



Breakthrough Invasive Pulmonary Aspergillosis During Isavuconazole Prophylaxis in Patients with Hematologic Malignancies: A single Center Experience

Lauren Fontana, DO¹; James S. Lewis II, PharmD ^{1,2} ; Morgan Hakki, MD¹

¹ Oregon Health & Science University
² Department of Pharmacy, Oregon Healthy and Science University

Background

- Prophylaxis against invasive mould fungal infection (IMI) is recommended in those with high-risk hematologic malignancies and hematopoietic cell transplant (HCT) recipients
- Isavuconazole (ISA) is an attractive candidate for prophylaxis due to its broad spectrum activity, ease of dosing, favorable side effect profile, and limited drug-drug interactions
- However, clinical experience with the use of ISA as prophylaxis is lacking

Research Objectives

- **Primary Objectives:**
 - Describe institutional clinical experience using ISA as a first-line prophylactic agent over a 13 month period (9/1/2016 to 9/31/2017)
 - Characterize breakthrough IMIs during receipt of ISA prophylaxis
 - Compare incidence of IMIs during ISA prophylaxis to other mould-active agents at our center

Methods

METHODS

Design:

- Retrospective cohorts of high risk inpatients and outpatients with hematologic malignancy and/or hematopoietic cell transplant (HCT) at Oregon and Health and Science University

IFI primary prophylaxis indicated in the following:

- New AML, refractory/relapsed AML, MDS
- Post-allogeneic HCT:
 - Primary prophylaxis if ≥ 14 days neutropenia prior to HCT
 - Graft versus host disease (GVHD) or other conditions requiring high dose steroids

Inclusion Criteria:

- Patient population:
 - AML undergoing induction, re-induction, or salvage chemotherapy
 - MDS undergoing chemotherapy
 - Post-allogeneic HCT meeting criteria above
- ≥ 7 days uninterrupted ISA primary prophylaxis

Exclusion Criteria:

- Previous IFI requiring secondary prophylaxis or receiving ISA for treatment of established infection
- < 7 days of primary prophylaxis

Methods (Cont.)

➤ Outcomes:

- **Primary Outcomes:**
 - Breakthrough probable or proven IMI per EORTC/MSG criteria
 - If uncertainty about a diagnosis the case underwent independent, blinded review by 2 transplant ID clinicians
- **Secondary Outcomes:**
 - Duration of neutropenia and duration of prophylaxis prior to IFI
 - Understand characteristics about predisposing factors that could lead to IFI
- **Statistical Analysis:**
 - Univariate analysis comparing outcomes and incidence of breakthrough infections
 - Description of variables extracted from each patient's chart

Results

Table 1: Characteristics of patients on ISA prophylaxis

Factor	Patients
Total patients	132
Average age in years (Median)	60 (19-83)
Gender	75 (56.8%)
Male	57 (43.1%)
Female	
Race	122 (92.4%)
White	3 (2.2%)
Black	7 (5.3%)
Other	
Median duration of prophylaxis in days	21 (7-401)
Underlying Disease	
Acute Myeloid Leukemia (AML)	65
Relapsed Refractory AML	63
Myelodysplastic Syndrome	17
Myelofibrosis	6
Aplastic Anemia	8
Other*	24
Total HSCT	69

Table 2: Indications for ISA prophylaxis per course

Indication	Number
Total courses:	183
Post HSCT:	
Primary prophylaxis	16 (8.7%)
GVHD/Steroid Responsive Indication	41 (22.4%)
AML:	
Induction	40 (21.8%)
Consolidation	13 (7.1%)
Maintenance	3 (1.6%)
AML (Relapsed/Refractory)	
Re-induction	40 (21.9%)
Consolidation/salvage	6 (3.3%)
Maintenance	6 (3.3%)
MDS:	4 (2.2%)
Aplastic Anemia:	5 (2.7%)
Other:	8 (4.4%)

Table 3: Characteristics of IFI breakthrough infections while on ISA prophylaxis

Patient	Age	Sex	Type of Malignancy ^a	HCT	Organism	Infection site	Duration of neutropenia (days)	ISA trough level ^b	Duration of prophylaxis (days) ^c	MIC of ISA ^d	Indication for steroids	Outcome
1	64	F	Myelofibrosis	Y	<i>Aspergillus fumigatus</i>	Lung	28	3.1	12	0.5	N/A	Death
2	57	M	AML	N	<i>Fusarium dimerum</i>	Lung	33	2.6	15	N/A	N/A	Death
3	74	F	AML	N	<i>Aspergillus species</i>	Lung	45	6.3	10	N/A	N/A	Death
4	45	F	AML (Rel/Ref)	Y	<i>Fusarium species</i>	Blood, vitreous	15	N/A	9	N/A	GVHD	Death
5	65	M	AML (Rel/Ref)	N	<i>Aspergillus fumigatus</i>	Lung	57	4.3	32	N/A	N/A	Death
6	30	M	AML (Rel/Ref)	Y	<i>Aspergillus fumigatus</i>	Lung	183	3.3	37	N/A	Organizing pneumonia	Alive
7	64	F	AML (Rel/Ref)	N	<i>Aspergillus species</i>	Lung	49	3.7	21	N/A	N/A	Alive
8	67	M	AML (Rel/Ref)	Y	<i>Syncephalastrum racemosum</i>	Lung	35	N/A	24	2	N/A	Death
9	60	M	AML (Rel/Ref)	N	<i>Rhizopus microsporus</i>	Lung	25	N/A	14	N/A	N/A	Death

^aUnderlying cause of hematologic malignancy
^bTrough level (mcg/ml) within 72 hours of breakthrough infection
^cDuration of isavuconazole prophylaxis prior to breakthrough infection
^dMIC of Isavuconazole if susceptibilities performed

Results (Cont.)

Table 4: Breakthrough rate per antifungal course and indication (2015 to the present)

Indication	Posaconazole	Voriconazole	Isavuconazole
AML	0.5% (1/196) (IPA)	0% (0/137)	3.5% (2/56) (1 <i>Fusarium</i> , 1 IPA)
AML (relapsed/refractory)	3.6% (3/84) (1 IPA, 2 <i>Mucor</i>)	6.2% (1/17) (<i>Scedosporium</i>)	11.5% (6/52) (3 IPA, 1 <i>Syncephalastrum</i> , 1 <i>Rhizopus</i> , 1 <i>Fusarium</i>)
Post HCT	0% (0/71)	0% (0/27)	6.2% (1/16) (IPA)

Discussion

- Incidence of breakthrough probable or proven IPA on ISA was greater than expected despite adequate ISA serum levels
- Due to unexpected high rate of IPA on ISA our institution switched back to POS for primary prophylaxis
- After switching back to POS there have not been any breakthrough infections

Strength:

- All patients were high risk for IFI warranting prophylaxis

Limitation:

- Single center retrospective study which limits the generalizability of results

Future endeavors:

- Analyze for breakthrough IFI from 2017 to 2018 with POS and VOR as our formulary medications for primary prophylaxis

Conclusion:

- Further studies are needed to determine the role of ISA prophylaxis in high risk hematologic malignancy patients

References

1. Maertens, et al. Lancet. 206; 387:760-760
2. Falci D and Pasqualotto A. Infection and Drug Resistance. 2013; 6: 163-174
3. Auberger, et al. J antimicrob Chemother. 2012; 67: 2268-2273
4. Rausch, et al. CID Brief Report. 2018: 1-4