Intravenous and Tablet Formulation of Posaconazole in Antifungal Therapy and Prophylaxis: A Retrospective, Non-Interventional, Multicenter Analysis of Patients Treated in German Tertiary-Care Hospitals

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Abstract

Background
Novel formulations (gastro-resistant tablet and intravenous solution) of posaconazole (POS) have been approved in prophylaxis and therapy of invasive fungal diseases (IFDs). The aim of this multicenter non-interventional study was to analyze treatment strategies and clinical effectiveness of these new options.

Methods
We set up a registry on the science platform www.ClinicalSurveys.net and members of the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO) were invited to provide clinical data on 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
One hundred eighty hospitalized patients (151 in the posaconazole prophylaxis group and 29 in the posaconazole therapy group) from six German tertiary care centers treated between 07/2014 – 03/2016 were included into our analysis. Seventy-six patients were female (42%) and median age was 58 years (range: 19 – 77 years). Most patients (n= 111; 62%) had an acute myeloid leukemia as primary underlying disease. In the posaconazole prophylaxis group and posaconazole therapy group, mean POS serum levels at steady-state were 1,154 µg/L (n= 40; 95% CI: 911 – 1,396 µg/L) and 1,097 µg/L (n= 19; 95% CI: 817 – 1,378 µg/L), respectively (P= 0.776). In the posaconazole prophylaxis group, nine (6%) probable/proven fungal breakthroughs were reported. In the posaconazole therapy group, 17 and 12 patients received POS as first line therapy and salvage therapy, respectively. Most frequent indications were possible (n= 9) and probable (n= 7) mucormycosis. The median overall duration of POS therapy was 18 days (IQR 7 – 23 days). Thirteen patients (45%) had progressive IFD under treatment with novel POS formulations.

Conclusions
Our study demonstrates clinical effectiveness of antifungal prophylaxis with novel POS formulations. In patients treated for possible/probable/proven IFD, the observed tolerability and overall mortality was comparable to previous studies with other antifungals in similar patient population.

Introduction

Posaconazole (POS), a triazole broad-spectrum antifungal agent with activity against many pathogenic fungi, was primarily approved as prophylaxis against invasive fungal diseases (IFDs) in 2006 [1,2].

Given the acceptable tolerability and toxicity profile of the drug and an increasing number of IFDs [3], systemic antifungal prophylaxis with POS has become a widely used standard to prevent IFDs, which remain associated with high morbidity and mortality in hematologic patients [4,5].

Initially, only POS oral solution became available on the market, which shows a bioavailability limited by gastric pH and intake of high-fat meals [6]. Low and very low steady state serum levels were reported [7].

Several recent studies suggest superior pharmacokinetics and pharmacodynamics of novel POS formulations (tablet and intravenous solution) [8-11].

Further studies demonstrated clinical efficacy, stable POS serum levels ≥1,000 µg/L, and a favorable safety and tolerability of novel POS formulations [12-14].

We hypothesized that the new formulations would allow safe and stable administration of POS to severely ill patients, improving effectiveness and extending the use to patients needing intensive care or high-dosed treatment for established infections.

Primary aims were to analyze treatment indication, administration route, risk factors, adverse drug reactions, serum concentrations, effectiveness, and outcome of novel POS tablet and intravenous solution in different strategies.

Methods

Study design
Retrospective, non-interventional, web-based, multicenter study conducted in German tertiary care hospitals.

For study conduction, we used the Clinical Surveys.net online-platform, which was set up in cooperation with the Global park 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 who received POS tablet and/or intravenous solution for prophylaxis or therapy of IFDs for ≥3 days during an inpatient stay between 05/2014 – 03/2016 were included into our study.

POS related adverse reactions were assessed by the participating investigator.

Assessment of successful antifungal prophylaxis with novel POS formulations was rated based on evidence of possible, probable, and proven IFD [15].

Further assessment of success or failure of antifungal therapy with novel POS formulations were rated by the participating investigators in adherence to the EORTC/MSG criteria [16].

POS steady-state $C_{ss,ss}$ serum levels >700 µg/L for antifungal prophylaxis and >1,000 µg/L for antifungal therapy were defined as target values [17, 18].

Data documentation
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 POS formulations.

Central data monitoring and plausibility checking, subsequent to documentation, was performed by the academic authors of the UHC.

Statistical analysis
IBM SPSS Statistics software version 23 (IBM Corp., Armonk, NY, USA) was used. Data analysis was split into two groups of patients who received novel POS formulations for antifungal prophylaxis (posaconazole prophylaxis group) or antifungal therapy (posaconazole therapy group), respectively.

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, Heidelberg, Jena, and Würzburg) were documented into our registry:

- Five patients were excluded due to incomplete documentation and/or non-fulfillment/fulfillment of in-/exclusion criteria
- 151 (84%) and 29 (16%) patients patients were included into the POS prophylaxis group and POS therapy group, respectively
- All patients were treated with a daily dose of 300mg as recommended by national guidelines [31]
- In the POS therapy group, 17 and 12 patients received POS as first line therapy and salvage therapy, respectively
- Patients were treated with POS as 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)
- Increased liver function values (n= 4), nausea (n= 3), and dyspnea (n= 2) were the most documented adverse drug reactions with at least possible relationship to POS treatment
- In the POS prophylaxis group, the overall survival rate of patients with probable/proven fungal breakthrough was 44% (n=4)
- In the group of patients with failure of POS therapy (16/29), five patients (31%) died related to or likely related to IFD

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)
Hemato-oncological 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 lymp.	7 (5)	3 (10)
- Other	7 (5)	4 (14)
Risk factor for IFD; n (%)		
- Age >65 years	26 (17)	7 (24)
- Allogeneic SCT	66 (44)	19 (66)
- Autologous SCT	1 (<1)	1 (3)
- Chemotherapy	117 (78)	19 (66)
- Hemodialysis	3 (2)	2 (7)
- Mech. 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)
Comedication that potentially may interact with POS; 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)
End of hospitalization; n (%)		
- Death	21 (14)	14 (48)
- Transfer to another hospital/rehab. center	6 (4)	3 (10)
- Regular	124 (82)	12 (41)

*Based on EORTC/MSG criteria [15]
†Based on EORTC/MSG criteria [16]

Table 2: Administration route, success rate, and outcome of patients received novel POS formulations

Item	Posaconazole prophylaxis group (n= 151)	Posaconazole therapy group (n=29)
POS administration route; n (%)		
- Patients received only POS tablet	143 (95)	13 (45)
- Patients received only POS iv	2 (1)	11 (38)
- Patients received POS tablet and iv	6 (4)	5 (17)
Duration of POS administration (days); median (IQR) / mean (95% CI)		
- Tablet	19 (13 – 26) / 23 (20 – 27)	5 (0 – 15) / 8 (4 – 11)
- iv	0 (0 – 0) / 1 (0 – 2)	7 (0 – 18) / 12 (5 – 18)
POS 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 IFD	n.a.	13 (45)
- Other	0	3 (10)
Overall LOS (days); Median (IQR) / Mean (95% CI)	37 (26 – 52) / 46 (41 – 51)	52 (32 – 84) / 65 (50 – 79)

Figure 1: Breakthrough IFDs during POS prophylaxis

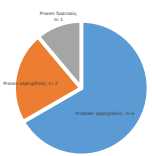


Figure 2: Indication for POS therapy

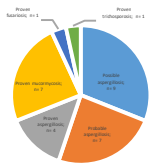
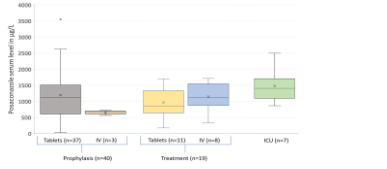


Figure 3: Posaconazole $C_{ss,ss}$ serum levels measured at steady-state during antifungal prophylaxis and therapy (Box-whisker plot)



Y-axis: Posaconazole serum level in µg/L; x within the boxes represents the mean values; ICU, intensive care unit; i.v., intravenous; p.o., per os

Discussion

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 POS formulations (gastro-resistant tablet and intravenous solution) in Europe.

POS serum levels
Our data demonstrates stable mean POS serum levels at steady-state of 1,154 µg/L (95% CI: 911 – 1,396 µg/L) for antifungal prophylaxis and 1,097 µg/L (95% CI: 817 – 1,378 µg/L) for antifungal therapy (see figure 3).

These results are in line with several studies in patients with hematological/oncological underlying diseases also reaching these targeted exposure ranges [12-14, 19].

Highest mean POS serum levels at steady-state were measured for antifungal therapy of patients treated on an ICU (see figure 3). This result is noteworthy because recently published studies demonstrated serum levels of POS oral solution below target values [20, 21].

Safety
Our study demonstrated only a small number of adverse drug reactions rated as at least possibly associated with novel POS formulations. Compared to other studies we can see very similar results, especially with respect to liver and renal function abnormalities [22-24].

Antifungal prophylaxis
Our data analysis suggests efficacy of novel POS 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 (see figure 1).

This result is also within the range of breakthrough IFDs in other studies, reporting a rate of breakthrough IFDs during posaconazole prophylaxis with novel formulations between 0-15% [19, 22, 23, 25, 26].

Antifungal therapy
With respect to patients who received POS therapy of IFDs (n= 29), our study reports a success rate of 45%. Progression of mycosis was the most important factor for treatment failure (see table 2).

It must be considered that 12 out of 29 patients (41%) received novel POS 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 POS salvage-therapy. In this context a high rate of morbidity and mortality is known, whereby patients who received POS oral solution as salvage therapy showed improved outcome compared to controls [27, 28].

The failure rate (e.g. progression of mycosis), as reported by the participating investigators, is higher than those in previously reported studies [22, 24, 29].

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 [30].

Limitations of the study
Because of the retrospective study design, participating investigators were not blinded.

Cause-effect relationship between the administration of novel POS formulations and e.g. adverse drug reactions cannot be assessed as in randomized clinical trials.

TDM analysis of novel POS 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 POS formulations as first line therapy was included into the study, meaning that interpretation of these data is, unfortunately, limited.

References

1. Cornely OA, Maertens J, Winston DJ et al. N Engl J Med, 356(4), 348-359 (2007) **2.** Ullmann AJ, Lipton JH, Vesole DH et al. N Engl J Med, 356(4), 335-347 (2007) **3.** Lass-Flörl C. Mycoses, 52(3), 197-205 (2009) **4.** Herbrecht R, Caillot D, Cordonnier C et al. J Antimicrob Chemother, 67(11), 2731-2738 (2012) **5.** Naeyhus D, Horn D, Aneiase E et al. Clin Infect Dis, 48(1), 265-273 (2009) **6.** Krishna G, Moton A, Ma L, Medlock MM, Mcleod J. Antimicrob Agents Chemother, 53(1), 958-966 (2009) **7.** Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, Mclachlan AJ. Antimicrob Agents Chemother, 56(11), 5508-5510 (2012) **8.** Krishna G, Ma L, Martinho M, O'Mara E. Antimicrob Agents Chemother, 56(8), 4196-4201 (2012) **9.** Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. J Antimicrob Chemother, 67(11), 2725-2730 (2012) **10.** Maertens J, Cornely OA, Ullmann AJ et al. Antimicrob Agents Chemother, 58(7), 3610-3617 (2014) **11.** Duarte RF, Lopez-Jimenez J, Cornely OA et al. Antimicrob Agents Chemother, 58(10), 5758-5765 (2014) **12.** Jeong W, Heyward P, Shanmuganathan N et al. J Antimicrob Chemother, 71(12), 3540-3547 (2016) **13.** Cornely OA, Duarte RF, Haider S et al. J Antimicrob Chemother, 71(3), 718-726 (2016) **14.** Pham AN, Bulatis JS, Lewis JS, 2nd. Mycoses, 59(4), 226-233 (2016) **15.** De Pauw B, Walsh TJ, Donnelly JP et al. Clin Infect Dis, 46(12), 1813-1821 (2008) **16.** Segal BH, Herbrecht R, Stevens DA et al. Clin Infect Dis, 47(5), 674-683 (2008) **17.** Chau MM, Kong DC, van Hal SJ et al. Intern Med J, 44(12b), 1364-1368 (2014) **18.** Lewis L, Bräggemann R, Padoin C, Maertens J, Marchetti O, Groll A, Johnson E, Arendrup M. Triazole Antifungal Therapeutic Drug Monitoring presented at ECIL 6 meeting. **19.** Cumpston A, Caddell R, Shillingburg A et al. Antimicrob Agents Chemother, 59(8), 4424-4428 (2015) **20.** Ray J, Campbell L, Rudham S, Nguyen Q, Marriott D. Ther Drug Monit, 33(4), 387-392 (2011) **21.** Stoninger D, Berghorst S, Hafer S et al. Antimicrob Agents Chemother, 56(8), 4468-4470 (2012) **22.** Jeong W, Heyward P, Shanmuganathan N et al. J Antimicrob Chemother, 71(12), 3540-3547 (2016) **23.** Belling M, Kanate AS, Shillingburg A et al. Leuk Res Treatment, 2017, 3460892 (2017) **24.** Kim JH, Benefield RJ, Ditolla K. Mycoses, 59(11), 726-733 (2016) **25.** Chin A, Pergam SA, Fredricks DN, Hoenigle AN, Baker RE, Jain R. Antimicrob Agents Chemother, 61(10) (2017) **26.** Tverdek FP, Hare ST, Aitken SL, Granwehr B, Kontoyiannis DP. Antimicrob Agents Chemother, 61(8) (2017) **27.** Walsh TJ, Raad I, Patterson TF et al. Clin Infect Dis, 44(1), 2-12 (2007) **28.** Raad, II, Hanna HA, Boktour M et al. Leukemia, 22(3), 496-503 (2008) **29.** Yi WM, Schoeppler KE, Jaeger J et al. Am Clin Microbiol Antimicrob, 16(1), 60 (2017) **30.** Zilberberg MD, Kollef MH, Arnold H et al. BMC Infect Dis, 10, 150 (2010) **31.** Mellinghoff SC, Panse J, Alakel N et al. Ann Hematol, 97(2), 197-207 (2018)

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