International Journal of Infectious Diseases 83 (2019) 130–138

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Intravenous and tablet formulation of posaconazole in antifungal therapy and prophylaxis: A retrospective, non-interventional, multicenter analysis of hematological patients treated in tertiary-care hospitals

Sebastian M. Heimann[a], Olaf Penack[b], Werner J. Heinz[c], Tobias Rachow[d], Gerlinde Egerer[e], Johanna Kessel[f], Annika Y. Claßen[a,g], Jörg Janne Vehreschild[a,g,*]

[a] University Hospital of Cologne, Department I of Internal Medicine, Cologne, Germany
[b] Charité University Medicine, Division of Hematology, Oncology and Tumor Immunology, Berlin, Germany
[c] University of Würzburg Medical Center, Med. Clinic II, Würzburg, Germany
[d] Jena University Hospital, Department II of Internal Medicine, Jena, Germany
[e] Heidelberg University Hospital, Department of Hematology, Oncology, and Rheumatology, Heidelberg, Germany
[f] University Hospital of Frankfurt, Department II of Internal Medicine, Infectiology, Frankfurt, Germany
[g] German Center for Infection Research, Partner Site Bonn-Cologne, Cologne, Germany

ARTICLE INFO

Article history:
Received 18 February 2019
Received in revised form 3 April 2019
Accepted 4 April 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Invasive fungal infection
Neutropenia
Posaconazole serum level
Clinical effectiveness
High-risk patient

ABSTRACT

Objectives: Novel formulations (gastro-resistant tablet and intravenous solution) of posaconazole (POS) have been approved in prophylaxis and therapy of invasive fungal diseases (IFDs). Study aim was to analyze treatment strategies and clinical effectiveness.
Methods: We set up a web-based registry on www.ClinicalSurveys.net for documentation of comprehensive data of patients who received novel POS formulations. Data analysis was split into two groups of patients who received novel POS formulations for antifungal prophylaxis (posaconazole prophylaxis group) and antifungal therapy (posaconazole therapy group), respectively.
Results: Overall, 180 patients (151 in the posaconazole prophylaxis group and 29 in the posaconazole therapy group) from six German tertiary care centers and hospitalized between 05/2014 – 03/2016 were observed. Median age was 58 years (range: 19 – 77 years) and the most common risk factor for IFD was chemotherapy (n = 136; 76%). In the posaconazole prophylaxis group and posaconazole therapy group, median POS serum levels at steady-state were 1,068 μg/L (IQR 573–1,498 μg/L) and 904 μg/L (IQR 728–1,550 μg/L), respectively ($P = 0.776$). During antifungal prophylaxis with POS, nine (6%) probable/proven fungal breakthroughs were reported and overall survival rate of hospitalization was 86%. The median overall duration of POS therapy was 18 days (IQR: 7 – 23 days). Fourteen patients (48%) had progressive IFD under POS therapy, of these five patients (36%) died related to or likely related to IFD.
Conclusions: Our study demonstrates clinical effectiveness of antifungal prophylaxis with novel POS formulations. In patients treated for possible/probable/proven IFD, we observed considerable mortality in patients receiving salvage treatment and with infections due to rare fungal species.

Introduction

Posaconazole, a triazole broad-spectrum antifungal agent with activity against many pathogenic fungi, was primarily approved as prophylaxis against invasive fungal diseases (IFDs) in 2005. Clinical trials demonstrated efficacy of posaconazole oral solution compared to fluconazole or itraconazole in patients with hematologic malignancies during neutropenia following chemotherapy or in patients with immunosuppressive treatment of GvHD after receipt of an allogeneic stem-cell transplantation (Cornely et al., 2007; Ullmann et al., 2007). Given the acceptable tolerability and toxicity profile of the drug and an increasing incidence of IFDs (Lass-Florl, 2009), systemic antifungal prophylaxis (SAP) with posaconazole has become a widely used standard to prevent IFDs, which remain associated with high morbidity and mortality rates in hematologic

* Corresponding author at: University Hospital of Cologne, Department I of Internal Medicine, Kerpenerstr. 62, 50937 Köln, Germany.
E-mail address: joerg.vehreschild@uk-koeln.de (J.J. Vehreschild).

https://doi.org/10.1016/j.ijid.2019.04.006

patients (Herbrecht et al., 2012; Neofytos et al., 2009). While SAP with posaconazole adds to the economical burden of prescribing hospitals, management of IFDs is associated with substantial costs (Heimann et al., 2015a; Menzin et al., 2009; Rieger et al., 2012), and recent studies have demonstrated effectiveness regarding clinical outcomes and costs of prophylactic posaconazole (Heimann et al., 2014; Heimann et al., 2015b).

Initially, only posaconazole oral solution became available, which shows a bioavailability limited by gastric pH and intake of high-fat meals (Krishna et al., 2009). Low and very low steady-state serum levels were reported (Dolton et al., 2012). Several recent studies suggest superior pharmacokinetics and a similar safety profile of novel posaconazole formulations (tablet and intravenous solution) (Duarte et al., 2014; Krishna et al., 2012a; Krishna et al., 2012b; Maertens et al., 2014). A first multicenter observational study analyzing 61 hematological patients receiving posaconazole intravenous solution for antifungal prophylaxis and therapy demonstrated clinical efficacy with stable posaconazole serum levels of ≥1,000 μg/L, without any breakthrough IFDs (Jeong et al., 2016). Other studies, including one phase III interventional trial, analyzed the use of posaconazole tablet for antifungal prophylaxis with comparable results attaining target posaconazole serum levels while maintaining a favorable safety and tolerability profile (Cornely et al., 2016; Pham et al., 2016).

We hypothesized that the new formulations would allow safe and stable administration of posaconazole to severely ill patients, improving effectiveness and extending the use to patients who need intensive care or high-dosed treatment for established infections. A retrospective, multicenter study of high-risk patients treated in German tertiary care hospitals was performed to analyze treatment indication, administration route, risk factors, adverse drug reactions, serum concentrations, effectiveness, and outcome of novel posaconazole tablet and intravenous solution in different strategies.

Patients & methods

Study design

The study at hand is a retrospective, non-interventional, web-based, multicenter study conducted in German tertiary care hospitals and was planned and carried out by the academic authors of the University Hospital of Cologne (UHC). For study conduction, we used the ClinicalSurveys.net online-platform, which was set up in cooperation with the Globalpark AG, Hürth, Germany (now QuestBack GmbH, Cologne, Germany).

Patients and definitions

Female and male patients, 18 years of age or older, with a hematological or oncological underlying disease and who received posaconazole tablet and/or intravenous solution for primary prophylaxis or therapy of IFDs for ≥3 days during an inpatient stay between 05/2014 – 03/2016 were included into our study. Patients still on posaconazole at time of study start were excluded and patient follow-up was performed until hospital discharge of the initial inpatient stay during which novel posaconazole formulations were administered. Posaconazole related adverse reactions were assessed in the opinion of the participating investigator, whereby relatedness to posaconazole administration was defined and eligible as proven, probable, possible, unlikely, and not assessable. Assessment of successful antifungal prophylaxis with novel posaconazole formulations was rated based on evidence of possible, probable, and proven IFD (De Pauw et al., 2008). Further assessment of success or failure of antifungal therapy with novel posaconazole formulations were rated by the participating investigators in adherence to the EORTC/MSG criteria by Segal et al. (Segal et al., 2008). Posaconazole steady-state C_{MIN} serum levels >700 μg/L for antifungal prophylaxis and >1,000 μg/L for antifungal therapy were defined as target values (Chau et al., 2014; Lewis et al., 2015).

Data documentation

Documentation of data into electronic case report forms was performed by using the epidemiological research platform www.ClinicalSurveys.net. This platform enables an up-to-date, secure, and fast data entry platform in adherence to good epidemiological practice guidelines. Physicians and academic researchers of the Infectious Disease Working Party of the German Society of Hematology and Medical Oncology (AGIHO/DGHO) were invited to provide retrospective clinical data on patients who received novel posaconazole formulations. Based on inpatient chart-review, the following data items were anonymously documented by the participating investigators after the patient completed treatment: demographics, underlying disease, treatment indication, risk factors for IFD, full antifungal regimen, concurrent medication (interacting drugs), treatment course (e.g. microbiological results, clinical findings, laboratory parameters), duration of inpatient stay (general ward, bone marrow transplant ward, intensive care unit (ICU)), adverse events attributed to posaconazole assessed by the investigator, treatment outcome (e.g. response, failure, breakthrough IFD, treatment switch), overall outcome (alive, death, reason for death), resistance test results of breakthrough IFD, if diagnosed, classification of IFD, and serum levels of novel posaconazole formulations (multiple levels, measured up to seven times during the inpatient stay, were possible to be documented). Central data monitoring and plausibility checking, subsequent to documentation, was performed by the academic authors of the UHC.

Statistical analysis

All completely documented cases were included into the statistical analysis, which was performed using IBM SPSS Statistics software version 23 (IBM Corp., Armonk, NY, USA). Our data analysis was split into two groups of patients who received novel posaconazole formulations for antifungal prophylaxis (posaconazole prophylaxis group) or antifungal therapy (posaconazole therapy group), respectively. With respect to analysis of posaconazole serum levels at steady-state, we additionally analyzed subgroups of patients received posaconazole tablets and intravenous solution for antifungal prophylaxis and therapy, respectively. Furthermore, steady-state levels for patients who received novel posaconazole formulations for therapy and who were treated on ICU for at least 72 h were analyzed separately. For descriptive purposes, median and interquartile range (IQR) as well as mean and standard deviation (SD) were used. Data were tested for normal distribution by using Kolmogorov-Smirnov test. Student's t-test and Mann-Whitney U-test were applied to test significance of normally and non-normally distributed data between patients who received novel posaconazole formulations as prophylaxis or therapy, respectively. A P value <0.05 was considered statistically significant. The observed timeframe for all statistical analyses was from day of hospital admission until discharge or patients' death.

Ethical consideration

The local ethics committee approved the study prior to invitation of other centers to participate and beginning of data documentation (ID approval: 16-071; Ethics Commission of Cologne University`s Faculty of Medicine, University of Cologne,

Cologne, Germany). Additionally, according to §67 (6) of German drug law, our study was registered at competent authorities and organizations of the German healthcare insurances (National Association of Statutory Health Insurance "GKV-Spitzenverband", National Association for Statutory Health Insurance Physicians "Kassenärztliche Bundesvereinigung", Association of German private healthcare insurers "Verband der Privaten Krankenversicherung e.V."), as well as the Federal Institute for Drugs and Medical Devices ("BfArM").

Results

Within the observed timeframe from 05/2014–03/2016, 185 patients from six participating German tertiary care centers (university hospitals of Berlin Charité, Cologne, Frankfurt/Main, Heidelberg, Jena, and Würzburg) were documented in our registry. Five patients were excluded due to incomplete documentation and/or non-fulfillment/fulfillment of in-/exclusion criteria. Out of the remaining 180 patients, 151 (84%) and 29 (16%) patients were included into the posaconazole prophylaxis group and posaconazole therapy group, respectively. Most patients had an acute myeloid leukemia (n = 111; 62%) as primary underlying disease. Chemotherapy (n = 136; 76%), neutropenia defined as a neutrophil count <500/μl (n = 133; 74%), and treatment with immunosuppressants (n = 108; 60%) and/or corticosteroids (n = 91; 51%) were the most important risk factors for IFD. A detailed overview of further patient characteristics is presented in Table 1.

Patients included in the posaconazole prophylaxis group were regularly treated with a dose of 300 mg posaconazole per day, as recommended by current guidelines of the Infectious Diseases Working Party of the German Society for Haematology and Oncology (AGIHO/DGHO) (Mellinghoff et al., 2018). Twenty-two out of 151 patients (15%) received a loading dose of 600 mg/day. However, participating investigators reported nine (6%; 95% CI: 3.0%–11.1%) cases of breakthrough IFD during posaconazole prophylaxis. In the posaconazole therapy group, most patients received posaconazole tablet and/or intravenous formulation as first line therapy (n = 17). Further 12 patients were treated with novel posaconazole formulations for salvage therapy, following first line treatment failure of liposomal amphotericin B (n = 8), voriconazole (n = 2), amphotericin B (n = 1), and liposomal amphotericin B/caspofungin (n = 1). Five patients were treated with liposomal amphotericin B concomitant to posaconazole therapy. All patients were treated with a therapeutic dose of posaconazole of 300 mg per day, whereby six patients (21%) received a loading dose of 600 mg/day. In one patient, therapeutic dose was changed from 300 mg to 600 mg posaconazole per day. As presented in Table 2, increased liver function values was the most common adverse drug reaction with at least possible relationship to posaconazole treatment (n = 4; 2%). Investigators rated antifungal prophylaxis with novel posaconazole formulation as success in 132 out of 151 cases (87%). The success rate in the posaconazole therapy group was 45% (13/29 patients). In the residual patients of the posaconazole therapy group, failure was commonly attributed to progression of mycosis.

Further subgroup analyses with respect to assessment of posaconazole therapy showed success rates for treatment of possible, probable, or proven IFD of 67% (6/9 patients), 29% (2/7 patients), and 38% (5/13 patients), respectively. Furthermore, participating investigators rated posaconazole first line therapy in 53% (9/17 patients) and posaconazole salvage therapy in 33% (4/12 patients) as success. With respect to fungal pathogens identified for therapy of IFD, the highest success rate was documented in therapy of trichosporosis (1/1 patient; 100%) and mucormycosis (4/7 patients; 57%), followed by aspergillosis (8/20 patients; 40%), and fusariosis (0/1 patient; 0%).

Table 1
Patient characteristics (N = 180).

Item	Posaconazole prophylaxis group (n = 151)	Posaconazole therapy group (n = 29)
Age (years); median (range)	58 (19–77)	56 (24–77)
Female gender; n (%)	65 (43)	11 (38)
Hematological underlying disease; n (%)		
- ALL	17 (11)	4 (14)
- AML	103 (68)	8 (28)
- CLL	2 (1)	1 (3)
- CML	0	3 (10)
- MDS	15 (10)	6 (21)
- Non-Hodgkin lymphoma	7 (5)	3 (10)
- Other	7 (5)	4 (14)
Risk factor for IFD; n (%)		
- Age >65 years	26 (17)	7 (24)
- Allogeneic stem cell transplantation	66 (44)	19 (66)
- Autologous stem cell transplantation	1 (<1)	1 (3)
- Chemotherapy	117 (78)	19 (66)
- Hemodialysis	3 (2)	2 (7)
- Mechanical ventilation	10 (7)	11 (38)
- Neutropenia	119 (79)	14 (48)
- Treatment on ICU	23 (15)	13 (45)
- Treatment with immunosuppressives	86 (57)	22 (76)
- Treatment with corticosteroids	70 (46)	21 (72)
Co-medication that potentially may interact with posaconazole treatment; n (%)		
- Cyclosporin A	43 (29)	11 (38)
- H2 antagonists	41 (27)	7 (24)
- Midazolam	5 (3)	3 (10)
- Mitoxantrone	5 (3)	0
- Proton-pump inhibitors	67 (44)	25 (86)
- Sirolimus	6 (4)	3 (10)
- Statins	6 (4)	1 (3)
- Tacrolimus	21 (14)	2 (7)
- Other	5 (3)	1 (3)

ALL; acute lymphocytic leukemia, AML; acute myeloid leukemia, CLL; chronic lymphocytic leukemia, CML; chronic myeloid leukemia, ICU; intensive care unit, IFD; invasive fungal disease, MDS; myelodysplastic syndrome.`

Table 2
Administration route, success rates, adverse drug reactions, and outcome of patients received novel posaconazole formulations.

Item	Posaconazole prophylaxis group (n = 151)	Posaconazole therapy group (n = 29)
Posaconazole administration route; n (%)		
- Patients received only posaconazole tablet	143 (95)	13 (45)
- Patients received only posaconazole iv	2 (1)	11 (38)
- Patients received posaconazole tablet and iv	6 (4)	5 (17)
Duration of posaconazole administration (days); median (IQR)/mean (SD)		
- Tablet	19 (13–26)/23 (20)	5 (0–15)/8 (9)
- iv	0 (0–0)/1 (6)	7 (0–18)/12 (17)
Breakthrough IFD[a]; n (%)		
- Probable aspergillosis	6 (4)	n.a.
- Proven aspergillosis	2 (1)	n.a.
- Proven fusariosis	1 (<1)	n.a.
Indications for posaconazole therapy; n (%)		
- Possible aspergillosis	n.a.	9 (31)
- Probable aspergillosis	n.a.	7 (24)
- Proven aspergillosis	n.a.	4 (14)
- Proven mucormycosis	n.a.	7 (24)
- Proven fusariosis	n.a.	1 (3)
- Proven trichosporosis	n.a.	1 (3)
Posaconazole success rate as rated by the investigator; n (%)		
- Success	132 (87)	13 (45)
- Failure	19 (13)	16 (55)
Reason for failure as rated by the investigator; n (%)		
- Atypical pneumonia	10 (7)	n.a.
- Breakthrough IFD	9 (6)	n.a.
- Progression of mycosis	n.a.	14 (48)
- Other	0	2 (7)
Adverse drug reaction with at least possible relationship to posaconazole treatment; n (%)		
- Increased liver function values	4 (3)	–
- Nausea	2 (1)	–
- Psychosis	–	1 (3)
- Vertigo	1 (<1)	–
Overall hospital length of stay (days); median (IQR)/mean (SD)	37 (26–52)/46 (31)	52 (32–84)/65 (38)
End of hospitalization; n (%)[b]		
- Death	21 (14)	14 (48)
- Transfer to another hospital/rehabilitation center	6 (4)	3 (10)
- Regular hospital discharge	124 (82)	12 (41)

IFD; invasive fungal disease, iv; intravenous, IQR; interquartile range, n.a.; not applicable, SD; standard deviation.
[a] Based on EORTC/MSG criteria (De Pauw et al., 2008).
[b] Inconsistent sum due to rounding errors.

Serum levels of novel posaconazole formulations during antifungal prophylaxis and therapy

Two out of six participating centers performed TDM based on standardized protocols, and in the majority of patients steady-state was measured at day 4–6 (Dekkers et al., 2016). Posaconazole serum levels were documented in 40 patients in the posaconazole prophylaxis group (37 and three patients were treated with posaconazole tablets and intravenous solution, respectively) and 19 patients in the posaconazole therapy group (11 and eight patients were treated with posaconazole tablets and intravenous solution, respectively). Out of the 19 patients in the posaconazole therapy group, serum levels of seven patients who received posaconazole tablets and/or intravenous solution during an ICU stay were separately analyzed. Results for non-normally distributed posaconazole serum levels at steady-state are presented in Figure 1. The median posaconazole serum levels at steady-state of the predefined subgroups were as follows: patients who received posaconazole tablets for antifungal prophylaxis 1,122 μg/L (IQR 539 – 1,579 μg/L), patients who received posaconazole intravenous solution for antifungal prophylaxis 664 μg/L (IQR 561–692 μg/L), patients who received posaconazole tablets for antifungal therapy 858 μg/L (IQR 547–1,407 μg/L), and patients who received posaconazole intravenous solution for antifungal therapy 1,111 μg/L (IQR 868–1,709 μg/L). Patients who received posaconazole tablet and/or intravenous solution for antifungal therapy and were treated in ICU had a median posaconazole serum level at steady-state of 1,407 μg/L (IQR 881–1,713 μg/L). Looking at the co-medication of these ICU patients, cyclosporin A (n = 3), H2 antagonists (n = 2), midazolam (n = 2), and sirolimus (n = 2) were the most common agents that potentially may interact with posaconazole treatment. The median overall posaconazole serum level at steady-state in the posaconazole prophylaxis group and posaconazole therapy group was 1,067 μg/L (IQR 574–1,498 μg/L) and 904 μg/L (IQR 728–1,550 μg/L), respectively (P = 0.776).

With respect to the number of patients who achieved targeted posaconazole serum levels at steady-state, 25/37 patients (68%) and 0/3 patients (0%) who received posaconazole tablets and posaconazole intravenous solution for antifungal prophylaxis reached values >700 μg/L, respectively. Five out of 11 patients (45%) who received posaconazole tablets and 4/8 patients (50%) who received posaconazole intravenous solution for antifungal therapy achieved predefined values at steady-state >1,000 μg/L. Furthermore, more patients treated in the ICU with posaconazole tablets and/or intravenous solution for antifungal therapy achieved levels >1,000 μg/L at steady-state (5/7 patients; 71%).

Patients with probable/proven fungal breakthroughs during antifungal prophylaxis or failure of antifungal therapy

Patients with probable/proven fungal breakthrough infections during posaconazole prophylaxis (n = 9; 6%) and failure of posaconazole therapy (n = 16; 55%) as rated by the participating investigators were analyzed separately. Detailed information

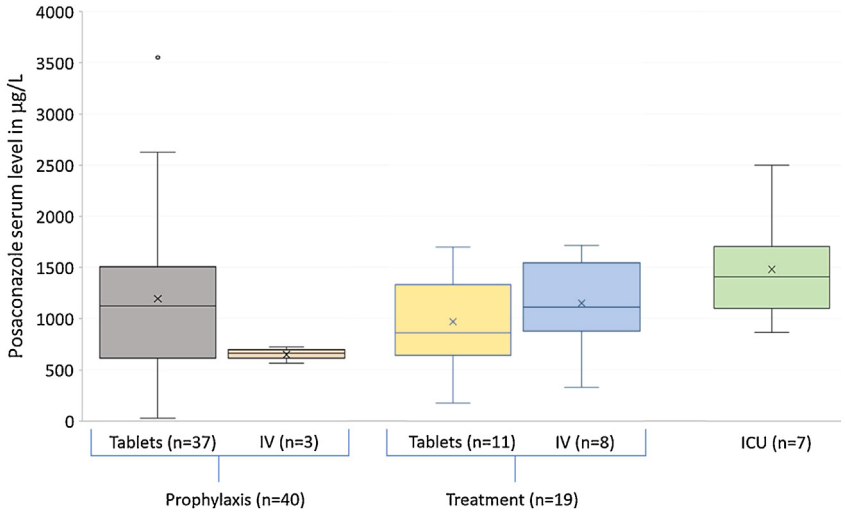

Figure 1. Posaconazole C_{MIN} serum levels measured at steady-state during antifungal prophylaxis and therapy (Box-whisker plot). y-axis: posaconazole serum level in µg/L; x within the boxes represents the mean values; ICU; intensive care unit, IV; intravenous.

regarding patient characteristics, antifungal treatment, posaconazole serum levels, and outcome are given in Tables 3 and 4. Probable/proven invasive aspergillosis (n = 8; 89%) was the most common breakthrough IFD during posaconazole prophylaxis and one case of proven fusariosis (n = 1; 11%) was documented (see Table 3). The median duration of posaconazole tablets administered was 21 days (IQR: 13–28 days). Posaconazole serum concentrations were measured in 3/9 patients (33%) and all patients reached the target value of >700 µg/L at steady-state. After cessation of posaconazole prophylaxis, 7/9 patients (78%) switched to antifungal therapy, resulting in clinical improvement of IFD in 5/9 patients (71%). The overall survival rate of patients with probable/proven fungal breakthrough was 44% (n = 4) and no adverse events attributed to posaconazole occurred within this subgroup.

With respect to the subgroup of patients with failure of posaconazole therapy, 12/16 patients (75%) with possible/probable/proven invasive aspergillosis, 3/16 patients (19%) with proven invasive mucormycosis, and 1/16 patient (6%) with proven invasive fusariosis were documented by the participating investigators (see Table 4). Eight out of 16 patients (50%) were treated with posaconazole as salvage therapy, predominately administered after failure of first line therapy with liposomal amphotericin B (n = 6; 75%). Ten patients (63%) received at least one dose of

Table 3
Patients received posaconazole as antifungal prophylaxis and developed probable/proven fungal breakthrough (n = 9).

Patient no.	Underlying disease	Age	Sex	Risk factor aSCT	Risk factor GvHD	POS formulation	Duration of POS (days)	POS serum level at steady-state	Breakthrough IFD[a]	Site	Antifungal agent switch following POS	Response to antifungal switch	Patient outcome
1	AML	48	Female	Yes	No	Tablet	17	2,147 µg/L	Proven fusariosis	Skin	LAmB	Clinical improvement of IFD	Death (not IFD related)
2	ALL	52	Male	No	No	Tablet	21	882 µg/L	Proven aspergillosis	Lung	LAmB	Clinical improvement of IFD	Alive
3	AML	48	Female	No	No	Tablet	19	2,363 µg/L	Probable aspergillosis	Lung	LAmB	Clinical improvement of IFD	Alive
4	Base of tongue cancer	71	Male	No	No	Tablet	5	n.a.	Probable aspergillosis	Lung	Voriconazole	Clinical improvement of IFD	Alive
5	ALL	53	Female	Yes	Yes	Tablet	26	n.a.	Probable aspergillosis	Lung	AmB, Voriconazole	Clinical improvement of IFD	Alive
6	AML	67	Male	Yes	Yes	Tablet	21	n.a.	Probable aspergillosis	Lung	No	–	Death (likely IFD related)
7	AML	60	Female	No	No	Tablet	30	n.a.	Probable aspergillosis	Lung	LAmB	Clinical worsening of IFD	Death (likely IFD related)
8	AML	55	Male	No	No	Tablet & iv	34 & 2	n.a.	Proven aspergillosis	Lung	Caspofungin	Clinical worsening of IFD	Death (IFD related)
9	AML	73	Male	No	No	Tablet	9	n.a.	Probable aspergillosis	Lung	No	–	Death (likely IFD related)

ALL; acute lymphocytic leukemia, AmB; amphotericin B; AML; acute myeloid leukemia, aSCT; allogeneic stem cell transplantation, GvHD; graft-versus-host disease, IFD; invasive fungal disease, iv; intravenous, LAmB; liposomal amphotericin B, n.a.; not available, POS; posaconazole.

[a] Rated based on EORTC/MSG criteria (De Pauw et al., 2008).

Table 4
Patients with failure of posaconazole therapy (n = 16).

Patient no.	Underlying disease	Age	Sex	Underwent aSCT	Risk factor GvHD	Type of IFD[a,b]	POS therapy	Antifungal agent prior to POS	POS formulation	Duration of POS (days)	POS serum level at steady-state	Reason for failure of POS therapy	Antifungal agent switch following POS	Response to antifungal agent switch	Patient outcome
1	AML	48	Male	No	No	Proven mucormycosis	Salvage	LAmB	iv	8	1,600 μg/L	Progression	No	–	Unknown, transferred to another hospital
2	Myelofibrosis	71	Female	No	No	Possible aspergillosis	First line	–	Tablet	18	390 μg/L	Progression	LAmB	Clinical improvement of IFD	Alive
3	ALL	71	Female	Yes	Yes	Probable aspergillosis	First line	–	Tablet	8	728 μg/L	Progression	No	–	Death (likely IFD related)
4	ALL	44	Male	No	No	Proven fusariosis	Salvage	LAmB	iv	7	n.a.	Progression	LAmB	Clinical worsening of IFD	Death (not IFD related)
5	AML	66	Male	No	No	Possible aspergillosis	Salvage	LAmB	Tablet	23	1,407 μg/L	Progression	LAmB	Clinical worsening of IFD	Death (not IFD related)
6	MDS	77	Male	No	No	Possible aspergillosis	Salvage	Voriconazole	iv & tablet	2 & 14	854 μg/L	Progression	No	–	Unknown, transferred to another hospital
7	NHL	44	Male	No	No	Probable aspergillosis	Salvage	AmB	Tablet	11	1,191 μg/L	Progression	No	–	Death (IFD related)
8	MDS	37	Male	Yes	Yes	Proven mucormycosis	Salvage	LAmB	iv	7	n.a.	Progression	No	–	Death (not IFD related)
9	NHL	53	Male	No	No	Proven aspergillosis	First line	–	Tablet	19	n.a.	Progression	LAmB	Clinical improvement of IFD	Death (likely IFD related)
10	MDS	58	Female	Yes	No	Probable aspergillosis	First line	–	Tablet & iv	4 & 66	1,695 μg/L	Detection of galactomannan antigen in serum at day of discharge	No	–	Unknown, transferred to a rehabilitation center
11	AML	55	Female	Yes	No	Probable aspergillosis	First line	–	iv	15	1,713 μg/L	Psychotic disorder under POS	LAmB	Clinical improvement of IFD	Death (not IFD related)
12	NHL	60	Male	Yes	No	Proven mucormycosis	First line	–	iv	9	2,498 μg/L	Progression	LAmB	Clinical worsening of IFD	Death (likely IFD related)
13	MDS	72	Male	Yes	Yes	Proven aspergillosis	First line	–	iv	19	547 μg/L	Progression	No	–	Death (not IFD related)
14	MDS	52	Male	Yes	Yes	Probable aspergillosis	Salvage	LAmB	iv	19	1,318 μg/L	Progression	LAmB	Clinical worsening of IFD	Death (not IFD related)
15	MDS	27	Female	Yes	Yes	Proven aspergillosis	Salvage	LAmB	Tablet & iv	5 & 55	881 μg/L	Progression	No	–	Death (not IFD related)
16	CML	65	Male	Yes	Yes	Proven aspergillosis	First line	–	Tablet	6	n.a.	Progression	AmB	Clinical worsening of IFD	Death (likely IFD related)

ALL; acute lymphocytic leukemia, AmB; amphotericin B; AML; acute myeloid leukemia, aSCT; allogeneic stem cell transplantation, CML; chronic myeloid leukemia, GvHD; graft-versus-host disease, IFD; invasive fungal disease, iv; intravenous, LAmB; liposomal amphotericin B, MDS; myelodysplastic syndrome, NHL; non-Hodgkin lymphoma, n.a.; not available, POS; posaconazole.

[a] Rated based on EORTC/MSG criteria (De Pauw et al., 2008).

[b] All possible/probable/proven IFDs were diagnosed at lung (Patient no. 1: lung, disseminated).

intravenous posaconazole. In one of these patients, adverse events attributed to intravenous posaconazole were documented (patient no. 11 developed a psychotic disorder, resulting in cessation of posaconazole). The median duration of posaconazole tablets and intravenous solution administered was 11 days (IQR: 6–19 days) and 9 days (IQR: 7–19 days), respectively. Furthermore, posaconazole serum levels of 12/16 patients (75%) could be analyzed, of whom five patients (42%) did not reach the target value of >1,000 μg/L at steady-state (patient no. 2, 3, 6, 13, 15). In case of antifungal agent switch following posaconazole therapy, antifungal treatment was continued with liposomal amphotericin B in 7/8 patients (88%), resulting in clinical improvement of IFD in three patients (43%). At the end of hospitalization, 5/16 patients (31%) died related to or likely related to IFD.

Discussion

To our knowledge, the study at hand is the first analysis evaluating data of adult hematological/oncological patients outside the controlled environment of a clinical trial with respect to safety, efficacy, and feasibility of antifungal prophylaxis and therapy of IFDs with novel posaconazole formulations (gastro-resistant tablet and intravenous solution) in Europe.

Looking at the TDM in antifungal prophylaxis and therapy of novel posaconazole formulations, current consensus guidelines recommend a target serum level of >700 μg/L and >1,000 μg/L for prophylaxis and therapy, respectively (Chau et al., 2014; Lewis et al., 2015). Our data demonstrates stable median posaconazole serum levels at steady-state of 1,067 μg/L (IQR 574–1,498 μg/L) for antifungal prophylaxis and 904 μg/L (IQR 728–1,550 μg/L) for antifungal therapy. These results are in line with several studies in patients with hematological/oncological underlying diseases reaching these targeted exposure ranges (Cornely et al., 2016; Cumpston et al., 2015; Jeong et al., 2016; Pham et al., 2016). Nevertheless, the rate of patients who achieved the targeted posaconazole serum levels at steady state is comparable to a study by Miceli et al. (2015), but lower compared to other published data (Durani et al., 2015; Liebenstein et al., 2018). Another study by Chin et al. reported a rate of only 44% of patients who reached stable posaconazole serum levels ≥1,000 μg/L in antifungal therapy, whereby outcome was unfortunately not reported (Chin et al., 2017). Interestingly, highest mean posaconazole serum levels at steady-state of patients included into our study were measured for antifungal therapy of patients treated on an ICU. This result is noteworthy because recently published studies, analyzing critically ill patients, demonstrated serum levels of posaconazole oral solution below target values (Ray et al., 2011; Storzinger et al., 2012). This may have been caused by drug-drug interactions between posaconazole and other drugs administered during the ICU stay, which were not part of this analysis.

Additionally, our data analysis suggests efficacy of novel posaconazole formulations, especially in antifungal prophylaxis. Out of 151 patients who received antifungal prophylaxis, a moderate number of nine (6%) breakthrough IFDs were reported by the participating investigators. This result is also within the range of breakthrough IFDs in other studies, reporting rates during posaconazole prophylaxis with novel formulations between 0–15% (Belling et al., 2017; Chin et al., 2017; Cumpston et al., 2015; Jeong et al., 2016; Tverdek et al., 2017), probably reflecting different exposure of patients to mold in various hospital settings and heterogeneity in patient-based risk factors.

With respect to patients who received posaconazole therapy of IFDs (n = 29), our study reports a success rate of 45%. Progression of mycosis was the most important factor for treatment failure. It must be considered that 12 out of 29 patients (41%) received novel posaconazole formulations as salvage-therapy, generally referring to antifungal treatment in patients intolerant or refractory to first-line therapy. Most patients included into our study received liposomal amphotericin B as first line therapy prior to posaconazole salvage-therapy. In this context of failure of liposomal amphotericin B as first line therapy, a high rate of morbidity and mortality is known, whereby patients who received posaconazole oral solution as salvage therapy showed improved outcome compared to controls (Raad et al., 2008; Walsh et al., 2007). Additionally, nine cases (31%) of rare proven mucormycosis, fusariosis, and trichosporosis were included in the therapy group, well known for high morbidity, mortality, and treatment costs (Heimann et al., 2019; Menzin et al., 2009; Seidel et al., 2017). Nevertheless, the failure rate as reported by the participating investigators is higher than those in previously reported studies (Jeong et al., 2016; Kim et al., 2016; Yi et al., 2017). The high mortality rate in this patient population underlines the urgent need of appropriate empiric and targeted antifungal therapy with respect to both, clinical outcome and associated costs (Zilberberg et al., 2010).

Furthermore, our study demonstrates only a small number of adverse drug reactions rated as at least possibly associated with novel posaconazole formulations, which is comparable to other published data (Belling et al., 2017; Jeong et al., 2016; Kim et al., 2016). However, a study by Pham et al. reported a relatively high rate of hepatotoxity of >10% of the observed patient population who received posaconazole tablet for prophylaxis and therapy of IFDs (Pham et al., 2016). A further phase 3 trial by Cornely et al. showed a relatively high rate of nausea (11%) and diarrhea (8%) as treatment related adverse events (Cornely et al., 2016). Based on the used methodology, it is plausible that the same effects may have occurred in our study patients, but were not rated as related to posaconazole by the investigators due to comorbidities and comedication as other likely causes.

Several limitations of our study should be noted. Because of the retrospective study design, participating investigators were not blinded. Furthermore, cause-effect relationship between the administration of novel posaconazole formulations and e.g. adverse drug reactions cannot be assessed as in randomized clinical trials. Additionally, medical record documentation and/or measures of antifungal patient management were different between the participating centers. For example, TDM analysis of novel posaconazole formulations is limited because not all patients had measured serum levels. However, we do not see any center effect with respect to our study results. As a subgroup of particular interest, only a small number of patients treated with novel posaconazole formulations as first line therapy was included into the study, meaning that interpretation of these data is, unfortunately, limited. Nevertheless, compared to the current literature, our study gives a comprehensive insight in patient characteristics, type and duration of posaconazole treatment, posaconazole serum levels at steady-state, and overall outcome of patients rated as failure of posaconazole therapy.

Despite the above-mentioned limitations, our multicenter, non-interventional study demonstrates that novel posaconazole formulations show a safety and efficacy profile, which is comparable to recently published data of posaconazole oral solution. Additionally, similar overall hospital length of stay and duration of antifungal prophylaxis could be shown in a phase IV study of real-life patient data (Vehreschild et al., 2010). Advantages of the new formulations are once-daily dosing, reliable pharmacokinetics including administration without high-fat meals, and availability of an intravenous solution for critically ill patients, who might be unable to take posaconazole oral solution and/or tablets. Cost-effectiveness seems to be a further advantage of novel posaconazole formulations compared to conventional prophylaxis regimens (Camara et al., 2017; Grau et al., 2018), although

additional analyses are required from different healthcare settings. Nevertheless, further prospective studies are needed to explore optimization of antifungal therapy and reduce overall morbidity and mortality as well as treatment costs.

Authorship

All authors materially participated in the research (acquisition and documentation of data) and article preparation (interpretation of data and critical reading). Study conception & design, statistical analysis, and preparation of the manuscript was performed by S.M. H. and J.J.V. All authors have approved the final version of the article for publication.

Funding

The study was supported by an unrestricted research grant from MSD Sharp & Dohme GmbH. It was designed, planned, and performed by the academic authors of the UHC.

Declaration/conflict of interest

S.M.H. has received research and travel grants from Astellas and Merck, research grants from Basilea, Gilead, and 3M and travel grants from Pfizer, received lecture honoraria from Astellas and Merck, and is a consultant to Basilea, Gilead, and Merck. O.P. has received honoraria and travel support from Astellas, Gilead, Jazz, MSD, Neovii Biotech and Pfizer. He has received research support from Bio Rad, Gilead, Jazz, Neovii Biotech, Pierre Fabre, Sanofi and Takeda. He is member of the advisory board to Alexion, Jazz, Gilead and MSD. W.J. H. received research grants from MSD Sharp & Dohme/Merck and Pfizer; serves on the speakers' bureaus of Alexion, Astellas, Basilea, Bristol-Myers Squibb, Gilead Sciences, Janssen, MSD Sharp & Dohme, and Pfizer; and received travel grants from Alexion, Astellas, Lilly, MSD Sharp & Dohme, Novartis and Pfizer. J.K. received travel grants from Astellas and Gilead Sciences. A.Y.L. has received lecture honoraria from MSD. J.J.V. has personal fees from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, Deutsches Zentrum für Infektionsforschung, Uniklinik Freiburg/Kongress und Kommunikation, Akademie für Infektionsmedizin, Universität Manchester, Deutsche Gesellschaft für Infektiologie, Ärztekammer Nordrhein, Uniklinik Aachen, Back Bay Strategies, Deutsche Gesellschaft für Innere Medizin and grants from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, Deutsches Zentrum für Infektionsforschung, Bundesministerium für Bildung und Forschung. G.E. and T.R. declares no declarations of interest.

Acknowledgements

The authors of the UHC would like to thank all contributed persons of participated centers, especially Sandra Fuhrmann (UHC), Martina Gronkowski and Annedore Gisbert (Heidelberg University Hospital).

References

Belling M, Kanate AS, Shillingburg A, Lu X, Wen S, Shah N, et al. Evaluation of serum posaconazole concentrations in patients with hematological malignancies receiving posaconazole suspension compared to the delayed-release tablet formulation. Leuk Res Treat 2017;2017:3460892.

Camara R, Gozalbo I, Jurado M, Sanz J, Aragon B, Grau S. Cost-effectiveness of posaconazole tablets for invasive fungal infections prevention in acute myelogenous leukemia or myelodysplastic syndrome patients in Spain. Adv Ther 2017;34(9):2104–19.

Chau MM, Kong DC, van Hal SJ, Urbancic K, Trubiano JA, Cassumbhoy M, et al. Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy, 2014. Intern Med J 2014;44(12b):1364–88.

Chin A, Pergam SA, Fredricks DN, Hoofnagle AN, Baker KK, Jain R. Evaluation of posaconazole serum concentrations from delayed-release tablets in patients at high risk for fungal infections. Antimicrob Agents Chemother 2017;61(10).

Cornely OA, Duarte RF, Haider S, Chandrasekar P, Helfgott D, Jimenez JL, et al. Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. J Antimicrob Chemother 2016;71 (3):718–26.

Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356(4):348–59.

Cumpston A, Caddell R, Shillingburg A, Lu X, Wen S, Hamadani M, et al. Superior serum concentrations with posaconazole delayed-release tablets compared to suspension formulation in hematological malignancies. Antimicrob Agents Chemother 2015;59(8):4424–8.

De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease 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. Clin Infect Dis 2008;46 (12):1813–21.

Dekkers BGJ, Bakker M, van der Elst KCM, Sturkenboom MGG, Veringa A, Span LFR, et al. Therapeutic drug monitoring of posaconazole: an update. Curr Fungal Infect Rep 2016;10:51–61.

Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ. Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. Antimicrob Agents Chemother 2012;56 (11):5503–10.

Duarte RF, Lopez-Jimenez J, Cornely OA, Laverdiere M, Helfgott D, Haider S, et al. Phase 1b study of new posaconazole tablet for prevention of invasive fungal infections in high-risk patients with neutropenia. Antimicrob Agents Chemother 2014;58(10):5758–65.

Durani U, Tosh PK, Barreto JN, Estes LL, Jannetto PJ, Tande AJ. Retrospective comparison of posaconazole levels in patients taking the delayed-release tablet versus the oral suspension. Antimicrob Agents Chemother 2015;59(8):4914–8.

Grau S, Camara R, Jurado M, Sanz J, Aragon B, Gozalbo I. Cost-effectiveness of posaconazole tablets versus fluconazole as prophylaxis for invasive fungal diseases in patients with graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Eur J Health Econ 2018;19(4):627–36.

Heimann SM, Cornely OA, Vehreschild MJ, Glossmann J, Kochanek M, Kreuzer KA, et al. Treatment cost development of patients undergoing remission induction chemotherapy: a pharmacoeconomic analysis before and after introduction of posaconazole prophylaxis. Mycoses 2014;57(2):90–7.

Heimann SM, Cornely OA, Wisplinghoff H, Kochanek M, Stippel D, Padosch SA, et al. Candidemia in the intensive care unit: analysis of direct treatment costs and clinical outcome in patients treated with echinocandins or fluconazole. Eur J Clin Microbiol Infect Dis 2015a;34(2):331–8.

Heimann SM, Vehreschild MJ, Cornely OA, Franke B, von Bergwelt-Baildon M, Wisplinghoff H, et al. A cost and resource utilization analysis of micafungin bridging for hemato-oncological high-risk patients undergoing allogeneic stem cell transplantation. Eur J Haematol 2015b;94(6):526–31.

Heimann SM, Vehreschild MJ, Cornely OA, Heinz WJ, Grüner B, Silling G, et al. Healthcare burden of probable and proven invasive mucormycosis: a multicenter cost-of-illness analysis of patients treated in tertiary care hospitals between 2003–2016. J Hosp Infect 2019;101(3):339–46.

Herbrecht R, Caillot D, Cordonnier C, Auvrignon A, Thiebaut A, Brethon B, et al. Indications and outcomes of antifungal therapy in French patients with haematological conditions or recipients of haematopoietic stem cell transplantation. J Antimicrob Chemother 2012;67(11):2731–8.

Jeong W, Haywood P, Shanmuganathan N, Lindsay J, Urbancic K, Ananda-Rajah MR, et al. Safety, clinical effectiveness and trough plasma concentrations of intravenous posaconazole in patients with haematological malignancies and/or undergoing allogeneic haematopoietic stem cell transplantation: off-trial experience. J Antimicrob Chemother 2016;71(12):3540–7.

Kim JH, Benefield RJ, Ditolla K. Utilization of posaconazole oral suspension or delayed-released tablet salvage treatment for invasive fungal infection. Mycoses 2016;59(11):726–33.

Krishna G, Ma L, Martinho M, O'Mara E. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrob Agents Chemother 2012a;56 (8):4196–201.

Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. J Antimicrob Chemother 2012b;67(11):2725–30.

Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother 2009;53(3):958–66.

Lass-Florl C. The changing face of epidemiology of invasive fungal disease in Europe. Mycoses 2009;52(3):197–205.

Lewis R, Brüggemann R, Padoin C, Maertens J, Marchetti O, Groll A, Johnson E, Arendrup M. Triazole Antifungal Therapeutic Drug Monitoring Presented at ECIL 6 Meeting. Available from:. 2015. https://www.ebmt.org/Contents/Resources/Library/ECIL/Documents/2015%20ECIL6/ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf.

Liebenstein TK, Widmer KM, Fallon MJ. Retrospective analysis of goal drug level attainment of posaconazole for invasive fungal infection prophylaxis in patients

with acute myeloid leukemia pre- and post-switch to tablet formulation. J Oncol Pharm Pract 2018;24(8):599–603.
Maertens J, Cornely OA, Ullmann AJ, Heinz WJ, Krishna G, Patino H, et al. Phase 1B study of the pharmacokinetics and safety of posaconazole intravenous solution in patients at risk for invasive fungal disease. Antimicrob Agents Chemother 2014;58(7):3610–7.
Mellinghoff SC, Panse J, Alakel N, Behre G, Buchheidt D, Christopeit M, et al. Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). Ann Hematol 2018;97(2):197–207.
Menzin J, Meyers JL, Friedman M, Perfect JR, Langston AA, Danna RP, et al. Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. Am J Health Syst Pharm 2009;66(19):1711–7.
Miceli MH, Perissinotti AJ, Kauffman CA, Couriel DR. Serum posaconazole levels among haematological cancer patients taking extended release tablets is affected by body weight and diarrhoea: single centre retrospective analysis. Mycoses 2015;58(7):432–6.
Neofytos D, Horn D, Anaissie E, Steinbach W, Olyaei A, Fishman J, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis 2009;48(3):265–73.
Pham AN, Bubalo JS, Lewis 2nd JS. Comparison of posaconazole serum concentrations from haematological cancer patients on posaconazole tablet and oral suspension for treatment and prevention of invasive fungal infections. Mycoses 2016;59(4):226–33.
Raad II, Hanna HA, Boktour M, Jiang Y, Torres HA, Afif C, et al. Novel antifungal agents as salvage therapy for invasive aspergillosis in patients with hematologic malignancies: posaconazole compared with high-dose lipid formulations of amphotericin B alone or in combination with caspofungin. Leukemia 2008;22(3):496–503.
Ray J, Campbell L, Rudham S, Nguyen Q, Marriott D. Posaconazole plasma concentrations in critically ill patients. Ther Drug Monit 2011;33(4):387–92.
Rieger CT, Cornely OA, Hoppe-Tichy T, Kiehl M, Knoth H, Thalheimer M, et al. Treatment cost of invasive fungal disease (Ifd) in patients with acute myelogenous leukaemia (Aml) or myelodysplastic syndrome (Mds) in German hospitals. Mycoses 2012;55(6):514–20.
Segal BH, Herbrecht R, Stevens DA, Ostrosky-Zeichner L, Sobel J, Viscoli C, et al. Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. Clin Infect Dis 2008;47(5):674–83.
Seidel D, Duran Graeff LA, Vehreschild M, Wisplinghoff H, Ziegler M, Vehreschild JJ, et al. Fungi scope—global emerging fungal infection registry. Mycoses 2017;60(8):508–16.
Storzinger D, Borghorst S, Hofer S, Busch CJ, Lichtenstern C, Hempel G, et al. Plasma concentrations of posaconazole administered via nasogastric tube in patients in a surgical intensive care unit. Antimicrob Agents Chemother 2012;56(8):4468–70.
Tverdek FP, Heo ST, Aitken SL, Granwehr B, Kontoyiannis DP. Real-life assessment of the safety and effectiveness of the new tablet and intravenous formulations of posaconazole in the prophylaxis of invasive fungal infections via analysis of 343 courses. Antimicrob Agents Chemother 2017;61(8).
Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007;356(4):335–47.
Vehreschild JJ, Ruping MJ, Wisplinghoff H, Farowski F, Steinbach A, Sims R, et al. Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. J Antimicrob Chemother 2010;65(7):1466–71.
Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007;44(1):2–12.
Yi WM, Schoeppler KE, Jaeger J, Mueller SW, MacLaren R, Fish DN, et al. Voriconazole and posaconazole therapeutic drug monitoring: a retrospective study. Ann Clin Microbiol Antimicrob 2017;16(1):60.
Zilberberg MD, Kollef MH, Arnold H, Labelle A, Micek ST, Kothari S, et al. Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study. BMC Infect Dis 2010;10:150.