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Variability of Voriconazole Trough Levels in Haematological Patients: Influence of Comedications with cytochrome P450 (CYP) Inhibitors and/or with CYP Inhibitors plus CYP Inducers

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Abstract: Voriconazole plasma exposure greatly varies among haematological patients. The purpose of this study was to identify the magnitude of influence of comedications with CYP inhibitors and/or with CYP inhibitors plus CYP inducers on voriconazole trough level (C_{min}). Voriconazole C_{min} was retrospectively assessed among haematological patients who underwent therapeutic drug monitoring (TDM). Univariate and multivariate linear mixed-effect regression analyses were performed to identify the independent predictors of normalized C_{min}. Of the 83 included patients, 35 had comedications with CYP inhibitors (omeprazole or pantoprazole) and 21 with CYP inhibitors (omeprazole or pantoprazole) plus CYP inducers (methylprednisolone, dexamethasone, phenobarbital, rifampin or carbamazepine). Median C_{min} value (n = 199) was 2.4 mg/L with a wide range of distribution (<0.2–13.5 mg/L). Median (IQR) normalized voriconazole C_{min} value was significantly higher in the presence of CYP inhibitors (4.20 mg/L, 3.23–5.51 mg/L) than either in the absence of interacting cotreatments (2.55 mg/L, 1.54–3.47 mg/L) or in the presence of CYP inhibitors plus CYP inducers (2.16 mg/L, 1.19–3.09 mg/L). The presence of CYP inhibitors was highly significantly associated with C_{min} >5.5 mg/L (OR: 23.22, 95% CI: 3.01–179.09, $p = 0.003$). No significant association emerged when CYP inhibitors were coadministered with CYP inducers (OR: 3.53, 95% CI: 0.36–34.95, $p = 0.280$). The amount of expected C_{min} increase was significantly influenced by both the type and the dose of the administered proton pump inhibitor. The study highlights that the benefit from TDM of voriconazole may be maximal in those patients who are cotreated with CYP inhibitors and/or with CYP inhibitors plus CYP inducers, especially when receiving proton pump inhibitors (PPIs) at very high dosages intravenously.

Invasive fungal infections (IFI) are among the most challenging life-threatening infections which may affect haematological patients [1]. Several risk factors have been identified. Patients with acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS) during remission induction chemotherapy or with the presence of other conditions of severe and prolonged immunosuppression are considered at high risk of IFI [1]. Aspergillosis is one of the most frequent IFI occurring in these patients [1], and early diagnosis coupled with early initiation of antifungal therapy is considered of utmost importance for the reduction in invasive aspergillosis-related mortality.

Several international guidelines nowadays recommend voriconazole as a first choice for the treatment of invasive aspergillosis [2–4]. However, it should not be overlooked that voriconazole is a highly lipophilic azole antifungal which is extensively metabolized by several isoforms of the cytochrome P450 (CYP), mainly by CYP2C19 and to a lesser extent by CYP2C9 and CYP3A4 [5]. This means that voriconazole exposure may greatly vary among different individuals even when the recommended dose per kg of body-weight is administered. Factors responsible for this intra- and interindividual pharmacokinetic variability may be related either to genetic polymorphisms of CYP [6] or to drug–drug pharmacokinetic interactions with CYP inhibitors and/or with CYP inducers [7,8].

Consistently, considering that early appropriate treatment is considered the cornerstone of a successful management of invasive aspergillosis [3], recent guidelines recommend therapeutic drug monitoring (TDM) as a mandatory tool for individualizing drug exposure with voriconazole within the first week of treatment [9]. The suggested range for optimal serum exposure is considered a trough level (C_{min}) comprised between 1–1.5 and 4.5–5.5 mg/L. This may maximize the likelihood of optimal treatment while avoiding the risk of underexposure with treatment failure or of overexposure with drug-related toxicity [10–12].

It has been recently suggested that a multidisciplinary team approach involving also the clinical pharmacologist for optimal TDM-guided dose adjustments of azole antifungals may be worthwhile for the management of patients with suspected or diagnosed invasive fungal disease [13]. Interestingly, up-to-date combination of antifungal agents showed no definitive benefit compared to voriconazole monotherapy in the treatment of invasive aspergillosis [14,15]. This allows suggesting that the optimization of voriconazole exposure based on TDM may further impact the decreasing aspergillosis-related mortality rate.

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Our study retrospectively assessed voriconazole C_{min} in a population of haematological patients at risk of IFI who underwent TDM-guided dose adjustments during voriconazole monotherapy. The main intent was that of identifying which factors could have been responsible for a significant variability of drug exposure over time.

Methods

Study design. This retrospective study included haematological patients at high risk of IFI who were admitted at the haematological centres of two major Italian tertiary hospitals (Azienda Ospedaliero-Universitaria Santa Maria della Misericordia of Udine and Azienda Ospedaliero-Universitaria Policlinico of Modena) and who underwent TDM-guided dose adjustments of voriconazole in the period between September 2009 and December 2013. The study was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria of Udine.

At the start of treatment, voriconazole total daily dose and route of administration were chosen by the attending clinician. TDM for dosage optimization of voriconazole was performed at clinician discretion. At each TDM session, a venous blood sample was collected at steady-state (after at least 4 days of unmodified treatment) just before the next administration for trough serum concentration (C_{min}). Times for blood collections were carefully checked, and the samples deemed inappropriate were excluded from the analysis.

Dosage adjustments of voriconazole were performed in those patients presenting with potential drug underexposure or overexposure. Adequate exposure was defined as C_{min} ranging between 1 and 5.5 mg/L [10].

To better understand the influence that different covariates might have had on voriconazole C_{min}, all analyses were carried out referring to C_{min} values that were normalized to the currently recommended dose per kg of body-weight, which is 4 mg/kg every 12 hr (normalized C_{min}). This enabled to avoid any inaccuracy deriving from differences between patients in the real administered dose.

Voriconazole serum concentrations were analysed by means of a validated liquid chromatography–tandem mass spectrometry method [16]. Precision and accuracy were assessed by performing replicate analyses of quality control samples against calibration standards. Intra- and interassay coefficients of variation were always <5%. The limit of quantification was 0.2 mg/L.

Data collection. For each patient, the following data were retrieved: demographics, type and site of IFI (classified as proven, probable or possible based on the EORTC/MSG criteria) [17], fungal isolate (when available), duration of treatment, voriconazole daily dosage and C_{min} at each instance of TDM, number of TDM instances, cotreatments (drug, route of administration and daily dose). Among the latter, particular attention was paid to the presence of comedications with CYP inhibitors and/or with CYP inducers which might have potentially affected voriconazole clearance.

Clinical outcome. Clinical outcome was classified as complete response, partial response, no response and not assessable according to the treatment response. A patient was defined as complete responder if signs and symptoms of the infection disappeared after voriconazole treatment; as partial responder, in case of partial clinical and/or laboratory evidence of response to voriconazole; as non-responder or unassessable, when no favourable clinical response was observed after voriconazole treatment due to failure or to death for underlying disease, respectively.

Statistical analysis. Median with 25th and 75th interquartile range (IQR) was used for descriptive statistics. Kruskal–Wallis test was used to compare data among the groups. To analyse statistical difference between each group and others, Mann–Whitney or Fisher's exact test was used for continuous or categorical data, respectively. Bonferroni correction for multiple comparisons was applied, as appropriate. Univariate and multivariate linear mixed-effect models for repeated measures were performed to identify the independent predictors of normalized C_{min}. Logistic regression analysis was used to estimate the odds ratios for having C_{min} >4.5 and/or >5.5 mg/L. A p value <0.05 was required to achieve a statistical significance.

All statistical analyses were performed with Systat version 13 (Systat Software, Inc., 1735 Technology Dr #430, San Jose, CA 95110, USA).

Results

Patient characteristics and voriconazole treatment.

After retrieving 116 clinical records, 83 high-risk haematological patients were included in the analysis. Patient demographics, clinical and microbiological characteristics are presented in table 1. Voriconazole treatment was started mainly intravenously (45/83, 54.2%) at a median (IQR) dose of 6.1 mg/kg/day (5.3–7.4 mg/L). Fifty-six of 83 patients (67.5%) were cotreated with drugs interacting with voriconazole. Comedications concerned CYP inhibitors (omeprazole or pantoprazole) in 35 patients or CYP inhibitors (omeprazole or pantoprazole) plus CYP inducers (methylprednisolone, dexamethasone, phenobarbital, rifampin or carbamazepine) in other 21 patients. No patients had comedications solely with CYP inducers. No patients had CYP inducers/inhibitors stopped or added during the voriconazole therapy course. Overall, favourable clinical outcome was observed in 67.4% of patients.

Voriconazole trough levels and identification of influencing variables.

Overall, 199 C_{min} values were retrieved and showed a median value of 2.4 mg/L (range: <0.2 to 13.5 mg/L). Univariate and multivariate analyses of variables potentially associated with normalized voriconazole C_{min} are reported in table 2. In the univariate analysis, normalized C_{min} values were significantly associated with cotreatment with pantoprazole, methylprednisolone or rifampin. In the multivariate analysis, cotreatments with CYP inhibitors and/or CYP inducers retained a statistical significance in influencing normalized voriconazole C_{min} (average increase in normalized voriconazole C_{min} of 1.7 mg/L for omeprazole and of 1.6 mg/L for pantoprazole; average decrease in normalized voriconazole C_{min} ranging between 1.6 mg/L for methylprednisolone and 4.1 mg/L for carbamazepine).

Box and whiskers plots of normalized voriconazole C_{min} stratified according to the absence or presence of interacting cotreatments are depicted in fig. 1. The median (IQR) normalized C_{min} value was significantly higher in the presence of cotreatment with CYP inhibitors (4.20 mg/L, 3.23–5.51 mg/L) than either in the absence of interacting cotreatments (2.55 mg/L, 1.54–3.47 mg/L) or in the presence of CYP inhibitors plus CYP inducers concomitantly (2.16 mg/L, 1.19–3.09 mg/L).

Interestingly, with regard to subtherapeutic levels, normalized C_{min} values <1 mg/L occurred significantly more frequently both in patients receiving no interacting cotreatments

Table 1.
Patients' characteristics.

Demographics	
Total number of patients	83
Age (years), median (IQR)	54 (41–62)
Sex, n (male/female)	51/32
Body-weight (kg), median (IQR)	70 (63–81)
Underlying disease, n (%)	
AML	44 (53.0)
Aggressive lymphoma	14 (16.9)
ALL	12 (14.5)
MPD	4 (4.8)
CLL/MM	4 (4.8)
MDS	2 (2.4)
Bone marrow aplasia	2 (2.4)
ITP	1 (1.2)
Fungal infection, n (%)	
Type of infection	
Proven	15 (18.1)
Probable	38 (45.8)
Possible	30 (36.1)
Site of infection	
Single localization	
Lung	65 (78.3)
Nasal sinuses	4 (4.8)
Blood	3 (3.6)
CNS	2 (2.4)
Multiple localization	9 (10.9)
Microbiological isolates	
Aspergillus spp.	
A. fumigatus, A. flavus, A. niger, A. terreus	11, 2, 2, 1
Candida spp.	
C. tropicalis, C. krusei	2, 1
Hyalohyphomycosis	
Fusarium, Scedosporium	1, 1
Others	3
Voriconazole treatment characteristics	
At first TDM	
Dose/kg/day, median (IQR)	6.1 (5.3–7.4)
Route of administration, n (IV/oral)	38/45
C_{min} (mg/L), median (IQR)	2.5 (1.5–3.8)
At subsequent TDM	
Dose/kg day, median (IQR)	6.4 (5.6–7.4)
Route of administration, n (IV/oral)	45/71
C_{min} (mg/L), median (IQR)	2.8 (1.9–3.9)
Total number of C_{min}	199
Number of TDM instances, median (IQR)	2 (1–3)
Number of comedications, median (IQR)	8 (5–10)
Duration of therapy (days), median (IQR)	36 (18–81)
Clinical outcome, n (%)	
Complete response	17 (20.5)
Partial response	39 (46.9)
No response	15 (18.1)
Not assessable	12 (14.5)

ALL, acute lymphatic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphatic leukaemia; CNS, central nervous system; ITP, idiopathic thrombocytopenic purpura; IV, intravenous route of administration; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPD, myeloproliferative disease; Oral, oral route of administration; TDM, therapeutic drug monitoring.

(7/67 patients, 10.45%) and in those receiving CYP inhibitors plus CYP inducers concomitantly (11/59 patients, 18.64%) than in those receiving CYP inhibitors only (0/73 patients, 0.00%). As far as supratherapeutic concentrations are concerned, normalized C_{min} values >5.5 mg/L were significantly more frequently observed in individuals cotreated with CYP inhibitors (18/73 patients, 24.65%) than in those receiving no interacting cotreatment (1/67 patients, 1.49%) or in those cotreated with both CYP inhibitors and CYP inducers (3/59 patients, 5.08%).

Table 3 reports the odds ratios of having normalized voriconazole C_{min} above the toxicity thresholds when in the presence of interacting cotreatments. Interestingly, the presence of CYP inhibitors was highly significantly associated with both thresholds (for C_{min} >4.5 mg/L, OR: 7.50, $p < 0.001$; for C_{min} >5.5 mg/L, OR: 23.22, $p = 0.003$). Conversely, no significant association emerged when CYP inhibitors were administered concomitantly with CYP inducers (for C_{min} >4.5 mg/L, OR: 0.94, $p = 0.924$; for C_{min} >5.5 mg/L, OR: 3.53, $p = 0.280$).

Fig. 2 shows the box and whiskers plots of normalized voriconazole C_{min} observed in patients not receiving interacting cotreatments in comparison with those observed in patients who received different types of CYP inhibitors at various doses. Overall, a statistically significant difference emerged between the six groups ($p < 0.001$). In particular, normalized C_{min} values in the absence of interacting cotreatments were always significantly lower than those observed in the presence of CYP inhibitors, irrespective of the type and the administered dose ($p < 0.015$). Additionally, the comparative analysis showed that normalized C_{min} values were significantly lower in patients receiving oral pantoprazole at 20 mg/day than in patients receiving either IV omeprazole at 80 mg/day ($p < 0.015$) or IV pantoprazole at 80 mg/day ($p = 0.03$).

Discussion

This retrospective study is the first to directly compare in real life the influence that the absence or presence of cotreatments with CYP inhibitors and/or with CYP inhibitors plus CYP inducers may have on the maintenance of appropriate exposure to voriconazole in high-risk haematological patients.

The findings suggest that dose-normalized voriconazole C_{min} may be significantly influenced by various interacting drugs, but to a very different extent in relation to the type and to the administered dose of the drug.

At multivariate analysis, cotreatment with omeprazole or pantoprazole was significantly associated with an almost 2 times increase in dose-normalized voriconazole C_{min}. Conversely, coadministration of methylprednisolone, dexamethasone, phenobarbital, rifampin or carbamazepine was associated with an average decrease in dose-normalized voriconazole C_{min} ranging between 1.65 and 4.19 mg/L. Interestingly, all of these interacting drugs were shown to inhibit [18,19] or to induce the activity of CYP2C19 [20,21], which is the most relevant CYP isoform involved in voriconazole metabolism.

These findings are partially confirmatory of those previously observed by other authors. In a multi-centre retrospective study among 201 adult patients, multiple linear regression analysis showed that cotreatment with corticosteroids was associated with decreasing voriconazole concentrations, whereas cotreatment with various PPIs was associated with increasing voriconazole concentrations [22].

Table 2.
Univariate and multivariate mixed-effect linear regression of variables potentially associated with normalized voriconazole C_{min}[1] (n = 199).

Variable	Univariate analysis		Multivariate analysis	
	Unstandardized β-coefficient (95% CI)	*p*	Unstandardized β-coefficient (95% CI)[1]	*p*
Age (years)	−0.005 (−0.025, 0.015)	0.611		
Sex (male *versus* female)	0.512 (−0.114, 1.139)	0.109		
ALT (UI/L)	0.0 (−0.003, 0.003)	0.816		
Route of administration (IV *versus* oral)	0.409 (−0.167, 0.987)	0.164		
Number of comedications	0.046 (−0.046, 0.137)	0.324		
Creatinine clearance (mL/min)	−0.002 (−0.006, 0.002)	0.346		
Cotreatment with:				
CYP inhibitors				
Omeprazole (78/199)	0.223 (−0.355, 0.801)	0.450	1.714 (0.956, 2.471)	<0.001
Pantoprazole (52/199)	0.734 (0.065, 1.401)	0.031	1.644 (0.905, 2.383)	<0.001
CYP inducers				
Methylprednisolone (38/199)	−1.187 (−1.892, −0.480)	0.001	−1.651 (−2.336, −0.966)	<0.001
Dexamethasone (16/199)	−0.693 (−1.786, 0.400)	0.214	−1.927 (−3.053, −0.801)	0.001
Phenobarbital (3/199)	−1.146 (−3.055, 0.762)	0.239	−2.634 (−4.521, −0.747)	0.006
Rifampin (2/199)	−3.381 (−5.686, −1.076)	0.004	−3.179 (−5.345, −1.014)	0.004
Carbamazepine (2/199)	−3.354 (−8.329, 1.622)	0.186	−4.193 (−8.398, 0.013)	0.051

[1]C_{min} normalized to a voriconazole dose of 4 mg/kg every 12 hr; ALT, alanine aminotransferase; CYP, cytochrome P450; IV, intravenous;

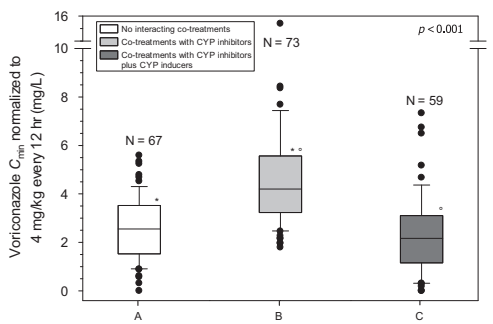

Fig. 1. Box (median and 25th–75th percentiles) and whiskers (5th–95th percentiles) plots of normalized voriconazole C_{min} observed in patients receiving no interacting cotreatments (A), in those receiving CYP inhibitors (B) and in those receiving CYP inhibitors plus CYP inducers simultaneously (C). Filled circles are outliers; n is the number of observations in each group. *p*-value was <0.001 for Kruskal–Wallis test. A statistically significant difference at *post hoc* Bonferroni test was obtained for A *versus* B ($p < 0.001$) and B *versus* C ($p < 0.001$).

Our findings are unique in that they demonstrate for the first time that the average increase in dose-normalized voriconazole C_{min} caused by cotreatment with PPIs may be almost completely counteracted when omeprazole or pantoprazole are coadministered with some CYP inducers. The absence of any significant effect on voriconazole C_{min} when glucocorticoids and PPIs are coadministered was recently reported also by Wang *et al.* who observed no overall effect on voriconazole C_{min} among 151 patients, most of whom were receiving dexamethasone and omeprazole [23]. Additionally, just previously some case reports suggested that both phenobarbital and carbamazepine may lower voriconazole C_{min} [24–26], in agreement with their inductory activity of CYP2C19 and CYP3A4 [27].

Consistently, we recommend clinicians to bear in mind the negative influence that enzyme-inducing antiepileptic drugs may have on voriconazole exposure and to prefer antiepileptic drugs with no impact on voriconazole metabolism (i.e. levetiracetam) [28] whenever an anticonvulsant treatment is needed for haematological patients receiving voriconazole.

As far as the risk of drug-related toxicity is concerned, it is worth noting that about one-fourth of patients receiving cotreatment with PPIs had voriconazole C_{min} >5.5 mg/L in comparison with only a minority of those having cotreatment with both PPIs and CYP inducers or of those not having interacting cotreatments. Of note, comedication with PPIs increases the odds of more than 20 times than in the absence of these interacting cotreatments.

The magnitude of the interaction with PPIs was greatly influenced by both the type and the dosage of the interacting drug. The ranking of influence was 20 mg oral pantoprazole <40 mg IV pantoprazole <40 mg IV omeprazole <80 mg IV omeprazole <80 mg IV pantoprazole. Previous studies showed

Table 3.
Odds ratios of having voriconazole C_{min}[1] above the toxicity thresholds of 4.5 and 5.5 mg/L in the presence of interacting cotreatments.

Type of cotreatment	C_{min}[1] >4.5 mg/L (n = 41)			C_{min}[1] >5.5 mg/L (n = 22)		
	OR	95% CI	*p*	OR	95% CI	*p*
No interacting cotreatments	1.00	–	–	1.00	–	–
Cotreatment with CYP inhibitors	7.50	2.88, 19.57	<0.001	23.22	3.01, 179.09	0.003
Cotreatment with CYP inhibitors plus CYP inducers	0.94	0.27, 3.26	0.924	3.53	0.36, 34.95	0.280

[1]C_{min} normalized to a voriconazole dose of 4 mg/kg every 12 h; CYP, cytochrome P450.

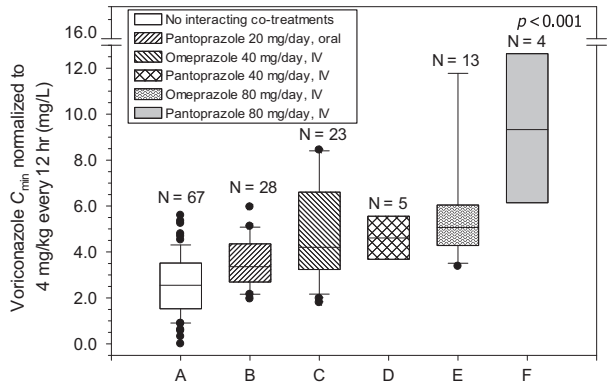

Fig. 2. Box (median and 25th–75th percentiles) and whiskers (5th–95th percentiles) plots of normalized voriconazole C_{min} observed in patients receiving no interacting cotreatments (A) and in those receiving potentially interacting proton pump inhibitors [oral pantoprazole 20 mg (B), IV omeprazole 40 mg (C), IV pantoprazole 40 mg (D), IV omeprazole 80 mg (E), IV pantoprazole 80 mg (F)]. Filled circles are outliers; n is the number of observations in each group. *p*-value was <0.001 for Kruskal–Wallis test. A statistically significant difference at *post hoc* Bonferroni test was obtained for A *versus* B ($p < 0.015$), A *versus* C ($p < 0.015$), A *versus* D ($p < 0.015$), A *versus* E ($p < 0.015$), A *versus* F ($p < 0.015$), B *versus* E ($p < 0.015$) and B *versus* F ($p = 0.03$).

increased voriconazole concentrations with PPIs [22,29–31], due to an inhibition of CYP2C19. However, to our knowledge, none of these assessed the magnitude of the influence. *In vitro* studies showed that omeprazole is a more potent inhibitor of CYP2C19 in comparison with pantoprazole [19]. The Ki of CYP 2C19 in a competitive inhibition model was 0.4–1.5 μM for omeprazole and 14 to 69 μM for pantoprazole [19]. Considering the incomplete oral bioavailability of PPIs [32], this might explain why low dosage of oral pantoprazole was found to have only mild impact on voriconazole C_{min}. Conversely, when omeprazole and pantoprazole were administered intravenously at very high dosages, the increase in voriconazole C_{min} promoted by both agents was very relevant. This seems to suggest that the different *in vitro* inhibitory potencies of omeprazole and pantoprazole against CYP2C19 might be less relevant *in vivo* under these circumstances.

Consistently, clinicians should be aware that cotreatment with PPIs might expose patients to an increased risk of voriconazole toxicity, especially when omeprazole or pantoprazole is administered intravenously at dosages ≥40 mg. Under these circumstances, TDM-based dosage adjustments of voriconazole should be considered absolutely mandatory.

We recognize that our study has some limitations. The small sample size and the lack of CYP2C19 genotyping because of the retrospective nature of the study are probably the most relevant ones. However, as all of our patients were of Caucasian origin, it is expected that this should have affected marginally our results, considering that the percentage of poor metabolizers for CYP2C19 accounts for <3% in this population [33]. We recognize that the estimation of covariate effects by using dose-normalized concentrations could be biased by the nonlinear pharmacokinetics of voriconazole. Finally, we were unable to find specific relationships between voriconazole exposure and clinical outcome because most of TDM-based adjustments of drug exposure were made within the first week of treatment. However, it should be noticed that overall, more than two-thirds of patients had a favourable clinical response at the end of treatment.

In conclusion, our study confirms that TDM of voriconazole should be considered very helpful in optimizing drug exposure among haematological patients at high risk of IFI, in accordance with the current recommendation. Additionally, it highlights that the benefit from this approach may be expected to be maximal in those patients who are cotreated with CYP inhibitors and/or with CYP inhibitors plus CYP inducers, especially when receiving PPIs intravenously at very high dosages.

Acknowledgements

This study was carried out as part of our routine work.

Conflicts of Interest

F. P. has received funds for speaking at symposia organized on behalf of Gilead Sciences, Merck Sharp & Dohme and Pfizer and has served on scientific advisory boards for Pfizer. M. L. serves in Advisory Boards for Merck Sharp & Dohme and Gilead Sciences and received honoraria from these two pharmaceutical industries and from Pfizer and Nanogen. All other authors declared no conflict of interest.

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