Clinical Infectious Diseases

MAJOR ARTICLE

Isavuconazole Prophylaxis in Patients With Hematologic Malignancies and Hematopoietic Cell Transplant Recipients

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Background. Isavuconazole (ISA) is an attractive candidate for primary mold-active prophylaxis in high-risk patients with hematologic malignancies or hematopoietic cell transplant (HCT) recipients. However, data supporting the use of ISA for primary prophylaxis in these patients are lacking.

Methods. We conducted a retrospective review of breakthrough invasive fungal infections (bIFIs) among adult hematologic malignancy patients and HCT recipients who received ≥7 days of ISA primary prophylaxis between 1 September 2016 and 30 September 2018. The incidence of bIFIs in patients receiving ISA was compared to those receiving posaconazole (POS) and voriconazole (VOR) during the same time period.

Results. One hundred forty-five patients received 197 courses of ISA prophylaxis. Twelve bIFIs (*Aspergillus fumigatus* [5], *Aspergillus* species [2], Mucorales [2], *Fusarium* species [2], and *Candida glabrata* [1]) occurred, representing 8.3% of patients and 6.1% of courses, after a median duration of 14 days of ISA prophylaxis. All bIFIs occurred during periods of neutropenia. Seven patients (58.3%) died within 42 days of onset of bIFI. In addition, bIFIs complicated 10.2% of ISA, 4.1% of POS, and 1.1% of VOR courses among patients with de novo or relapsed/refractory acute myeloid leukemia during the study period, with invasive pulmonary aspergillosis (IPA) complicating 6.8% of ISA, 1.3% of POS, and zero VOR courses.

Conclusions. Although ISA has been approved for treatment of invasive *Aspergillus* and mucormycosis, we observed an increased rate of bIFI, notably IPA, using ISA for primary prophylaxis. These results support the need for further study to determine the role of ISA as primary prophylaxis.

Keywords. isavuconazole; prophylaxis; breakthrough invasive fungal infection; hematopoietic cell transplant; hematologic malignancy.

Despite advances in diagnostics, preventive strategies, and treatment, invasive fungal infections (IFIs) remain associated with significant morbidity and mortality in patients with hematologic malignancies and hematopoietic cell transplant (HCT) recipients [1]. The use of mold-active prophylaxis, specifically posaconazole, is recommended in patients with prolonged neutropenia due to chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), and in HCT recipients requiring augmented immunosuppression for graft-vs-host disease (GVHD) [2–4] based on studies demonstrating reduced IFIs, mostly invasive aspergillosis, and improved all-cause mortality with posaconazole [5, 6].

Isavuconazole is a novel antifungal agent that displays excellent activity against *Candida* species and most *Aspergillus* species including *Aspergillus fumigatus*, and variable activity against the Mucorales [7]. Isavuconazole was licensed for the treatment of invasive aspergillosis in patients with hematologic malignancies based on noninferiority compared to voriconazole, and for the treatment of mucormycosis infections based on the results of a single-arm study combined with a case-control analysis [8–10].

A consensus decision was made at our institution to replace posaconazole with isavuconazole as the first-line agent of choice for primary prophylaxis of IFIs in high-risk hematologic malignancy patients and HCT recipients. In addition to the above-mentioned demonstrated efficacy in treatment of invasive *Aspergillus* and mucormycosis infections, this decision was also based on its ease of dosing, favorable side effect profile, limited drug–drug interactions, lack of prolongation of QT interval, and lack of need for routine therapeutic drug monitoring [10]. Here, we report our experience using isavuconazole as the first-line mold-active agent for the primary prophylaxis of IFIs in these patients.

Received 27 February 2019; editorial decision 27 March 2019; accepted 2 April 2019; published online April 8, 2019.

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Clinical Infectious Diseases® 2019;70(5):723–30

DOI: 10.1093/cid/ciz282

METHODS

Patient Population and Prophylaxis Strategies

This was a retrospective study of adult (≥18 years of age) hematologic malignancy patients and allogeneic HCT recipients who received ≥7 days of uninterrupted mold-active primary prophylaxis as either an inpatient or an outpatient at Oregon Health and Science University (OHSU) from 1 September 2016 to 30 September 2018. The OHSU Pharmacy database was queried for any isavuconazole, voriconazole, and posaconazole prescription written during the study period. From 2010 through 31 August 2016, posaconazole was first-line prophylaxis during induction and consolidation chemotherapy for AML (de novo or relapsed/refractory) or MDS, and allogeneic HCT recipients receiving high-dose steroids (≥30 mg/day prednisone or equivalent) for GVHD (or another steroid-responsive condition) or with ≥14 days of neutropenia immediately prior to beginning allogeneic HCT conditioning chemotherapy. Mold-active prophylaxis was used for other indications at the discretion of the hematologic malignancy/HCT teams and/or infectious diseases. Starting 1 September 2016, posaconazole was replaced by isavuconazole and voriconazole according to estimated risk for IFI. Patients with relapsed/refractory AML, MDS, and HCT recipients requiring high-dose steroids or with prolonged pretransplant neutropenia received isavuconazole. Patients with de novo AML received voriconazole. Isavuconazole was administered to all patients intravenously or orally at standard loading and maintenance doses [8, 9]; therapeutic drug monitoring was not routinely performed. Voriconazole was dosed to achieve a target trough level of ≥1 μg/mL. Some patients did not receive the prophylactic agent of choice per institutional protocol due to various barriers and consequently received another mold-active azole in its place. Following an unexpectedly high number of breakthrough cases of invasive pulmonary aspergillosis (IPA) during isavuconazole prophylaxis described in this report, posaconazole replaced isavuconazole as of 1 October 2017; patients with de novo AML continued to receive voriconazole.

Identification and Classification of IFIs

The electronic medical records of all patients meeting inclusion criteria were reviewed to determine whether an IFI occurred. IFIs were classified as proven, probable, or possible according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infection Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria [11]. Only proven or probable IFIs were included in this study. Possible IFIs were not routinely included with an exception made for an additional category, "possible with positive polymerase chain reaction (PCR)," for patients who fulfilled host and radiographic criteria but who had only a positive pan-fungal or mold-specific PCR result from bronchoalveolar lavage fluid (BALF) or lung tissue [12, 13] with no other plausible pathogen identified. Breakthrough IFI (bIFI) was defined as onset of IFI after receipt of ≥7 days of prophylaxis while still receiving the prophylactic agent. The date of onset was defined as the date at which the patient met either EORTC/MSG radiographic or microbiologic criteria. A new course of prophylaxis was documented if there was a break of >7 days between stopping and restarting the specified antifungal. Additional clinical and microbiological data were obtained from review of the electronic medical record. Death was recorded if it occurred within 42 days of the date of onset of bIFI [14].

Antifungal Resistance Testing

Susceptibility testing was performed as part of routine clinical care on cultured isolates, when available, by either Associated Regional and University Pathologists, Inc or the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio [15]. *CYP51A* gene profiling was performed on DNA extracted from 3 BALF samples from 3 patients in which *A. fumigatus* DNA was detected by pan-fungal PCR performed at the University of Washington [12, 16] as part of routine clinical care. All 3 DNA samples were subjected to nested PCR for *CYP51A* gene amplification as previously described [17]. The entire coding region of the *CYP51A* gene was sequenced in both directions and aligned against the sequence from *A. fumigatus* wild-type strain (ATCC 13073).

Statistical Analysis

All analyses were performed using Fisher exact 2-tailed test, logistic regression, and Mann-Whitney *U* test where appropriate (SPSS version 25, IBM Corp).

RESULTS

Characteristics of Isavuconazole Prophylaxis Courses and Patients

One hundred forty-five patients received 197 courses of isavuconazole primary prophylaxis between 1 September 2016 and 30 September 2018, with 187 courses (95%) being administered between 1 September 2016 and 30 September 2017, when isavuconazole was first-line treatment for primary prophylaxis at our institution. Patient characteristics and indications for isavuconazole prophylaxis are provided in Table 1. The median duration per isavuconazole prophylaxis course was 22 days (interquartile range, 15–54 days).

bIFIs During Isavuconazole Prophylaxis

There were 12 bIFIs (11 proven/probable, 1 possible with positive PCR) in 12 patients (Table 2), representing 8.3% of patients who received prophylaxis and 6.1% of courses of prophylaxis. bIFI occurred after a median duration of 14 days (range, 8–125 days) of prophylaxis. Eleven of the 12 bIFIs (91.7%) occurred between 1 September 2016 and 30 September 2017, when 95% of isavuconazole courses were administered. Eleven

Table 1. Characteristics of Patients and Indications for Isavuconazole Prophylaxis

Characteristic	No. (%)
Total No. of patients	145
Age, y, median (range)	60 (19–85)
Sex, No. (%)	
Male	70 (48.3)
Female	75 (51.7)
Total courses, No.	197
Duration of prophylaxis, days, median (IQR)	22 (15–54)
Indications for prophylaxis, No. (% of total courses)	
De novo AML	54 (27.4)
Induction	38
Consolidation	15
Other[a]	1
Relapsed/refractory AML	60 (30.5)
Reinduction/salvage	50
Consolidation	6
Other[b]	4
Miscellaneous HM[c], No. (% of total courses)	20 (10.1)
Post-HCT, No. (% of total courses)	63 (32)
High-dose steroid use[d]	44
Prolonged pre-HCT neutropenia	19

Abbreviations: AML, acute myeloid leukemia; HCT, hematopoietic cell transplant; HM, hematologic malignancy; IQR, interquartile range.

[a]Donor lymphocyte infusion.

[b]Decitabine, azacitidine, hydroxyurea.

[c]Myelodysplastic syndrome (8), acute promyelocytic leukemia (2), acute lymphoblastic leukemia (3), aplastic anemia (5), chronic myelogenous leukemia (1), chronic lymphocytic leukemia (1).

[d]Graft-vs-host disease (40), idiopathic pneumonitis syndrome (1), diffuse alveolar hemorrhage (1), bronchiolitis obliterans (2).

bIFIs (91.7%) occurred in patients undergoing chemotherapy for AML or acute lymphoblastic leukemia, and 1 occurred post-HCT during prophylaxis for prolonged pre-HCT neutropenia. No bIFI occurred during 44 courses of prophylaxis among HCT recipients receiving high-dose steroids. All patients were hospitalized and neutropenic at the time of bIFI, with a median duration of neutropenia of 25.5 days (range, 9–180 days) prior to bIFI onset.

Eleven of 12 (91.7%) bIFIs were due to invasive mold infections. IPA accounted for 7 (58.3%) bIFIs, of which 5 were due to *A. fumigatus* based on culture (n = 1) or PCR identification (n = 4), and 2 were due to *Aspergillus* species on the basis of a positive serum or BALF galactomannan test. *Fusarium* species (n = 2) and Mucorales (n = 2: *Syncephalastrum monosporum/racemosum* [1] and *Rhizopus microsporus/azygosporus* [1]) accounted for the 4 other breakthrough mold infections. One breakthrough yeast infection, *Candida glabrata* fungemia, occurred.

Isavuconazole trough levels were obtained within 72 hours of bIFI in 5 (41.6%) cases, all 5 being breakthrough IPA, with a median of 3.7 μg/mL (range, 3.3–6.3 μg/mL). Due to poor culture yield, isavuconazole phenotypic antifungal susceptibility testing could be performed only on a single *A. fumigatus* isolate (minimum inhibitory concentration [MIC] = 0.5 μg/mL) and an *S. monosporum/racemosum* isolate (MIC = 2 μg/mL). *CYP51A* gene sequencing performed on *A. fumigatus* DNA found in 3 BALF samples (patients 3, 6, and 7) did not demonstrate mutations known to be associated with azole resistance (Supplementary Table 1). Susceptibility testing that did not include isavuconazole was performed on both *Fusarium* species isolates and the *C. glabrata* isolate (Table 2).

Comparison of bIFIs During Isavuconazole, Posaconazole, and Voriconazole Primary Prophylaxis in Patients Undergoing Treatment for AML

The rate of breakthrough cases of IPA among patients receiving isavuconazole prophylaxis was greater than expected based on historical experience at our institution [18]; as such, isavuconazole was replaced by posaconazole as of 1 October 2017. Patients with de novo AML continued to receive voriconazole. We retrospectively reviewed bIFIs among patients receiving posaconazole or voriconazole during the entire study period. We limited this analysis to patients receiving prophylaxis during induction chemotherapy for de novo AML and reinduction or salvage chemotherapy for relapsed/refractory AML, as these 2 indications together accounted for 61% of isavuconazole courses (Table 1) and 75% of bIFIs during isavuconazole prophylaxis (Table 2).

A total of 88, 73, and 90 courses of isavuconazole, posaconazole, and voriconazole primary prophylaxis, respectively, were administered to 85, 68, and 88 patients, respectively (Table 3). Approximately 95% of isavuconazole courses were administered between 1 September 2016 and 30 September 2017, and 79.7% of posaconazole courses were administered between 1 October 2017 and 30 September 2018. As expected, based on our institutional guidelines, the numbers of patients with de novo and relapsed/refractory AML who received isavuconazole and posaconazole were similar, whereas voriconazole was used predominantly in patients with de novo AML.

In patients with de novo AML, there was a trend toward longer durations of neutropenia and prophylaxis among posaconazole courses compared to isavuconazole. Breakthrough IFIs occurred during 3 of 38 (7.9%) courses of isavuconazole prophylaxis for this indication compared to 1 of 37 courses (2.7%) of posaconazole prophylaxis ($P = .6$), and 0 of 72 courses of voriconazole prophylaxis ($P = .04$, voriconazole vs isavuconazole) (Table 4). In patients receiving reinduction or salvage chemotherapy for relapsed/refractory AML, the durations of neutropenia and prophylaxis were similar across agents. bIFIs occurred during 6 of 50 (12%) courses of isavuconazole compared with 2 of 36 (5.5%) courses of posaconazole and 1 of 18 (5.5%) courses of voriconazole prophylaxis (Table 4). Comparisons of the incidence of bIFIs between isavuconazole and posaconazole or voriconazole did not reach statistical significance.

Table 2. Breakthrough Invasive Fungal Infections During Isavuconazole Prophylaxis

Patient	Date of Onset	Age/Sex	Underlying Malignancy	HCT	Prophylaxis Indication	Chemotherapy	Pathogen	Mycological Diagnosis	EORTC/MSG Classification	Duration of Neutropenia, d[a]	Duration Prophylaxis, d[a]	Trough Level, μg/mL[b]	ISA MIC, μg/mL	Therapy	Outcome[c]
1	30 Oct 2016	74/F	AML	N	Induction	FLAG-IDA	*Aspergillus* spp	Serum GM	Probable	26	10	6.3	ND	ISA	Death (34)
2	30 Nov 2016	71/M	AML	N	Induction	Study	*Aspergillus* spp	Serum GM	Probable	18	15	ND	ND	ISA	Alive
3	27 Mar 2017	30/M	R/R AML	N	Reinduction	Decitabine	*Aspergillus fumigatus*	BALF GM, BALF PCR	Probable	180	125	3.3	ND[d]	Amb	Alive
4	5 Apr 2017	57/M	R/R AML	N	Reinduction	FLAG-IDA	*Fusarium dimerum*	BALF culture	Probable	25	8	ND	ND[e]	ISA	Death (8)
5	29 Apr 2017	45/F	R/R AML	Y	Reinduction	FLAG-IDA	*Fusarium* spp	Blood culture	Proven	9	9	ND	ND[f]	Amb	Alive
6	5 May 2017	64/F	R/R AML	N	Reinduction	7 + 3	*A. fumigatus*	BALF GM, BALF PCR	Probable	38	13	3.7	ND[d]	VOR	Alive
7	28 May 2017	65/M	R/R AML	N	Reinduction	FLAG-IDA	*A. fumigatus*	BALF GM, BALF PCR	Probable	38	40	4.3	ND[d]	VOR	Death (19)
8	5 Jul 2017	60/M	R/R AML	N	Reinduction	MEC	*Rhizopus microsporus* or *azygosporus*	Histopathology, Lung tissue PCR	Proven	11	14	ND	ND	Amb, POS	Alive
9	13 Aug 2017	64/F	MF	Y	Pre-HCT neutropenia	NA	*A. fumigatus*	Sputum culture	Probable	16	12	ND	0.5	Mica	Death (12)
10	3 Sept 2017	67/M	R/R ALL	Y	Reinduction	FLAG-IDA	*Syncephalastrum monosporum* or *racemosum*	BALF culture, BALF PCR	Probable	27	22	ND	2	POS	Death (14)
11	8 Sept 2017	53/F	AML	N	Induction	7 + 3	*A. fumigatus*	BALF PCR	Possible w/ PCR+	21	20	3.4	ND	Mica	Death (27)
12	30 Jul 2018	25/M	R/R ALL	N	Targeted therapy	CAR-T	*Candida glabrata*	Blood culture	Proven	82	14	ND	ND[g]	Mica	Death (7)

Abbreviations: 7 + 3, cytarabine, anthracycline; ALL, acute lymphocytic leukemia; Amb, AmBisome; AML, acute myeloid leukemia; BALF, bronchoalveolar lavage fluid; CAR-T, chimeric antigen receptor T-cell therapy; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infection Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group; F, female; FLAG-IDA, fludarabine, cytarabine, idarubicin; GM, galactomannan; HCT, hematopoietic cell transplant; ISA, isavuconazole; M, male; MEC, mitoxantrone, etoposide, cytarabine; MF, myelofibrosis; MIC, minimum inhibitory concentration; Mica, micafungin; N, no; NA, not applicable; ND, not determined; PCR, polymerase chain reaction; POS, posaconazole; R/R, relapsed/refractory; VOR, voriconazole; Y, yes.

[a]Prior to breakthrough invasive fungal infection (bIFI).

[b]Performed within 72 hours of bIFI.

[c]Defined as occurring within 42 days of date of onset of bIFI, with interval (days) from date of onset to date of death provided when applicable.

[d]*CYP51A* gene sequencing performed (refer to text and Supplementary Table 1).

[e]MICs: itraconazole (ITRA) ≥16, POS ≥16, VOR = 8.

[f]MIC ≥16 for ITRA, POS, and VOR.

[g]MICs: fluconazole = 16, POS = 2, ITRA = 1.

Table 3. Comparison of Courses of Isavuconazole, Posaconazole, and Voriconazole Primary Prophylaxis in Patients Undergoing Treatment for Acute Myeloid Leukemia

Characteristic	ISA	POS	*P* Value[a]	VOR	*P* Value[b]
Total patients, No.	85	68		88	
Total courses, No.	88	73		90	
Indication					
De novo AML, induction chemotherapy					
Patients, No. (% of total patients)	38 (45)	37 (54)	.25	72 (82)	< .0001
Courses, No. (% of total courses)	38 (43)	37 (51)	.4	72 (80)	< .0001
Duration of neutropenia, days, median (IQR)	24.5 (21–44)	31 (23–76)	.07	26 (19–42)	.9
Duration of prophylaxis, days, median (IQR)	20 (16–24)	28 (16–62)	.09	19 (15–25)	.6
Anthracycline chemotherapy, No. (% of courses per indication)	29 (76.3)	27 (73)	.8	61 (84.7)	.3
R/R AML, reinduction/salvage chemotherapy					
Patients, No. (% of total patients)	47 (55)	31 (46)		16 (18)	
Courses, No. (% of total courses)	50 (57)	36 (49)		18 (20)	
Duration of neutropenia, days, median (IQR)	28.5 (15–64)	35 (16–57)	.9	38 (27–56)	.5
Duration of prophylaxis, days, median (IQR)	19.5 (16–32)	22 (15–50)	.8	27 (16–43)	.4
Anthracycline chemotherapy, No. (% of courses per indication)	38 (75.3)	27 (75)	1	15 (83)	.7

Abbreviations: AML, acute myeloid leukemia; IQR, interquartile range; ISA, isavuconazole; POS, posaconazole; R/R, relapsed/refractory; VOR, voriconazole.

[a]ISA vs POS.

[b]ISA vs VOR.

Among both groups combined, bIFIs complicated 10.2% of courses of isavuconazole prophylaxis compared to 4.1% of posaconazole prophylaxis ($P = .2$). Evaluating the incidence of breakthrough IPA between isavuconazole (6.8%) and posaconazole (1.3%) revealed a similar trend that did not reach statistical significance. A combined comparison to voriconazole was not performed due to significant differences in the patient populations receiving prophylaxis with those 2 agents.

Table 4. Breakthrough Invasive Fungal Infections During Isavuconazole, Posaconazole, and Voriconazole Primary Prophylaxis in Patients Undergoing Treatment for Acute Myeloid Leukemia

Characteristic	ISA	POS	*P* Value	VOR	*P* Value[a]
Indication					
De novo AML induction chemotherapy					
bIFI, No.	3	1		0	
Organism, No.					
Aspergillus fumigatus	1[b]	0		0	
Aspergillus spp	2	0		0	
Candida glabrata	0	1		0	
Courses, No.	38	37		72	
bIFI, % of courses	7.9	2.7	.6	0	.04
R/R AML salvage/reinduction chemotherapy					
bIFI, No.	6	2		1	
Organism, No.					
Aspergillus fumigatus	3	1		0	
Rhizopus microsporus/azygosporus	1	0		0	
Fusarium spp	2	1		0	
Scedosporium apiospermum	0	0		1	
Courses, No.	50	36		18	
bIFI, % of courses	12	5.5	.4	5.5	.7
Total courses, No.	88	73		90	
Total bIFI, No. (% total courses)	9 (10.2)	3 (4.1)	.2	1 (1.1)	ND
Breakthrough IPA, No. (% total courses)	6 (6.8)	1 (1.3)	.1	0	ND
bIFI, non-IPA, No. (% total courses)	3 (3.4)	2 (2.8)	1	1 (1.1)	ND

Abbreviations: AML, acute myeloid leukemia; bIFI, breakthrough invasive fungal infection; IPA, invasive pulmonary aspergillosis; ISA, isavuconazole; ND, not determined; POS, posaconazole; R/R, relapsed/refractory; VOR, voriconazole.

[a]ISA vs VOR.

[b]Possible with positive polymerase chain reaction.

Treatment and Outcomes

Of the 7 patients with breakthrough IPA, 2 patients continued to receive isavuconazole due to clinical stability and long-term goals of care, 2 were changed to voriconazole, 2 were treated with micafungin due to hepatic and renal dysfunction that represented contraindications to azole and amphotericin therapy, and 1 was treated with liposomal amphotericin. One patient with breakthrough Mucorales infection (patient 10) was empirically changed from isavuconazole to posaconazole at clinical onset of infection but was transitioned to hospice care soon thereafter, and 1 patient (patient 8) did well after switching from isavuconazole first to liposomal amphotericin and then to posaconazole. Patient 4 with breakthrough *Fusarium* infection experienced rapid deterioration in condition concomitant with onset of bIFI, and escalation of antifungal therapy was not pursued. Patient 5 with breakthrough *Fusarium* was successfully managed with liposomal amphotericin. Overall, 7 patients (58.3%) with bIFI met study criteria for mortality, with death occurring at a median of 12 days (range, 7–34 days) following onset of bIFI.

DISCUSSION

Although approved for the treatment of invasive aspergillosis and mucormycosis, there is a relative paucity of experience using isavuconazole as primary prophylaxis in high-risk patients with hematologic malignancies and HCT recipients [14, 19]. Here, we report our single-center experience using isavuconazole as first-line, primary prophylaxis in these patients, representing the largest such series to date.

Breakthrough IFIs occurred in 8.3% of patients who received isavuconazole prophylaxis and 6.1% of administered courses of isavuconazole prophylaxis. There are limited data in the literature to provide a basis of comparison for these findings. No proven or probable bIFIs were reported in a phase 2 study of isavuconazole primary prophylaxis in 20 patients with de novo AML [19]. A more recent report described 5 bIFIs among 27 patients with leukemia (18.5%) receiving isavuconazole primary prophylaxis [14]. With such a relative lack of data, the most appropriate relevant "benchmark" or comparator may be posaconazole prophylaxis, where bIFIs have been described in 0–10.9% of patients [20]. However, comparisons to posaconazole are complicated by differences in defining bIFIs, heterogeneity among patient populations receiving prophylaxis, and study design.

Comparing bIFIs observed during isavuconazole prophylaxis to posaconazole and voriconazole across patients receiving prophylaxis for similar indications in this study (Tables 3 and 4) represents an opportunity to reduce some of the heterogeneity across studies. Among patients receiving prophylaxis for de novo or relapsed/refractory AML, there was a trend toward more bIFIs during receipt of isavuconazole compared to posaconazole that did not reach statistical significance. There were more bIFIs during courses of isavuconazole than voriconazole among patients with de novo AML, despite equivalent durations of neutropenia and prophylaxis; a formal analysis to determine whether receipt of isavuconazole is an independent risk factor for bIFI in these patients was not performed and is beyond the scope of this report.

Notably, 11 of 12 (91.7%) bIFIs during isavuconazole prophylaxis were due to molds, with IPA accounting for 7 (58.3%) bIFIs. In comparison, of the 5 bIFIs during isavuconazole primary prophylaxis described by Rausch et al, only 1 was due to a mold (Mucorales species) [14]. Another report described 3 cases of breakthrough *Aspergillus* infections during receipt of isavuconazole primary prophylaxis in patients with hematologic malignancies, but only one was due to *A. fumigatus* and the other 2 were *A. nigri* group molds, which may be inherently less susceptible to isavuconazole [21, 22].

Indeed, the trend toward more bIFIs during isavuconazole prophylaxis compared to posaconazole and the higher rate compared to patients with de novo AML receiving voriconazole prophylaxis observed this study were driven by breakthrough IPA. Notably, during the previous 6 years at our institution, only 5 cases of proven/probable breakthrough IPA occurred in 547 hematologic malignancy/HCT patients receiving posaconazole prophylaxis [18]. The seemingly high incidence of breakthrough IPA during isavuconazole prophylaxis compared to our institution's historical experience led to the decision to replace isavuconazole with posaconazole. Following this change, only 1 case of breakthrough IPA during posaconazole prophylaxis occurred over the ensuing 12 months.

The reason(s) underlying the cases of breakthrough IPA during isavuconazole prophylaxis remain to be determined. Although azole-resistant *A. fumigatus* is relatively uncommon in the United States [23], our ability to evaluate for such strains was limited by poor culture yield. Only 1 *A. fumigatus* isolate could be phenotypically tested, and that isolate was found to have a relatively low MIC (0.5 μg/mL). No *CYP51A* gene mutations associated with azole resistance were found in *A. fumigatus* isolates from 3 additional infections, suggesting lack of isavuconazole resistance, although the absence of such mutations does not exclude resistance [23–25]. As *A. fumigatus* was documented in 5 of 7 cases, we cannot exclude the possibility that 2 cases of IPA may have been due to infections with *Aspergillus* species inherently less susceptible to azoles than *A. fumigatus* [21, 26]. However, if azole-resistant *Aspergillus* species were emerging in our population, more breakthrough invasive *Aspergillus* infections might have been expected in patients receiving voriconazole and posaconazole prophylaxis during the study period. Environmental factors during the period when isavuconazole was the first-line agent may have contributed to the incidence of breakthrough IPA; however, no specific environmental source was found during a thorough evaluation of the environment of care on our hematologic malignancy/HCT unit. Additionally, more cases might have been expected among patients receiving posaconazole and

voriconazole during the study period had there been a common environmental source. Cases of IPA were distributed evenly throughout the 13-month period of isavuconazole prophylaxis, not suggestive of an outbreak or seasonal clustering [12]. Since all cases of breakthrough IPA occurred in hospitalized patients, noncompliance with isavuconazole leading to low serum levels was not a contributing factor, and isavuconazole trough levels obtained in 5 cases were consistent with mean trough levels from the SECURE trial [27, 28].

All breakthrough IPA during isavuconazole prophylaxis occurred in patients with prolonged neutropenia. A post hoc analysis of the SECURE trial [9] showed less overall success at the end of therapy for invasive aspergillosis in patients with unresolved neutropenia receiving isavuconazole compared to voriconazole [29]. Whether isavuconazole possesses inherently less *Aspergillus* fungicidal activity than voriconazole in the absence of neutrophils was one possible explanation posited for those findings, while recognizing the limitations of such a post hoc analysis [29]. Similarly, conclusions pertaining to the relative anti-*Aspergillus* activity of isavuconazole compared to voriconazole and posaconazole cannot be made based on our study. Therefore, the explanation(s) for our findings remain unclear and we eagerly await the results of 2 ongoing observational studies evaluating isavuconazole as primary prophylaxis in neutropenic hematologic malignancy patients and HCT recipients (ClinicalTrials.gov identifiers NCT03149055 and NCT03019939).

The 42-day mortality rate observed in our patients with bIFI (58.3%) was similar to that observed in Rausch et al (50%) [14] and highlights the difficulties in managing bIFIs in these patients. Indeed, the management of bIFIs involves complex decision making, often must be individualized based on factors related to both the patient and the organism, and is hampered by limited data to help guide therapy.

Our study has several important limitations. This is a retrospective, single-institution study. Isavuconazole trough levels were performed in <50% of bIFIs, although whether trough levels are informative in such cases is unclear [27, 28]. Phenotypic susceptibility testing was performed on only 2 of 12 fungal isolates, limiting the ability to determine the role of isavuconazole resistance as a factor contributing to our findings. Safety and tolerability were not specifically addressed; an interim analysis of these has been submitted for publication and is currently under review.

In conclusion, we observed a trend toward an increased incidence of bIFIs in neutropenic hematologic malignancy patients and HCT recipients during isavuconazole prophylaxis, most notably IPA. Despite proven efficacy in treating invasive aspergillosis and mucormycosis in similar patient populations [8, 9], our findings suggest that additional studies to determine the role of isavuconazole as primary prophylaxis in such patients are warranted.

Notes

Acknowledgments. The authors gratefully acknowledge Annie Lee for technical support.

Financial support. D. S. P. was supported by Astellas Pharma (Reference Center for Molecular Evaluation of Drug Resistance to Echinocandin and Triazole Antifungal Drugs) and by the National Institutes of Health.

Potential conflicts of interest. D. S. P. has received contracts from Astellas, Scynexis, Cidara, Amplyx, T2 Diagnostics, and N8, and serves on advisory boards for Astellas, Cidara, Amplyx, Scynexis, and Matinas. J. S. L. has served as a consultant for Merck, Achaogen, and Accelerate Diagnostics. Y. Z. has received funding from Scynexis. L. S. has received research funding from Merck Sharpe & Dohme. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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