomized study evaluated the outcomes of clinical practice based on voriconazole TDM in comparison with conventional voriconazole therapy. The baseline patient characteristics illustrate that randomization was successfully performed. Another advantage of our study design is that group assignment and voriconazole levels were blinded to the assessors of adverse events and attending physicians who were responsible for decisions on the duration of voriconazole therapy.

The proportion of CYP2C19 poor metabolizers has been measured and has been shown to be higher in Asians (15%–20%) than in Caucasians (2%–3%) [18]. The proportion of poor metabolizers in the present study was 13%, and the inclusion of only Korean patients may be one reason why the voriconazole concentrations in our study were higher than in previous reports [5, 9]. Another reason is that we used a weight-based dosage rather than a fixed dosage even in the oral form [8, 9, 19, 20]. Despite higher mean levels of
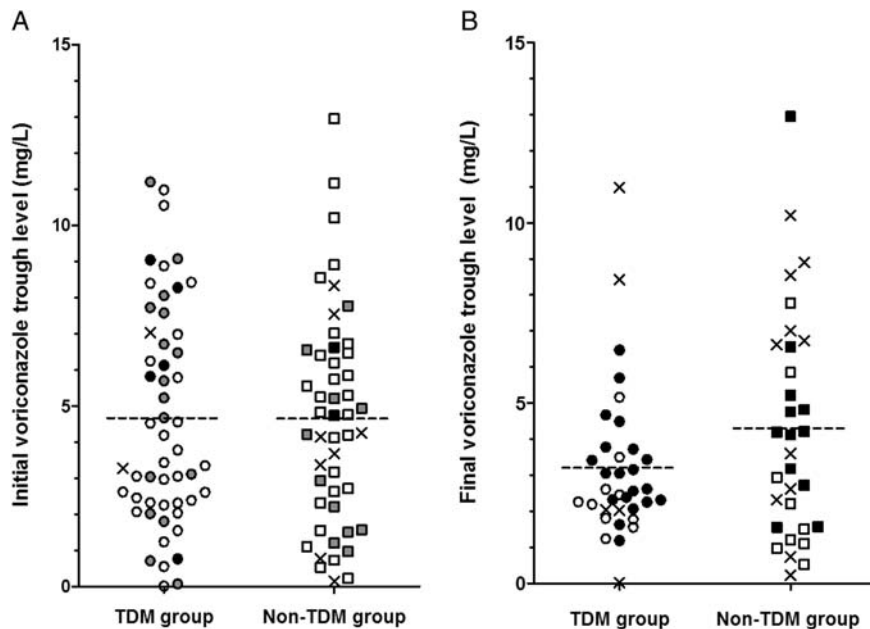
Figure 2. Initial or final voriconazole trough level. *A*, The solid circle or square denotes a severe adverse event, the gray circle or square denotes a non-severe adverse event, and x indicates drug discontinuation due to an adverse event. A dotted line represents the mean value. *B*, A solid circle or square denotes a complete response, an empty circle or square denotes a partial or stable response, and x indicates treatment failure. A dotted line represents the mean value. Abbreviation: TDM, therapeutic drug monitoring.

voriconazole in this study, adverse events were similar to those in previous investigations [2, 5, 21]. Elevation of hepatic enzymes was the most common adverse event, followed by hallucination and visual disturbance [3, 14].

Unlike previous studies, there was no difference in the incidence of adverse events between the TDM and non-TDM groups, which could be partly explained by a relatively early onset of adverse events. Considering that our study population included a relatively large number of poor metabolizers in whom the half-life of voriconazole may be prolonged (up to 32 hours), the timing of the blood sampling for TDM was determined as the fourth day after starting voriconazole therapy [12, 22, 23]. After dosage adjustment based on the TDM result, it would take an additional several days (up to 5–7 days) to reach the new steady-state concentration. However, because approximately 90% of voriconazole-related adverse events developed within 10 days after starting therapy, voriconazole TDM would not have reduced the incidence of adverse events in the study. However, incidence of adverse events might be lower if blood sampling for TDM can be done earlier in a population in which poor metabolizers are rare.

This study demonstrated that voriconazole TDM significantly reduced drug discontinuation due to adverse events. In the non-TDM group, the attending physician who did not know whether the voriconazole level was toxic or therapeutic could not wait in initiating voriconazole treatment cessation

when confronting an intolerable drug-related adverse event. On the contrary, in the TDM group, the attending physician could wait because adverse events were expected to be alleviated after dosage adjustment. However, the time delay between adverse events and drug discontinuation suggests that the attending physicians tried to continue voriconazole as long as they could (Figure 3).

Our dose adjustment strategy generally worked well, although more fine adjustments may be needed for 0.5–1.0 mg/L because a 100% dose increase overshot the target level in 2 of 3 patients with an initial level in this range. Our data demonstrated considerable intraindividual variation of serial voriconazole levels, as previously reported [9]. Furthermore, validation of the therapeutic range with our own data suggests that a lower cutoff of 1.0 mg/L can be low for treatment success [16, 19]. Considering these findings together, voriconazole TDM may have to be repeated if the level is in the range of 1–2 mg/L.

In this study, higher overall mortality in the non-TDM group can be explained by more frequent treatment failure in this group, to which more the common discontinuation of voriconazole might contribute. Treatment failure was common with both toxic and subtherapeutic levels of voriconazole, and these findings were noted in previous studies [8, 16]. Poor patient conditions aggravated by the toxic effect of voriconazole might contribute to treatment failure. On the

Table 3. Voriconazole-Related Adverse Events in Therapeutic Drug Monitoring (TDM) vs Non-TDM Groups

	TDM (n = 55)	Non-TDM (n = 53)	P Value
Possible or stronger relationship			
All events	23 (42)	22 (42)	.97[a]
Elevation of hepatic enzymes	15 (27)	14 (26)	.92[a]
Encephalopathy[b]	8 (15)	7 (13)	.84[a]
Others[c]	5 (9)	8 (15)	.34[a]
Severe events	7 (13)	5 (9)	.586[a]
Elevation of hepatic enzymes	4 (7)	3 (6)	>.99[d]
Encephalopathy	2 (4)	0	.49[d]
Others	2 (4)	2 (4)	>.99[d]
Probable or likely relationship			
All events	12 (22)	9 (17)	.53[a]
Elevation of hepatic enzymes	3 (6)	4 (8)	.71[d]
Encephalopathy	6 (11)	5 (9)	.80[a]
Others	3 (6)	2 (4)	>.99[d]
Severe events	2 (4)	2 (4)	>.99[d]
Elevation of hepatic enzymes	0	1 (2)	.49[d]
Encephalopathy	1 (2)	0	>.99[d]
Others	1 (2)	1 (2)	>.99[d]
Drug discontinuation due to adverse events	2 (4)	9 (17)	.02[a]

Data are No. (%).

Abbreviation: TDM, therapeutic drug monitoring.

[a] From the χ^2 test.

[b] Encephalopathy includes visual hallucination (n = 11) and confusion (n = 4).

[c] Others include visual disturbance (n = 5), rash (n = 3), electrolyte abnormality (n = 3), bad dreams (n = 1), and arrhythmia (n = 1).

[d] From Fisher's exact test.

Figure 3. Time to voriconazole-related adverse events (AEs) and time to drug discontinuation due to AEs. Abbreviations: AE, adverse event; TDM, therapeutic drug monitoring.

contrary, decreased clearance of voriconazole due to poor medical condition might contribute to a high level of voriconazole in patients with treatment failure. In the subgroup analyses including only patients with high voriconazole levels, a relatively short duration from toxic level to death and the absence of extraordinary adverse events such as arrhythmia may favor the latter explanation.

This study has a few limitations. First, only Korean adult patients were included at a single center, so caution may be needed when extrapolating these results to other ethnic groups or pediatric populations with pharmacokinetics different from those of adult patients [24]. However, our subgroup analyses that excluded CYP2C19 poor metabolizers showed results that were similar to those from the overall analyses. In addition, considering the higher proportion of patients with subtherapeutic voriconazole levels in African American and Caucasian populations [5, 9], voriconazole TDM may be more useful to reduce treatment failure in non-Asian populations. Second, the sample size may have been too small to detect a difference
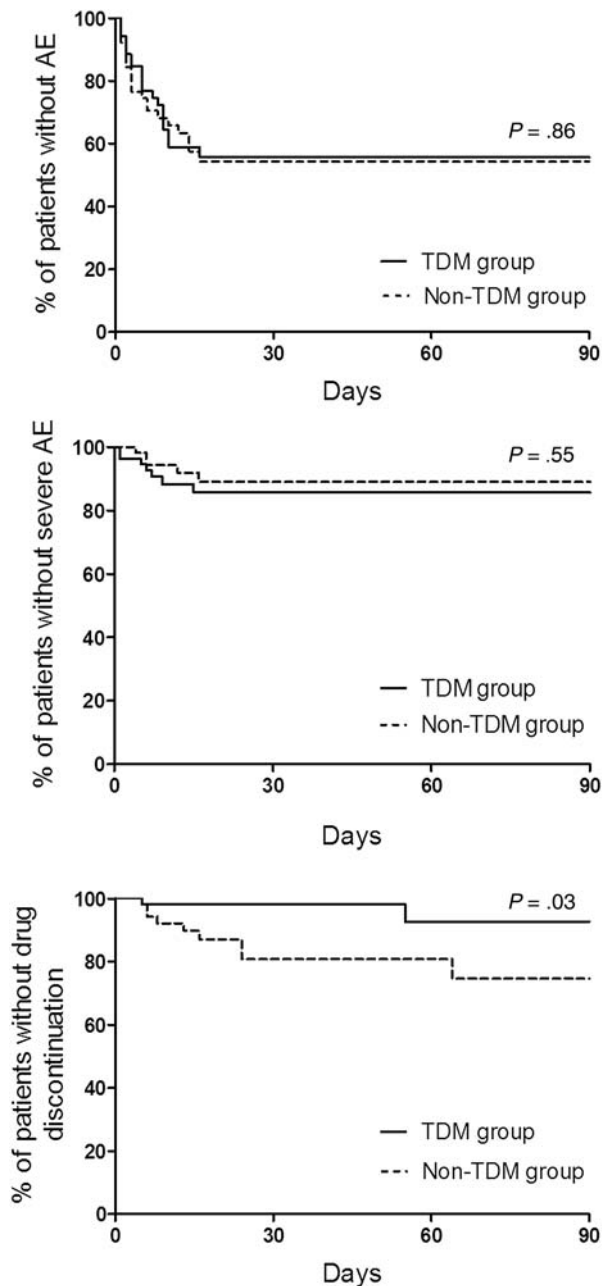
in the incidence of voriconazole-related adverse events between the TDM and non-TDM groups.

In conclusion, routine TDM of voriconazole may not reduce the incidence of drug-related adverse events because of the early occurrence of adverse events compared with the time needed for optimizing voriconazole levels based on TDM. However, voriconazole TDM did reduce drug discontinuations

Table 4. Treatment Response in Therapeutic Drug Monitoring (TDM) vs Non-TDM Groups

	TDM (n = 37)	Non-TDM (n = 34)	P Value
Treatment success	30 (81)	20 (59)	.04
Complete response	21 (57)	13 (38)	.12
Partial response	9 (24)	7 (21)	.71
Stable response	1 (3)	2 (6)	.60
Treatment failure	6 (16)	12 (35)	.07

Abbreviation: TDM, therapeutic drug monitoring.

due to adverse events and improved the treatment response in invasive fungal infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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