Tolerability of isavuconazole after posaconazole toxicity in leukemia patients

Adam J. DiPippo, PharmD, BCOP (1); Caitlin R. Rausch, PharmD, BCOP (1); Dimitrios P. Kontoyiannis, MD, ScD, FIDSA (2)

(1) Division of Pharmacy (2) Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston, TX

Adam J. DiPippo, PharmD, BCOP
ajdipippo@mdanderson.org

Dimitrios P. Kontoyiannis, MD, ScD, FIDSA
dkontoyi@mdanderson.org

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BACKGROUND

- Posaconazole (PCZ) is widely used for prevention and treatment of invasive fungal infections (IFIs) in adult leukemia patients due to its broad antifungal spectrum.
- However, issues with PCZ tolerability can result in treatment interruption or discontinuation.
- Isavuconazole (ISA) has a similar spectrum of activity to PCZ, and has a relatively lower incidence of hepatotoxicity compared to voriconazole in clinical studies.
- Given previous reports suggesting a lack of cross-sensitivity between liver toxicity and different azole antifungals, ISA may be a viable option in the setting of PCZ toxicity.
- However, there is currently no data describing real-world usage of ISA after PCZ toxicity.

OBJECTIVE

- To describe the safety and tolerability of ISA after PCZ toxicity in adult leukemia patients.

METHODS

- Retrospective cohort review of all adult patients (≥ 18 years of age) with leukemia being treated at The University of Texas MD Anderson Cancer Center.
- Time frame of interest was March 2015 to November 2017. Updated analysis includes a total of 23 identified patients.
- Included patients received ≥ 7 days of 372 mg of ISA (intravenous or oral) within 48 hours of PCZ discontinuation.
- Laboratory markers of toxicity include total bilirubin (T. bili), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and QTc interval.
- Toxicity markers were collected at five time points: prior to PCZ, at switch to ISA, two weeks after ISA, four weeks after ISA, and last date of ISA therapy.
- All toxicity was graded utilizing Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

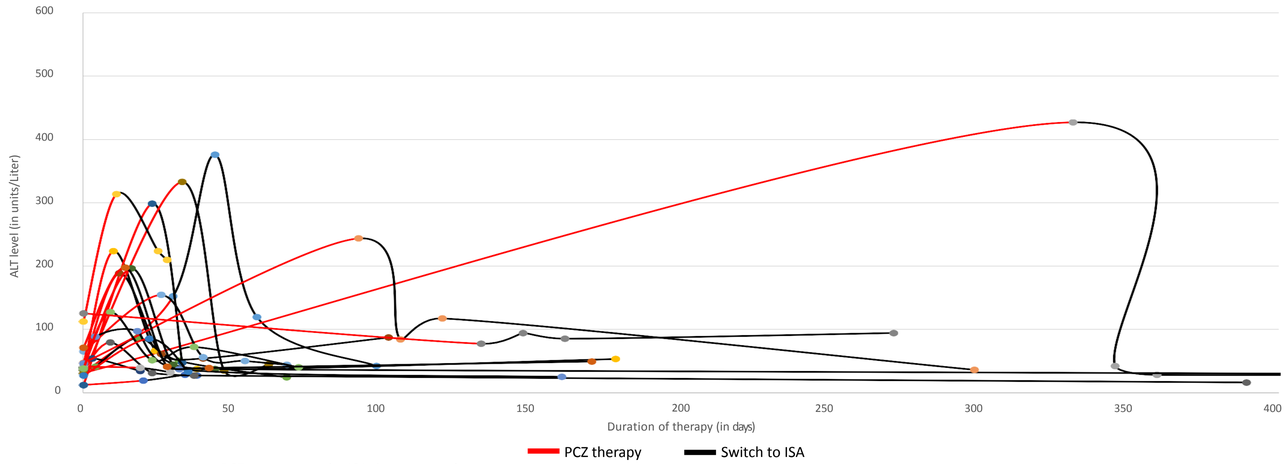
RESULTS

Table 1. Baseline Characteristics

Characteristic (N=23)		
Age (years)	67 (23-84)	
Gender—n (%)		
Male	15 (65)	
Female	8 (35)	
Diagnosis—n (%)		
AML	20 (88)	
ALL	1 (4)	
CMML	1 (4)	
MDS	1 (4)	
Disease Status—n (%)		
Induction	4 (17)	
Relapsed or refractory	16 (70)	
Post allogeneic SCT	3 (13)	
Number of days on PCZ treatment	16 (3-331)	
Number of days on ISA treatment	63 (9-388)$^{\delta}$	
Active chemotherapy treatment$^{\alpha}$	22 (96)	
Absolute neutrophil count$^{\Omega}$ (K/uL)—n (%)		
>1000	6 (26)	
500-1000	1 (4)	
100-500	6 (26)	
<100	10 (43)	
Duration of neutropenia$^{\Omega}$--n (%)		
> 14 days	12 (52)	
7-14 days	1 (4)	
< 7 days	3 (13)	
ISA indication—n (%)		
Prophylaxis	5 (22)	
Treatment	18 (78)	
PCZ level (ng/mL)	1470 (523-3420)	
Concomitant hepatotoxic medications	PCZ	ISA
Liposomal amphotericin B	7 (30)	7 (30)
Acetaminophen product	14 (61)	13 (57)
Chemotherapy	3 (13)	6 (26)
Other$^{\gamma}$	10 (43)	15 (65)
Concomitant investigational agent	5 (22)	5 (22)

Data presented as median (range) and n(%)
ISA: Isavuconazole; PCZ: Posaconazole; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; $^{\delta}$p = 0.006 for difference between ISA days and PCZ days; $^{\alpha}$within 3 months of ISA initiation; $^{\Omega}$At the time of ISA initiation; $^{\gamma}$Other: includes amiodarone, tacrolimus, tigecycline, and quinupristin-dalfopristin

Figure 1. ALT trends with ISA after PCZ toxicity



PCZ: posaconazole; ISA: isavuconazole;
ALT: alanine aminotransferase (reported in units/Liter)

Table 2. Summary of liver function tests on PCZ and ISA therapy

	Before PCZ	Last PCZ dose	Two weeks after ISA	Four weeks after ISA	Last ISA dose
Total bilirubin (in mg/dL)	1.15 (0.5-3.3)$^{\alpha}$	2.05 (0.3-6.1)$^{\alpha}$	1.15 (0.5-4.8)$^{\beta}$	0.95 (0.6-1.8)$^{\gamma}$	1.35 (0.4-6.3)$^{\alpha}$
Alanine aminotransferase (in units/L)	38.5 (12-125)$^{\alpha}$	153 (19-426)$^{\alpha}$	58.5 (28-375)$^{\beta}$	44.5 (23-119)$^{\gamma}$	38 (16-209)$^{\alpha}$
Aspartate aminotransferase (in units/L)	28.5 (13-54)$^{\delta}$	129 (50-572)$^{\epsilon}$	43.5 (14-165)$^{\zeta}$	28 (20-102)$^{\eta}$	63 (18-105)$^{\gamma}$

All values reported as Median (Range)
PCZ: posaconazole; ISA: Isavuconazole
$^{\alpha}$n=20; $^{\beta}$n=16; $^{\gamma}$n=14; $^{\delta}$n=10; $^{\epsilon}$n=13; $^{\zeta}$n=12; $^{\eta}$n=9

CONCLUSIONS

- ISA was well-tolerated after PCZ toxicity with no patient discontinuing ISA due to toxicity.
- Specifically, liver toxicity as assessed by laboratory values was reduced and QTc abnormalities resolved after switching PCZ to ISA.
- Our experience supports the approach of switching antifungal therapies within the same pharmaceutical class.
- Study limitations include its monocentric and retrospective nature with relatively few patients. Also the inability to account for all confounding variables such as disease and performance status.
- We conclude that ISA can be a safe alternative in the setting of PCZ toxicity in heavily immunocompromised leukemia patients.

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