Subtherapeutic Posaconazole Exposure and Treatment Outcome in Patients With Invasive Fungal Disease

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Background: Posaconazole exposure seems to be subtherapeutic in some patients with invasive fungal disease. Due to the pharmacokinetic variability of posaconazole, therapeutic drug monitoring may help to optimize the efficacy of this antifungal drug.

Methods: A retrospective study of patients treated with posaconazole from January 2008 to April 2014 and for whom posaconazole serum concentrations were available was conducted. Risk factors for underexposure of posaconazole were detected, and the relationship between posaconazole exposure and treatment outcome according to the European Organization for Research and Treatment of Cancer (EORTC) criteria was assessed.

Results: Seventy patients met the inclusion criteria, 45 patients received posaconazole as treatment, and 25 patients received posaconazole as a prophylactic. Posaconazole serum trough concentrations were <1.25 mg/L in 44.4% of patients receiving treatment and <0.7 mg/L in 40.0% of patients receiving prophylactic posaconazole. Multiple linear regression analysis showed a significant, independent, and negative association of the posaconazole serum trough concentration with a lack of enteral nutrition ($P < 0.001$), vomiting ($P = 0.035$), the use of a proton pump inhibitor or H_2-receptor antagonist ($P < 0.001$), a liquid diet ($P = 0.002$), concomitant chemotherapy ($P = 0.004$), and a posaconazole dose frequency of 2 times daily ($P = 0.015$). A higher posaconazole concentration was associated with a better treatment outcome [odds ratio = 22.22 (95% confidence interval, 3.40–145.33); $P = 0.001$].

Conclusions: Posaconazole exposure is insufficient in more than 40% of patients at risk of or with invasive fungal disease, and posaconazole exposure is positively correlated with a successful treatment outcome. Therapeutic drug monitoring of posaconazole can detect underexposure and can be helpful in treatment optimization.

Key Words: posaconazole, exposure, treatment outcome, therapeutic drug monitoring

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INTRODUCTION

Invasive aspergillosis (IA) is the leading cause of infection-related death in patients with acute leukemia and in hematopoietic stem-cell transplant (HSCT) recipients.[1] Risk factors for IA are prolonged neutropenia, immunosuppression after stem-cell or solid organ transplantation, AIDS, chronic granulomatous disease, and preexisting structural lung disease.[1,2] A crude mortality of up to 49% is seen and IA is associated with an increase in length of hospital stay and increased costs.[2–5] The guideline of the Infectious Diseases Society of America for the treatment of aspergillosis recommends the use of posaconazole for prophylaxis against IA in neutropenic patients with acute myelogenous leukemia or myelodysplastic syndrome and in HSCT recipients and as an alternative choice for salvage therapy for IA.[2] The recommended posaconazole dose is 200 mg 3 times daily for prophylaxis and 200 mg 4 times daily for IA treatment.[6]

Various pathophysiological changes in severely ill patients, such as cancer patients, can affect the pharmacokinetics of antimicrobial agents.[7,8] Furthermore, drug absorption issues (food, gastric pH) and drug–drug interactions contribute to the intraindividual and interindividual variability of the pharmacokinetics of posaconazole.[2,9–15] Data from earlier studies with posaconazole showed that average plasma concentrations (C_{av}), measured at steady state, of at least 0.7 mg/L for prophylaxis and 1.25 mg/L for treatment were associated with a better outcome.[16–18] However, these target concentrations are not achieved in a high proportion of patients with hematologic malignancies, resulting in suboptimal drug exposure.[19–22] Therapeutic drug monitoring (TDM) of posaconazole may play an important role in optimizing drug exposure and hence the efficacy of the antifungal treatment.[2,23] The purpose of this study was to determine risk factors for underexposure of posaconazole and to assess the relation between

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posaconazole exposure and the treatment outcome in patients with invasive fungal disease (IFD).

MATERIALS AND METHODS

Study Design and Data Collection

This retrospective study was conducted at the University Medical Center Groningen, a 1339-bed university hospital in the Netherlands. TDM of antimicrobial drugs is routinely performed in critically ill patients in our hospital. Patients were eligible for inclusion if the following criteria were met: (1) age ≥17 years, (2) admission between January 1, 2008 and March 31, 2014, (3) treatment with posaconazole, and (4) the availability of at least 1 steady-state serum trough concentration of posaconazole (ie, at least 7 days after the start of the posaconazole treatment and at least 7 days on the same dose regimen). The study was evaluated by the local ethics committee (Institutional Review Board 2013-491) and was approved in accordance with Dutch legislation because of its retrospective nature.

Data were collected through review of the medical records using a standardized case report form. Demographic and clinical data were collected including age, sex, body mass index, underlying condition, leukocyte count, C-reactive protein, hepatic function (gamma-glutamyl transferase (γ-GT), alanine aminotransferase (ALAT), bilirubin, and albumin concentration), presence of a HSCT, vomiting (scored positive if present for ≥2 days), diarrhea (for ≥2 days), chemotherapy during treatment with posaconazole, and the food intake of the patient. Furthermore, it was determined whether posaconazole was used for prophylaxis or salvage treatment. In the event that posaconazole was used as a treatment, the IFD was classified as proven, probable, or possible according to the 2008 definition of IFD from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group.[24] Additionally, data were collected on the posaconazole dose and frequency per day, route of administration (oral/nasogastric tube), posaconazole serum trough concentration, duration of posaconazole treatment, and interacting comedication.

Posaconazole Exposure

To evaluate the exposure, posaconazole serum trough concentrations were determined using a validated liquid chromatography-tandem mass spectrometry assay[25] and externally confirmed by proficiency testing.[26] Trough concentrations were determined at 8 hours after posaconazole administration for those patients administered posaconazole 3 times daily and at 6 hours after posaconazole administration in those patients administered posaconazole 4 times daily. A trough posaconazole concentration of ≥0.7 mg/L was considered adequate for prophylaxis and a trough concentration ≥1.2 mg/L as adequate for the treatment of IFD.[16–19] To determine risk factors for posaconazole underexposure, we assessed the association of the first posaconazole trough concentration at steady state with factors that could possibly influence the pharmacokinetics of posaconazole, including the patients' age, body mass index, hepatic function, and the C-reactive protein concentration.[6,27] Additionally, we compared posaconazole concentrations between patient groups with different gender, food intake, posaconazole dosing schedules, the occurrence of vomiting and diarrhea, concomitant treatment with chemotherapy, and the use of interacting comedication [proton pump inhibitors (PPIs), H_2-receptor antagonists, metoclopramide[10,14,28]]. Finally, we performed a multiple linear regression analysis to assess the relation between the posaconazole concentration and the explanatory variables.

Treatment Outcome and Treatment Optimization Strategies

For patients who received posaconazole as prophylaxis, the presence of a breakthrough fungal infection was noted. For patients who received posaconazole as treatment, the outcome was classified as complete, partial, or a stable response, progression of the disease, or death, according to the 2008 definition of responses to therapy and study outcomes in clinical trials of IFD from the MSC and EORTC Consensus Criteria,[29] at the end of treatment. A complete or partial response was defined as a successful treatment and progression of the disease or death as treatment failure. An ordinal regression analysis was performed to assess the relationship between posaconazole exposure and treatment outcome [with (1) successful treatment, (2) stable treatment, and (3) treatment failure] correcting for variables that may influence the treatment outcome, including the age and the immune status of the patient.

In patients with a subtherapeutic posaconazole concentration, we evaluated several strategies that were applied to increase the posaconazole concentration: (1) administration of posaconazole with an acidic beverage, (2) discontinuation of the PPI/H_2-receptor antagonist, (3) discontinuation of total parenteral nutrition (TPN) and start administering posaconazole with food, and (4) increase of the posaconazole dose.

Statistical Analyses

For the univariate analysis, a Spearman correlation coefficient was calculated to determine correlations between 2 continuous variables. For comparing 2 or more groups, the Mann–Whitney *U* test and Kruskal–Wallis test were used. To assess the relationship between the posaconazole exposure and several explanatory variables, variables with a *P* value of <0.10 from the univariate analysis and variables that theoretically can influence posaconazole exposure were included in the multiple linear regression analysis. Multiple linear regression analysis, with posaconazole concentration as a log-transformed dependent variable, was performed with backward analysis, thereby removing nonsignificant variables, starting with the one with the highest *P* value. After performing multiple linear regression, the residuals were checked. For the determination of the relationship between posaconazole exposure and treatment outcome in patients receiving curative treatment, an ordinal regression analysis was performed. All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM SPSS, Chicago, IL). A *P* value <0.05 was considered statistically significant.

RESULTS

A total of 81 patients received posaconazole. In 11 patients, posaconazole TDM was not performed or samples were obtained before steady state was reached and thus they were excluded from the analysis. Consequently, 70 patients met the inclusion criteria and their medical records were reviewed. The median age of the patients was 51 years [interquartile range (IQR), 38–59 years] and the most common underlying condition was a hematologic malignancy (78.6%). The patients' characteristics are summarized in Table 1. Twenty-eight patients (40.0%) received an HSCT and 22 patients (31.4%) received chemotherapy during treatment with posaconazole. Six patients (8.6%) received TPN, 17 patients (24.3%) had a nasogastric tube or a liquid diet, and 47 patients (67.1%) had a normal diet. Twenty-five patients (35.7%) received posaconazole for prophylaxis and 45 patients (64.3%) received posaconazole as a treatment (Table 1). In patients receiving posaconazole for prophylaxis, the posaconazole dose was 600 mg/d in 21 patients (84.0%) and 800 mg/d in 4 patients (16.0%). The median posaconazole serum trough concentration was 0.9 mg/L (IQR, 0.5–1.7 mg/L) and in 15 patients (60.0%), an adequate posaconazole trough concentration of ≥0.7 mg/L was achieved. For patients in the treatment group, the posaconazole dose was 800 mg/d in 36 patients (80.0%), 600 mg/d in 8 patients (17.8%), and 1 patient received a dose of 960 mg/d. The median posaconazole serum trough concentration was 1.2 mg/L (IQR, 0.6–1.6 mg/L) and 25 patients (55.6%) had an adequate posaconazole trough concentration of ≥1.2 mg/L. Overall, 30 patients (42.9%) received interacting comedication with a PPI/H_2-receptor antagonist, 7 patients (10.0%) received metoclopramide, 1 patient (1.4%) received rifampicin, and 1 patient (1.4%) received fosamprenavir. The median duration of treatment with posaconazole was 60 days (IQR, 26–103 days).

TABLE 1. Patient Characteristics and Indication for Antifungal Therapy With Posaconazole

Characteristic	Patients (n = 70)
Gender (no. male)	43 (61.4%)
Age (yrs, median, IQR)	51 (38–59)
BMI (kg/m^2, median, IQR)	23.4 (21.1–26.8)
Underlying condition (no.)	
Hematological malignancies	55 (78.6%)
Acute myeloid leukemia	23 (32.9%)
Acute lymphoblastic leukemia	9 (12.9%)
Non-Hodgkin's lymphoma	6 (8.6%)
Hodgkin's lymphoma	1 (1.4%)
Chronic myelogenous leukemia	3 (4.3%)
Chronic lymphocytic leukemia	4 (5.7%)
Multiple myeloma	3 (4.3%)
Myelodysplastic syndrome	6 (8.6%)
Solid organ transplantation*	8 (11.4%)
Other underlying condition†	7 (10.0%)
Posaconazole prophylaxis	25 (35.7%)
Posaconazole treatment	45 (64.3%)
Proven IFD	22 (31.4%)
Aspergillus fumigatus	11 (15.7%)
Aspergillus flavus	1 (1.4%)
Candida nonalbicans	3 (4.3%)
Scedosporium‡	2 (2.9%)
Rhizomucor§	2 (2.9%)
Absidia corymbifera	2 (2.9%)
Hormographiella aspergillata	1 (1.4%)
Probable IFD	7 (10.0%)
Possible IFD	16 (22.9%)

*Five patients lung transplantation, 3 patients liver transplantation.
†One Cystic fibrosis, 1 HIV, 1 aplastic anemia, 1 myelofibrosis, 1 hemoptysis, 1 thorax trauma, 1 common variable immunodeficiency.
‡One *Scedosporium prolificans*, 1 *Scedosporium apiospermum*.
§One *Rhizomucor pusillus*, 1 *Rhizomucor* not specified.
BMI, body mass index; IFD, invasive fungal disease; IQR, interquartile range.

Posaconazole Exposure

Univariate analysis showed a significant correlation between posaconazole concentration and serum albumin concentration (correlation coefficient 0.309; $P = 0.014$). The median posaconazole trough concentration was significantly lower in patients suffering from vomiting or diarrhea, patients who received concomitant chemotherapy, and in patients who received a PPI/H_2-receptor antagonist (Table 2). Furthermore, the posaconazole trough concentration was significantly different in patients with a different food intake. The median posaconazole trough concentration was 0.3 mg/L (IQR, 0.2–0.3 mg/L) in patients with a lack of enteral nutrition (and receiving TPN), 0.8 mg/L (IQR, 0.4–1.3 mg/L) in patients who had a nasogastric tube or a liquid diet, and 1.3 mg/L (IQR, 0.8–2.1 mg/L) in patients with a normal diet ($P < 0.001$). The median posaconazole trough concentration was similar in patients with different posaconazole dosing schedules, 1.0 mg/L (IQR, 0.6–1.7 mg/L) for 200 mg 3 times daily, 1.3 mg/L (IQR, 0.6–1.8 mg/L) for 200 mg 4 times daily, and 1.0 mg/L (IQR, 0.4–1.5 mg/L) for 400 mg 2 times daily ($P = 0.780$), in the univariate analysis. In the multiple linear regression analysis, variables obtained by the univariate analysis (albumin concentration, vomiting, diarrhea, chemotherapy, the use of a PPI/H_2-receptor antagonist, and food intake) and the posaconazole dose were included. The assumptions for linear regression were met, the residuals of the log-transformed posaconazole trough concentration did not deviate from normality, and the variance of the residuals was considered

TABLE 2. Posaconazole Concentration in Different Patient Groups

	Posaconazole Concentration (mg/L)		
Characteristic	Yes	No	P*
Gender (male)	1.0 (0.6–1.4)	1.2 (0.5–2.1)	0.461
Vomiting	0.3 (0.1–0.7)	1.2 (0.6–1.7)	0.006
Diarrhea	0.6 (0.4–1.1)	1.3 (0.6–2.1)	0.008
Chemotherapy	0.9 (0.4–1.4)	1.2 (0.6–2.1)	0.088
PPI/H_2-antagonist	0.6 (0.3–1.1)	1.4 (0.8–2.2)	<0.001
Metoclopramide	0.9 (0.3–1.4)	1.1 (0.6–1.7)	0.444

Posaconazole trough concentration expressed as median with interquartile range.
*Determined using the Mann–Whitney *U* test.
PPI, proton pump inhibitor.

TABLE 3. Multiple Linear Regression Model of Factors Significantly Associated With the Posaconazole Concentration

Factor	Effect	95% CI	*P*
Lack of enteral nutrition	−1.140	−1.741 to −0.539	<0.001
Vomiting	−0.866	−1.671 to −0.061	0.035
PPI/H_2-antagonist	−0.627	−0.923 to −0.331	<0.001
Nasogastric tube/liquid diet	−0.512	−0.829 to −0.195	0.002
Concomitant chemotherapy	−0.453	−0.758 to −0.147	0.004
Posaconazole frequency 2 times daily	−0.405	−0.727 to −0.083	0.015

R^2 of the model = 0.562, R^2 change = −0.014, compared with the model with all variables included.

CI, confidence interval; PPI, proton pump inhibitor.

homogeneous. The multiple linear regression analysis showed a significant, independent, and negative association of posaconazole trough concentration with a lack of enteral nutrition (and receiving TPN), vomiting, the use of a PPI/H_2-receptor antagonist, a liquid diet, concomitant chemotherapy, and a posaconazole dose of 400 mg 2 times daily (Table 3).

Treatment Outcome and Treatment Optimization Strategies

Of the 25 patients who received posaconazole for prophylaxis, 1 patient (4.0%) had a breakthrough infection with a *Rhizomucor* species resistant to posaconazole. Of the 45 patients (age: range 17–75 years) who received posaconazole for the treatment of an IFD, the outcome was classified as a complete response in 24 patients (53.3%) and as a partial response in 8 patients (17.8%). A stable response was seen in 6 patients (13.3%), progression of the disease was seen in 4 patients (8.9%), and 3 patients (6.7%) died during treatment with posaconazole. The median posaconazole trough concentration was 1.4 mg/L (IQR, 0.8–2.1 mg/L) in patients with a successful treatment (complete or partial response), 1.0 mg/L (IQR, 0.5–1.2 mg/L) in patients with a stable response, and 0.3 mg/L (IQR, 0.2–1.3 mg/L) in patients with treatment failure (fungal disease progression or death) ($P = 0.010$). The ordinal regression analysis showed a significant association of the posaconazole trough concentration with the treatment outcome, when corrected for the age of the patient and the time to recovery of leukocytes. A higher posaconazole concentration ($P = 0.001$) and a lower age of the patient ($P = 0.005$) were associated with a better treatment outcome, whereas recovery of leukocytes was not associated with the outcome (Table 4).

TABLE 4. Ordinal Regression Model of the Relationship of the Posaconazole Exposure With Treatment Outcome

Factor	OR	95% CI	*P*
Posaconazole concentration (mg/L)	22.22	3.40 to 145.33	0.001
Age (yrs)	0.92	0.86 to 0.97	0.005
Recovery of leukocytes (days)	1.00	0.96 to 1.05	0.841

CI, confidence interval; OR, odds ratio.

In 5 patients (20%) in the prophylaxis group and in 8 patients (17.8%) in the treatment group, an attempt to increase the posaconazole concentration was undertaken. In 4 of 5 patients in the prophylaxis group and in 4 of 8 patients in the treatment group, a therapeutic posaconazole concentration was achieved. Successful strategies were a dose increase (4 × 200 mg in the prophylaxis group, 4 × 300 mg and 4 × 400 mg in the treatment group), discontinuation of the PPI, and the start of enteral nutrition/increasing the food intake. In the other 5 patients, the posaconazole concentration remained subtherapeutic after administering posaconazole with an acidic beverage in 3 patients and the discontinuation of a PPI in 2 patients (of which 1 patient had no enteral food intake).

DISCUSSION

This study showed a subtherapeutic posaconazole concentration in 40% of the patients receiving posaconazole prophylaxis and in 44% of the patients receiving posaconazole treatment. Patients with a higher posaconazole trough concentration had a better treatment outcome.

Multiple linear regression analysis showed that posaconazole concentration was significantly associated with the food intake of the patients. Both the lack of enteral nutrition and a liquid diet had a negative effect on the posaconazole concentration, whereby the effect of no enteral nutrition was most powerful, which was in accordance with earlier findings.[11,21,30] The absorption of posaconazole is significantly increased when posaconazole is administered a (high-fat) meal.[6,30] When patients are not able to eat or only eat small amounts of a liquid diet, it is not likely that adequate posaconazole concentrations will be reached.[30] Furthermore, coadministration of posaconazole with a PPI or H_2-antagonist had a negative effect on the posaconazole concentration, due to a reduced absorption secondary to a decrease in gastric acid production, and was in agreement with earlier studies.[11,12,14,15,31,32] Administration of the posaconazole oral suspension to patients who are unable to eat or use a PPI/H_2-antagonist should therefore be avoided. The gastro-resistant tablet formulation of posaconazole that recently entered the market[33] or the intravenous formulation[34] that has recently been approved are more suitable for these patients. The posaconazole exposure of the tablet formulation was not reduced when posaconazole was administered with medication affecting gastric pH in healthy volunteers.[33] However, as for the oral suspension, the absorption of posaconazole from the tablet formulation is affected by food, the posaconazole area under the concentration–time curve increased by 51% when the tablet was administered a high-fat meal (compared with a 3–4 fold increase with the oral suspension).[35] For patients suffering from vomiting or who are unable to eat or tolerate oral medication, the intravenous formulation is the most obvious choice. The presence of diarrhea did not show a relation with the posaconazole exposure in the multiple linear regression analysis. Because the oral suspension of posaconazole is predominantly dissolved in the stomach at low pH,[30,33] the presence of intestinal problems is probably less important for posaconazole absorption. Furthermore, the use of chemotherapy during treatment with posaconazole was negatively associated with

posaconazole exposure. The observed lower posaconazole trough concentration may be the result of a reduced absorption because of mucositis, or possibly mucosal dysfunction, villus atrophy, or damaged microbiota.[11,12] Because posaconazole has a high protein binding of >98%,[36] and half of the patients with chemotherapy had a low albumin concentration, hypoalbuminemia can lead to an increased volume of distribution and an enhanced clearance of the free drug.[8] Hyperhydration during chemotherapy is not likely to explain the lower serum concentrations as posaconazole has a large volume of distribution of 7–25 L/kg.[36] Finally, the posaconazole concentration was associated with the frequency of posaconazole administration in the multiple linear regression analysis. A dose of 200 mg 4 times a day is recommended in the summary of product characteristics of posaconazole, and a dose of 400 mg 2 times a day is suggested as an alternative.[6] Because a dose of 2 times 400 mg gives a lower posaconazole concentration, a more fractionated dose of 4 times 200 mg is a better approach to achieve a sufficient posaconazole exposure. A dose of 2 times daily is possibly an option for patients who receive prolonged courses of posaconazole treatment at home and have a normal food intake and do not use medication that affects gastric pH. A study by Courtney et al[37] demonstrated that the absorption of posaconazole was saturated at a dose of 800 mg. However, this study tested 800 mg as a single dose. Increasing the posaconazole dose to 1200–1600 mg a day in 4 divided doses led to an increased posaconazole trough concentration in 2 patients. This strategy needs to be further studied in patients who receive the oral suspension and have low posaconazole concentrations.

The patients with a successful treatment outcome had a significantly higher posaconazole trough concentration, and there was a positive association of the posaconazole concentration with the treatment outcome. The age of the patient was negatively associated with treatment outcome. Older patients are likely to be more fragile and have more comorbid medical conditions, which can possibly influence the treatment outcome.[38,39] We could not demonstrate an effect of the immune status (for the duration of recovery of leukocytes and for the actual leukocyte count) of the patients on the treatment outcome. Only a single leukocyte count, obtained at the day of the posaconazole sample, was included in the analysis. The immune status of the patient plays a role in the clearance of the infection; however, the influence of the immune status could not be demonstrated with a single leukocyte count for each patient. When including the duration of the recovery of leukocytes in the analysis, we also could not demonstrate the influence of the immune status on the treatment outcome. Because posaconazole was mainly used as salvage treatment, the leukocytes of most patients had already recovered, except for 8 of 70 patients. Overall, response was favorable in 32 patients (71.1%), with a median posaconazole trough concentration of 1.4 mg/L in this patient group. Our results confirm that the posaconazole target concentration of at least 1.25 mg/L for salvage treatment of IA, which was proposed in the study of Walsh et al,[16] is associated with a better outcome. Due to the small amount of patients receiving prophylaxis in our study, we cannot make a statement about the proposed target concentration of 0.7 mg/L for prophylaxis.

A limitation of this study is its retrospective nature, although we expect selection bias to be limited since posaconazole concentrations were measured routinely in our hospital. In addition, we used strict criteria for completeness of the data for analysis and we used the EORTC criteria for the evaluation of the treatment outcome. Due to the retrospective nature of this study, we could not score the grade of the mucositis because this was not routinely scored. We therefore used the presence of diarrhea and chemotherapy during treatment with posaconazole as surrogate markers. Furthermore, we used the first steady-state trough concentration of posaconazole for the analysis. However, these concentrations were representative for the whole treatment course since we visually observed that posaconazole concentrations were stable over time.

Because a large proportion of the patients had a low posaconazole exposure and the exposure was associated with treatment outcome, we believe that TDM has added value for treatment with posaconazole. Posaconazole was used as a salvage treatment in our hospital, which explains the large number of proven cases of IA and the high number of non-Aspergillus infections. In the event that posaconazole is used as salvage therapy for IA because there are few alternative treatments, or when posaconazole is used as treatment for specific and life-threatening IFD, for example, caused by the class of Zygomycetes,[40,41] maximizing the posaconazole exposure is warranted and important for survival. We showed that a favorable outcome can be achieved in salvage therapy with posaconazole in patients with higher posaconazole concentrations. Additionally, posaconazole has been associated with an improved safety profile compared with voriconazole and posaconazole concentration-dependent adverse events have not been identified to date.[42] With the new tablet and intravenous formulation, posaconazole is also suitable for patients with no food intake, absorption problems, and the use of concomitant medication that affects gastric pH. Because the tablet cannot be crushed or chewed, the oral suspension will remain a treatment option for patients who are unable to take tablets, such as patients with dysphagia, which is present in 16%–23% of the general population[43,44] and in up to 51% of critically ill patients.[45] The posaconazole oral suspension can also be used in patient with a nasogastric tube; however, the posaconazole absorption is reduced in these patients and TDM is therefore recommended to ensure sufficient posaconazole exposure. The different posaconazole formulations in combination with TDM can help to ensure sufficient posaconazole exposure and assure the efficacy of the antifungal treatment. A prospective randomized clinical trial should be performed to determine whether therapeutic interventions, to increase the posaconazole exposure, result in an improved treatment outcome.

CONCLUSIONS

Posaconazole exposure was not sufficient in more than 40% of patients at risk of or with IFD and was negatively correlated with the lack of enteral nutrition, vomiting, the use of a PPI/H_2-receptor antagonist, a liquid diet, chemotherapy, and a posaconazole dose frequency of 2 times daily. A higher posaconazole concentration was positively associated with a better treatment outcome. TDM of posaconazole can detect

underexposure in patients at risk of and with IFD and can be helpful in treatment optimization.

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