**Co-administration of steroids is a risk factor for low trough concentrations of posaconazole delayed-released tablets in adult patients with hematological malignancies**

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**Abstract**

**Background**: Current guidelines recommend the use of posaconazole as primary prophylaxis to prevent invasive fungal infections (IFIs) in acute myeloid leukemia patients (AML) and in those undergoing HSCT with GVHD.

**Objectives:** To determine clinical variables associated with posaconazole exposure among adult patients with hematological malignancies who received posaconazole tablets for prophylaxis of IFIs.

#### Methods: Single-center retrospective study that included adult patients with hematological malignancies who received posaconazole delayed-release tablets for prophylaxis of IFIs after induction chemotherapy for acute leukemia or GVHD complicating HSCT in the period January 2016 - December 2017.

**Results:** Sixty-six consecutive patients with 176 posaconazole Cmin were included for evaluation in the study. Subtherapeutic posaconazole concentrations (< 0.7 mg/L) were observed at least once in 33.3 % of patients (22/66), and overall in 17.0% of TDM episodes (30/176). At multilevel linear regression, use of proton pump inhibitors (PPIs) (*p* = 0.008), use of intermediate or high dose steroids (> 0.7 mg/kg/daily) (*p* = 0.022) and male gender (*p* = 0.025) were significantly associated with decreased Cmin, whereas time from starting therapy (*p* = 0.032) was associated with increased Cmin in our patient population.

#### Conclusions: Posaconazole exposure during treatment with delayed-released tablet formulation may be affected by the use of intermediate or high dose steroids.

**Introduction**

Invasive fungal infections (IFIs) represent a major cause of morbidity and mortality among patients with acute leukemia who receive induction chemotherapy and among hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD).[1](#_ENREF_1) Recently, in this patient population the prevalence of IFIs has been reported to be 11.3%.[2](#_ENREF_2) The most common IFIs are represented by invasive aspergillosis (43-58% of IFIs), followed by invasive candidiasis (28-32.5% of IFIs) and zygomycosis (2.6-8% of FIFs), according to type of HSCT, underling disease and phase of treatment.[3](#_ENREF_3), [4](#_ENREF_4)

Current guidelines recommend the use of posaconazole as primary prophylaxis for the prevention of IFI in acute myeloid leukemia (AML) and for patients undergoing HSCT with GVHD.[5](#_ENREF_5) Posaconazole is a second-generation triazole agent, which is currently available in two oral formulations: a suspension and delayed-release tablets. The oral suspension has saturable absorption, that is improved by food or a high fat meal, and whose oral bioavailability may be decreased by the co-administration of gastric acid-lowering agents.[6](#_ENREF_6), [7](#_ENREF_7) A highly variable pharmacokinetic profile of posaconazole oral suspension often leads to suboptimal concentrations of posaconazole with an attendant risk of breakthrough IFIs.[8](#_ENREF_8)

A delayed-release tablet formulation was developed with the intention of overcoming some of the limitations of oral posaconazole suspension. Although the new formulation has a generally improved oral bioavailability, there are conflicting results in terms of posaconazole serum trough concentrations (Cmin) observed in real-life following administration of the standard 300 mg once daily dose. Some authors have documented better drug exposure [9](#_ENREF_9) that is independent of the regimen, clinical status and/or co-medications;[10](#_ENREF_10), [11](#_ENREF_11) whereas, others showed that attainment of therapeutic concentrations may still be problematic.[12](#_ENREF_12), [13](#_ENREF_13) The variability of posaconazole exposure may be caused by erratic absorption as well as enhanced clearance (CL). Furthermore, posaconazole is very highly bound to plasma proteins and its elimination is mediated by the UDP-glucuronosyltransferase (UGT) 1A4.[14](#_ENREF_14) Accordingly, hypoalbuminemia and/or the presence of factors that may upregulate the activity UGT1A4 may lead to an increase of posaconazole CL. A recent case report suggested that in a patient with acute myeloid leukemia receiving posaconazole as delayed-release tablets hypoalbuminemia and hyperbilirubinemia may have been responsible for an enhancement of posaconazole CL, leading to subtherapeutic concentrations.[15](#_ENREF_15)

 The aim of this single-center retrospective study was to determine risk factors associated with subtherapeutic concentrations of posaconazole among adult patients with hematological malignancies who received posaconazole tablets for prophylaxis of IFIs.

**Methods**

**Study Design**. This was a single-center retrospective study that included adult patients with hematological malignancies who were admitted at the Clinic of Hematology, Santa Maria della Misericordia University Hospital of Udine, Italy in the period January 2016 - December 2017. All patients received posaconazole delayed-release tablets for prophylaxis of IFIs after induction chemotherapy for acute leukemia or GVHD complicating HSCT. Therapeutic drug monitoring (TDM) of posaconazole was performed on all patients. The study was approved by the Regional Ethics Committee. Written informed consent was waived due to the retrospective and observational nature of the investigation.

 All the patients started therapy with an initial loading dose of 300 mg every 12h on day 1 and continued in the subsequent days with a maintenance dose of 300 mg once daily until the first episode of TDM, which was performed at steady-state (after 4 or more days from treatment initiation). The target Cmin was > 0.7 mg/L according to current recommendations for prophylaxis.[16](#_ENREF_16), [17](#_ENREF_17) Posaconazole concentrations were estimated using a previously described liquid chromatography-tandem mass spectrometry analytic method.[18](#_ENREF_18) The intra- and inter-day coefficients of variation were < 5% and the lower limit of detection was 0.1 mg/L.

 Data on demographic and clinical characteristics (age, weight, height, gender, underlying hematological disease, presence of acute or chronic GVHD, duration of posaconazole treatment), laboratory parameters (alanine aminotransferase, serum albumin, serum creatinine, serum bilirubin concentrations) and on all co-medications (with dosages) were retrieved for each patient at baseline and at each TDM episode. The following risk factors potentially affecting posaconazole absorption were collected for evaluation: use of a proton pump inhibitor (PPI), presence of mucositis and diarrhea.[13](#_ENREF_13) Additionally, the following risk factors potentially affecting the clearance of posaconazole were collected: presence of hypoalbuminemia, presence of hyperbilirubinemia[15](#_ENREF_15) and use of intermediate or high dose steroids (defined as > 0.7 mg/kg/day).

 **Statistical analysis**. The Kolmogorov Smirnov test was used to assess whether clinical data were normally distributed. The mean ± standard deviation, median and 25th-75th interquartile ranges (IQR) were used for descriptive statistics. Intra-individual and inter-individual variability of posaconazole Cmin was assessed by calculating the median of the coefficient of variation (CV) of all the Cmin measured in a single patient and the CV of the average Cmin of each patient, respectively. Univariate and multivariate linear mixed-effect model (with a random effect for patient accounting for correlation amongst repeated measurements of the same subjects) were performed to identify the independent predictors of posaconazole Cmin. Multivariate stepwise backward analysis included all variables significant at *p* ≤ 0.200 in the univariate analysis. Kruskal-Wallis test was used to compare continuous data among groups. Bonferroni correction for multiple comparisons was applied, as appropriate. A *p*-value < 0.05 was required for statistical significance. All statistical analysis and plotting were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

Sixty-six consecutive patients were included in the study. Patient demographics and clinical characteristics are summarized in Table 1. Males accounted for 65.2% (43/66) of the population. Median (IQR) age and body weight of the cohort were 58 years (49 - 64 years) and 75 kg (62 - 88.8 kg), respectively. The most frequent underlying disease was AML (46/66; 69.7 %) and 28 patients (28/66, 42.4%) underwent HSCT. Most of the patients received posaconazole prophylaxis after induction chemotherapy (48/66; 72.7 %). Fifty-one patients (51/66, 77.3%) were co-treated with PPI (pantoprazole, n = 48, median [IQR] dose of 40 [20-40] mg daily; omeprazole, n = 2, median [IQR] doses of 60 [50-60] mg daily; rabeprazole, n = 1, dose of 40 mg daily). Eighteen patients (18/66, 27.3%) received co-treatment with intermediate or high dose steroids (methylprednisolone, n = 14 patients, median [IQR] doses of 90 [80-140] mg daily; prednisone, n = 4 patients, median [IQR] doses of 75 [52.5-95] mg daily).

Overall, 176 posaconazole Cmin were included for evaluation. Median (IQR) posaconazole Cmin was 1.17 mg/L (0.86 – 1.59 mg/L), but concentrations ranged between 0.17 and 4.53 mg/L after fixed dosing. The overall CV% of posaconazole Cmin was 50.9%. Inter-individual and intra-individual variability were 42.7% and 32.6%, respectively. Low posaconazole concentrations (Cmin < 0.7 mg/L) was observed in 33.3 % of patients (22/66; 13 cotreated with PPI, 1 intermediate or high dose steroids), and with an overall frequency of 17.0% of TDM episodes (30/176). Dosage escalation of up to 400 mg daily was required in 9/66 patients (13.6%). Breakthrough possible IFIs were documented in two patients. The posaconazole Cmin at day 5 was 1.52 and 1.74 mg/L.

Figure 1 summarizes distributions of posaconazole Cmin in relation to the duration of treatment among the studied patients. Overall, a statistically significant progressive increase of posaconazole Cmin was observed in relation to the duration of treatment (*p* = 0.005). After correction for multiple comparisons, significant differences of median posaconazole Cmin were observed between week 1 and 4 (Cmin of 0.9 vs. 1.27 mg/L, *p* = 0.007) and week 1 and > 4 (Cmin of 0.9 vs. 1.37 mg/L, *p* < 0.001).

Univariate and multivariate mixed-effect linear regression analysis of the clinical variables associated with posaconazole Cmin are reported in Table 2. Multivariate analysis showed that in patients receiving posaconazole tablets, male gender, co-treatment with PPIs or with steroids was associated with a 28%, 45% or 44% reduction in Cmin. Conversely, time from starting therapy was associated with a minimal (0.03%) increase in Cmin in our patient population. The presence of acute myeloid leukemia, HSCT and mucositis of any grade were not found to be significantly associated with posaconazole exposure in our patient cohort.

Figure 2 compares box and whisker plots of posaconazole Cmin between patients co-treated with PPIs (n = 113 observations), those co-treated with intermediate or high dose steroids (n = 9 observations), those co-treated with PPIs plus intermediate or high dose steroids (PPI+ steroids, n = 20 observations), and those who did not receive these co-treatments (controls, n = 34 observations). Median posaconazole Cmin was significantly lower among patients receiving these co-treatments (*p* < 0.001). Following post-hoc analysis, each group of co-treatment had significantly lower median Cmin than controls (PPIs + steroids vs. controls, 0.74 vs. 1.52 mg/L, *p* < 0.00; steroids vs. controls, 1.01 vs. 1.52 mg/L, *p* = 0.003; PPIs vs. controls, 1.10 vs. 1.52 mg/L, *p* < 0.001).

**Discussion**

The use of posaconazole is recommended for patients with hematological malignancies who receive induction chemotherapy or for HSCT recipients with GVHD requiring immunosuppression.[5](#_ENREF_5) A target Cmin > 0.7 mg/L is advocated.[17](#_ENREF_17) Approximately 50 % of patients receiving standard dose of the oral suspension (200 mg q8h) achieve this target.[17](#_ENREF_17) In contrast, higher rates of target attainment are observed with the use of the delayed-released tablet formulation (80-90%).[9](#_ENREF_9), [19](#_ENREF_19), [20](#_ENREF_20)

Marked variability in posaconazole exposure is still observed in PK studies of the delayed-released tablet formulation.[12](#_ENREF_12), [13](#_ENREF_13), [21-23](#_ENREF_21) Patients receiving 300 mg daily have a median posaconazole Cmin concentration of 1.08-1.89 mg/L at steady state with a concentration range of < 0.1-7.89 mg/L. Our data are consistent with these observations. We observed a median Cmin 1.17 mg/L, with a range of 0.17-4.53 mg/L and an overall CV of 50.4%. The extent of inter- and intra-patient variability of 43.9% and 29.3%, respectively, is similar to that previously reported.[21](#_ENREF_21) Furthermore, the proportion of subtherapeutic Cmin is comparable (17.0% in our study vs. 15.4% and 29% in other studies).[12](#_ENREF_12), [22](#_ENREF_22)

Although the new delayed-release formulation seems to be less prone to suboptimal absorption, the pharmacokinetic variability of posaconazole may depend also on other factors that affect clearance. Identification of clinical factors associated with posaconazole exposure is of great clinical concern, as posaconazole underexposure was associated with the occurrence of breakthrough IFIs both in experimental animal models[24](#_ENREF_24) and in some clinical studies.[7](#_ENREF_7), [25](#_ENREF_25)

Our study shows that the use of PPI and/or the use of steroids at dosages ≥ 0.7 mg/kg daily are significant risk factors for drug underexposure. These findings are consistent with those reported previously. A retrospective study conducted among 157 patients with hematological malignancies treated with posaconazole tablets showed that at multivariate analysis the use of PPI (*p* = 0.015), the presence of diarrhea (*p* < 0.001), low baseline albumin concentrations (*p* = 0.011) and body weight > 90 kg (*p* = 0.047) were risk factors for subtherapeutic posaconazole concentrations.[13](#_ENREF_13) Body weight and diarrhea were significant risk factors for drug underexposure also in an earlier retrospective investigation.[12](#_ENREF_12) Conversely, no significant relationship between the use of PPI and the risk of suboptimal exposure was observed among hematological patients receiving posaconazole tablets vs. oral suspension,[19](#_ENREF_19) in lung transplanted patients[26](#_ENREF_26) and in healthy volunteers receiving a 400 mg daily dose.[10](#_ENREF_10) The presence of gastro-intestinal mucositis is not associated with the risk of posaconazole underexposure during the use of delayed-release tablets in two previous studies.[22](#_ENREF_22), [23](#_ENREF_23)

The most novel aspect of our analysis was the finding that corticosteroids may be risk factor for posaconazole underexposure in patients with hematological malignancy. Posaconazole is metabolized by UGT1A4.[14](#_ENREF_14) Intermediate or high dose steroids may have up-regulated the activity of this enzyme and resulted in increased clearance. This assumption is based on previous studies showing that UGT1A4 may be up-regulated by steroids (17β-estradiol) in pregnancy leading to an increased elimination of lamotrigine, which is a substrate for UGT1A4.[27](#_ENREF_27) UGT1A4 contains Pregnane-X-Receptor (PXR) response elements, which by acting as xenobiotic receptor for a wide range of compounds, including steroids, may induce the glucuronidation process.[27](#_ENREF_27), [28](#_ENREF_28) This hypothesis is supported by a retrospective analysis conducted among 52 hematologic patients by Chin et al.[22](#_ENREF_22) These authors found that at multivariate analysis patients not receiving treatment for GVHD [including also high-dose steroids (either ≥ 1 mg/kg/day for patients with acute GVHD or ≥ 0.8 mg/kg every other day for patients with chronic GVHD] had higher odds of achieving a therapeutic serum level than those receiving GVHD treatment (OR, 5.85; 95% CI, 1.09 to 31.5; P = 0.04).[22](#_ENREF_22) This suggests that TDM of posaconazole tablet could be especially important for patients receiving both PPI and steroids.

We recognize that our study has several limitations. The retrospective nature and the limited sample size may limit the generalizability of the findings and further prospective studies are required to confirm our findings. Nevertheless, our work suggests that posaconazole exposure during treatment with delayed-released tablet formulation may be affected by the use of steroids. A prospective clinical study is warranted to confirm our findings.

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| **Table 1.** Patient demographics and posaconazole treatment  |
| Total number of patients | 66 |
| Age (years) | 58 (49 - 64) |
| Gender (M/F) | 43/23 |
| Body weight (kg) | 75.0 (62.0 - 88.8) |
| Albumin (g/L) | 34.7 (31.4 - 37.0) |
| Total bilirubin (mg/dL) | 0.84 (0.58 - 1.37) |
| Alanine-aminotransferase (IU/L) | 38.0 (24.0 - 64.0) |
| Underlying disease |  |
|  | AML | 46 (69.7) |
|  | ALL | 5 (7.6) |
|  | Lymphoma/Chronic Lymphoproliferative Diseases | 8 (12.1) |
|  | MM | 3 (4.5) |
|  | MDS/Chronic Myeloproliferative Diseases | 4 (6.1) |
| Number of HSCTIndications for posaconazole | 28 |
|  | Prophylaxis after induction chemotherapy | 48 (72.7) |
|  | Prophylaxis for GVHD | 18 (27.3) |
| Posaconazole treatment |  |
|  | Dose (mg)  | 300 (300-300) |
|  | Total number of Cmin | 176 |
|  | Cmin (mg/L) | 1.17 (0.86 – 1.59) |
|  | Number of TDM instances  | 2 (1 - 3) |
|  | Time (days) to first TDM assessment | 6 (4 - 10) |
|  | Cmin (mg/L) at first TDM assessment | 0.93 (0.68 – 1.33) |
| Clinical outcome |  |
|  | Successful prophylaxis  | 61 (92.5) |
|  | Dead for other reasons | 3 (4.5) |
|  | Fungal infection (Possible) | 2 (3.0) |
| ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MM, multiple myeloma; TDM, therapeutic drug monitoring. Data for continuous variables are presented as median (IQR) or as median (min-max)°, and data for dichotomous variables are presented as number (%). |

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| **Table 2.** Univariate and multivariate mixed-effect linear regression analysis of clinical variables associated with posaconazole tablet Cmin (n=176) |
| Variables | Univariate analysis |  | Multivariate analysis |
| Unstandardized β-coefficient (95% CI ) | *p* |  | Unstandardized β-coefficient (95% CI ) | *p* |
| Age (years) | 0.003 (-0.008, 0.014) | 0.586 |  | - | - |
| Weight (kg) | -0.003 (-0.009, 0.004) | 0.413 |  | - | - |
| Male | -0.240 (-0.495, 0.014) | 0.063 |  | **-0.284 (-0.532, -0.036)** | **0.025** |
| Dose/kg daily (mg) | 0.082 (-0.020, 0.184) | 0.136 |  | 0.054 (-0.042, 0.151) | 0.264 |
| Days from starting therapy | 0.002 (0.000, 0.005) | 0.029 |  | **0.003 (0.000, 0.005)** | **0.032** |
| Albumin (g/L) | 0.024 (0.004, 0.045) | 0.021 |  | 0.013 (-0.007, 0.033) | 0.184 |
| Bilirubin (mg/dL) | -0.033 (-0.205, 0.138) | 0.698 |  | - | - |
| AML | -0.019 (-0.301, 0.264) | 0.894 |  | - | - |
| HSCT | 0.182 (-0.067, 0.431) | 0.149 |  | 0.164 (-0.104, 0.432) | 0.226 |
| Mucositis | 0.036 (-0.246, 0.319) | 0.798 |  | - | - |
| Co-treatment with PPI | -0.426 (-0.658, -0.193) | 0.008 |  | **-0.447 (-0.689, -0.204)** | **0.008** |
| Co-treatment with steroids (> 0.7 mg/kg/daily) | -0.349 (-0.633, -0.064) | 0.045 |  | **-0.439 (-0.729, -0.149)** | **0.022** |
| AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; PPI, proton pump inhibitors |

**Figure Legend**

**Figure 1.** Beeswarm plot of the distribution of posaconazole trough concentrations (n = 176) following administration of posaconazole tablets in hematologic patients, in relation to week of treatment. Solid lines identify median and 25th-75th percentiles within each group. The dashed line identifies posaconazole target level for prophylaxis (Cmin > 0.7 mg/L) of fungal infections. A *p*-value = 0.005 was obtained at Kruskal-Wallis test. A significant difference after *post-hoc* Bonferroni correction was observed between week 1 and week 4 (*p* = 0.007) and week 1 and week >4 (*p* < 0.001).

**Figure 2.** Box (median and 25th-75th percentiles) and whiskers (5th-95th percentiles) plot of posaconazole trough concentrations (Cmin) following administration of posaconazole tablets in hematologic patients receiving no interacting co-treatments (Controls; 34 observations in 20 patients), in those receiving proton pump inhibitors (PPIs; 113 observations in 43 patients), in those receiving intermediate or high dose steroids (> 0.7 mg/kg daily) (Steroids; 9 observations in 5 patients) and in those receiving proton pump inhibitors plus intermediate or high dose steroids (PPIs+ steroids; 20 observations in 13 patients). The dashed line identifies posaconazole target levels for prophylaxis (Cmin > 0.7 mg/L) of fungal infections. A *p*-value < 0.001 was obtained at Kruskal-Wallis test. A significant difference after post*-hoc* Bonferroni correction was observed between Controls and PPIs (*p* < 0.001), Controls and Steroids (*p* = 0.003) and Controls and PPIs+ Steroids (*p* < 0.001).

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