Clinical Infectious Diseases

MAJOR ARTICLE

Isavuconazole as Primary Antifungal Prophylaxis in Patients With Acute Myeloid Leukemia or Myelodysplastic Syndrome: An Open-label, Prospective, Phase 2 Study

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(See the Editorial Commentary by Young on pages 1764–6.)

Background. Mold-active primary antifungal prophylaxis (PAP) is routinely recommended in neutropenic patients with newly diagnosed acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS) undergoing remission-induction chemotherapy (RIC). Isavuconazole (ISAV) is an extended spectrum mold-active triazole and has superior tolerability and fewer significant drug–drug interactions compared with other triazoles.

Methods. In our investigator-initiated, phase 2 trial, treatment-naive adult patients with AML or MDS starting RIC received ISAV per the dosing recommendations in the US label until neutrophil recovery (absolute neutrophil count [ANC] $\geq 0.5 \times 10^9$/L) and attainment of complete remission, occurrence of invasive fungal infection (IFI), or for a maximum of 12 weeks. The primary endpoint was the incidence of proven/probable IFI during ISAV PAP and up to 30 days after the last dose.

Results. Sixty-five of 75 enrolled patients received ISAV PAP (median age, 67 years, median ANC at enrollment, 0.72×10^9/L). Thirty-two patients (49%) received oral targeted leukemia treatments (venetoclax, FTL3 inhibitors). Including the 30-day follow-up period, probable/proven and possible IFIs were encountered in 4 (6%) and 8 patients (12%), respectively. ISAV trough serum concentrations were consistently > 1 µg/mL, showed low intraindividual variation, and were not significantly influenced by chemotherapy regimen. Tolerability of ISAV was excellent, with only 3 cases (5%) of mild to moderate elevations of liver function tests and no QTc prolongations.

Conclusions. ISAV is a safe and effective alternative for PAP in patients with newly diagnosed AML/MDS undergoing RIC in the era of recently approved or emerging small-molecule antileukemia therapies.

Clinical Trials Registration. NCT03019939.

Keywords. isavuconazole; chemotherapy; invasive fungal infection; antifungal prophylaxis; leukemia.

Invasive fungal infections (IFIs), especially those caused by molds, remain an important concern during treatment of acute myeloid leukemia (AML) [1]. Mold-active primary antifungal prophylaxis (PAP) is widely recommended in neutropenic patients with newly diagnosed AML or high-risk myelodysplastic syndrome (MDS) who undergo curative-intent chemotherapy [2]. Posaconazole prophylaxis has been shown to result in fewer IFIs than fluconazole and was associated with a survival advantage in this population [3]. Posaconazole is, therefore, widely endorsed as the preferred drug for PAP in patients with AML/MDS [2]. However, this agent can lead to significant drug–drug interactions (DDIs) through inhibition of cytochrome P450 3A4 (CYP3A4) and p-glycoprotein as well as prolongation of the QTc interval [4].

Currently available targeted antileukemic agents such as the BCL-2 antagonist venetoclax and fms3-like tyrosine kinase 3 (FLT3) inhibitors midostaurin, gilteritinib, and sorafenib have demonstrated high rates of complete remission (CR) and decreased rates of relapse when incorporated as part of remission-induction chemotherapy (RIC) in AML [5, 6]. Coadministration of strong CYP3A4 inhibitors, such as posaconazole, is commonly prohibited in clinical trial settings due to concerns of DDIs, especially QTc prolongation. Therefore, pharmacokinetic data for these combinations are limited [7]. As achievement of CR is the single most important early determinant of outcome in AML [8, 9], there is an urgent need for discovery of alternative PAP agents that are devoid of the DDI issues of posaconazole in the growing context of new targeted antileukemia treatments [10]. Consequently, there has been increased interest in the use

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of isavuconazole (ISAV) as an alternative triazole for PAP during RIC in patients with AML/MDS. ISAV is an extended-spectrum triazole with superior tolerability, reliability of absorption, and fewer significant DDIs. Importantly, this triazole does not cause QTc prolongation and, while optimal therapeutic concentrations and a potential need for therapeutic drug monitoring remain to be defined, routine monitoring of serum concentrations is not recommended [11]. ISAV is approved for the treatment of invasive aspergillosis and mucormycosis, the 2 most common mold infections in patients with hematological malignancies [11]. To that end, we conducted a single-institution, investigator-initiated, prospective, phase 2 trial of ISAV as PAP in patents with AML/MDS during RIC.

PATIENTS AND METHODS

Study Design

The full protocol (NCT03019939) that details assessment, enrollment procedures, administration of the study drug, monitoring, and treatment of enrolled patients is available at https://clinicaltrials.gov/ct2/show/NCT03019939. In brief, untreated adult (≥ 18 years old) patients who were or were anticipated to become neutropenic as a result of their first RIC for AML/MDS were eligible. In patients who had already begun antileukemic treatment, ISAV had to be initiated within 4 days. Use of systemic antifungals for > 72 hours during the week prior to ISAV initiation was not permitted. ISAV was administered orally as its pro-drug, isavuconazonium sulfate, and dosed per the US label [12]: Patients received 2 capsules of isavuconazonium sulfate (2 × 186 mg, equivalent to 2 × 100 mg ISAV) every 8 hours for 6 doses (48 hours) and, thereafter, 2 capsules once daily. ISAV PAP was administered until recovery from neutropenia (absolute neutrophil count [ANC] ≥ 0.5×10^9/L) and attainment of complete remission with (CR) or without (CRi) complete count recovery [13], development of proven, probable, or possible IFI as per European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria [14], development of unacceptable toxicity as graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [15], patient withdrawal or death, or for a maximum of 12 weeks. For patients who received multiple cycles of antileukemic therapy within 12 weeks without attainment of CR/CRi and an ANC ≥ 0.5×10^9/L, ISAV prophylaxis continued in between cycles. The primary endpoint was the occurrence of proven/probable IFI during the study period (up to 30 days from the last ISAV dose). Clinical and laboratory markers of toxicity (complete blood count, biochemical tests) were evaluated at baseline, weekly while patients were on ISAV PAP, and following the cessation of ISAV in all enrolled patients. Electrocardiography was performed at baseline and after 10 days of ISAV. This study was conducted at MD Anderson Cancer Center, a tertiary care cancer hospital. The protocol was approved by the institutional review board and all patients signed informed consent prior to enrollment.

Pharmacokinetic Analyses

ISAV plasma concentrations were determined immediately before dosing on days 8 and 15 using a validated, ultraperformance liquid chromatography, single quadrupole mass spectrometry analytical assay [16]. In brief, a standard curve was prepared by spiking blank human plasma with ISAV (BAL4815), followed by the addition of an internal standard (valethamate bromide) to each sample. All samples were buffered and loaded onto conditioned solid phase extraction columns, which were then washed with 5% ammonia solution (NH_4OH) and 15% methanolic water. The samples were eluted with 1 mL of methanol and 1 mL of an acidic methanolic mixture (2% formic acid in methanol), and the combined eluates were dried under a stream of nitrogen. The dried residues were reconstituted with 60:40 acetonitrile/water and analyzed using a mass to charge ratio (m/z) for ISAV of 438.2. The lowest limit of quantitation was 0.25 μg/mL of ISAV.

Statistical Analysis

Two-group comparisons of continuous variables were performed using the 2-sided Mann-Whitney *U* test (unpaired analysis) or Wilcoxon signed-rank test (paired analysis). A *P* value of < .05 was considered significant. GraphPad Prism 8 and Microsoft Excel 2013 were used for data tabulation, statistical analyses, and compilation of diagrams.

RESULTS

Seventy-five patients were enrolled between 28 April 2017 and 26 July 2019, but only 65 patents received ISAV PAP (Figure 1). Ten patients did not receive the study drug due to insurance issues (n = 4), investigator decision (n = 3), incomplete screening tests (n = 2), or caspofungin use within the past week (n = 1). The median age of the 65 evaluable patients was 67 years (range, 21–86 years), with a median absolute neutrophil count of 0.72×10^9/L (range, 0.00–23.18) at enrollment (Table 1). Ninety-five percent of evaluable patients had AML and 5% MDS. Thirty patients (46%) received high-intensity RIC (Table 1), defined as regimens containing high-dose cytarabine (>1 g/m^2/day) or those with cytarabine administered continuously in combination with an anthracycline. Thirty-two of 65 (49%) patients received venetoclax and/or a FLT3 tyrosine kinase inhibitor (TKI) as a component of RIC; the numbers of patients who received venetoclax, FLT3 TKIs, or both venetoclax and FLT3 TKIs were 25, 5, and 2 respectively (Table 1). The median age of patients who received venetoclax and/or a FLT3 TKI was 69 years (range, 31–79 years).

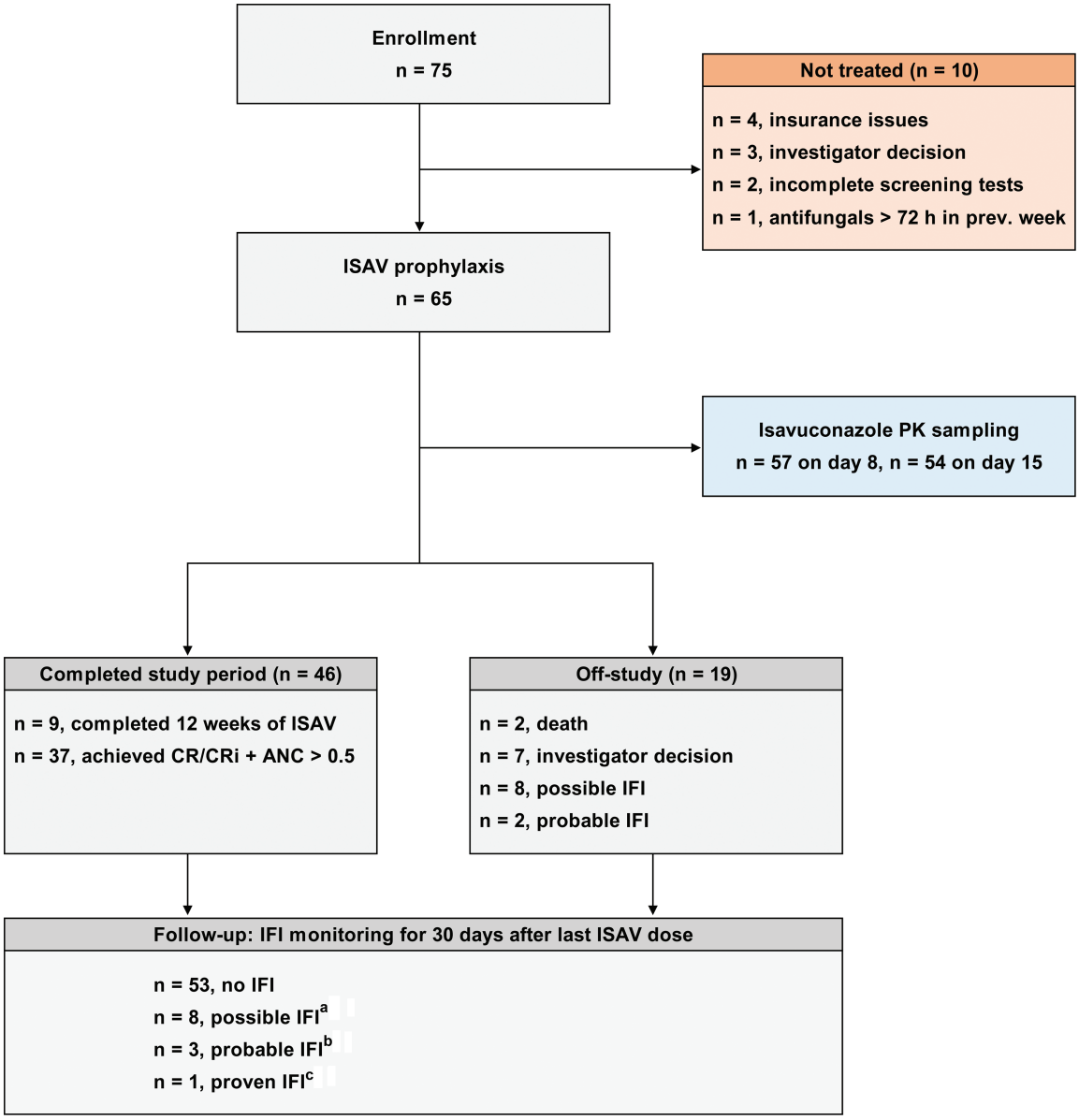

Figure 1. Trial flowchart summarizing the reasons for discontinuation of isavuconazole (ISAV) prophylaxis as well as the incidence of possible, probable, or proven invasive fungal infection (IFI) per 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria [14] at the time of ISAV discontinuation and at the end of the follow-up period (30 days after the last dose of ISAV). The IFI classification of 3 patients changed during the follow-up period: [a]1 patient who had stopped ISAV upon investigator decision had follow-up chest computed tomography consistent with fungal lung infection during the follow-up period; [b]1 patient was upgraded from possible to probable IFI during the follow-up period due to a positive serum *Aspergillus* antigen assay; [c]*Candida glabrata* was isolated from a gluteal abscess in a patient who had stopped ISAV upon achievement of complete remission. Abbreviations: ANC, absolute neutrophil count; CR/CRi, complete remission with or without complete count recovery; PK, pharmacokinetics.

The reasons for discontinuation of ISAV PAP were achievement of CR with neutrophil recovery (n = 37), completion of 12 weeks of PAP (n = 9), possible IFI (n = 8), probable IFI (n = 2), investigator decision (n = 7), and death (n = 2, 1 due to leukemia progression, 1 due to cardiac arrest) (Figure 1 and Table 2). Among the 7 patients who discontinued ISAV due to an investigator decision, 2 patients (3%) had abnormal computed tomographic (CT) scans, not consistent with a fungal infection, but were switched to other antifungals at the treating physician's discretion. Three patients (5%) had mild to moderate elevations of aminotransferases or total bilirubin as detailed below and were switched to caspofungin. Two patients (3%) were transitioned to alternative azole prophylaxis at the discretion of the treating physician due to greater clinical experience and comfort with other commercially available azole antifungals.

The CR rate in the entire cohort was 57% (37/65 patients), and similar (56%) in the 32 patients who received venetoclax,

Table 1. Demographics of the 65 Evaluable Patients

Characteristic	No. (%)
Age, y, median (range)	67 (21–86)
Sex, No. (%)	
Male	36 (55)
Female	29 (45)
Diagnosis, No. (%)	
AML	62 (95)
MDS	3 (5)
Absolute neutrophil count at enrollment, median (range)	0.72 (0.00–23.18)
RIC received	
High-intensity RIC,[a] no. (%)	30 (46%)
Without FLT3 TKI or venetoclax	22
With FLT3 TKI	5
With venetoclax	2
With FLT3 TKI + venetoclax	1
Hypomethylating agents,[b] no. (%)	25 (38)
Without FLT3 TKI or venetoclax	1
With venetoclax	23
With FLT3 TKI + venetoclax	1
Low-intensity chemotherapy,[c] no. (%)	10 (15)

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; RIC, remission-induction chemotherapy; TKI, tyrosine kinase inhibitor.

[a]Fifteen CLIA (cladribine, idarubicin, and cytarabine); 5 CLIA + sorafenib; 1 CLIA + venetoclax; 1 CLIA + midostaurin + venetoclax; 3 FLAG (fludarabine, cytarabine, and granulocyte colony-stimulating factor) + idarubicin; 1 FLAG + idarubicin + GO (gemtuzumab-ozogamicin); 1 FLAG + GO; 1 fludarabine, cytarabine, and idarubicin; 1 CPX-351 (liposomal cytarabine-daunorubicin); 1 CPX-351 + venetoclax.

[b]One decitabine; 23 decitabine + venetoclax; 1 decitabine + venetoclax + sorafenib.

[c]One low-dose cytarabine; 9 cladribine + low-dose cytarabine.

FLT3 TKIs, or both. The survival rate during the study period was high (92% [60/65 patients]). The median duration of severe neutropenia (ANC < 0.5×10^9/L) and ISAV PAP was 23 (range, 3–86; mean, 32) days and 33 (range, 8–87; mean, 42) days, respectively.

The incidence of probable and possible IFIs during ISAV PAP was 15% (n = 10). All patients were profoundly neutropenic (ANC, 0.00–0.13) and not in CR when they developed ISAV-breakthrough IFI (b-IFI; Table 3). Two patients (3%) developed probable pulmonary aspergillosis (1 patient with focal mass–like opacity with ground glass halo on CT and elevated *Aspergillus* galactomannan [GM] antigen in bronchoalveolar lavage [BAL] fluid; the other patient with bilateral lower lobe opacities on CT and elevated *Aspergillus* GM antigen in BAL). Another 8 patients (12%) had possible fungal pneumonia based on pulmonary radiologic findings alone (Figure 1 and Table 3); lower respiratory fungal cultures remained negative at 4 weeks and GM was not detected in serum or BAL fluid except in 1 patient, who was upgraded to probable b-IFI during the follow-up period (see below).

The median time to occurrence of b-IFI from initiation of ISAV prophylaxis was 22 days (range, 8–57 days). All 10 patients with b-IFIs received antifungal treatment (liposomal amphotericin B with another triazole in 7, caspofungin plus posaconazole in 2, posaconazole alone in 1; Table 3) and 8 of 10 were alive 42 days after the diagnosis of b-IFI (Table 3). Nine of 10 patients with b-IFIs received venetoclax-based RIC (5 patients) or high-intensity regimens (cladribine, cytarabine plus idarubicin [CLIA] in 4 patients; Table 3). In comparison, 38 of 55 patients who did not develop b-IFIs received venetoclax-based regimens or the CLIA regimen as RIC. None of the 7 patients receiving FTL3 TKIs developed a b-IFI and all achieved CR. Neither of the 2 patients who died within 42 days of the diagnosis of b-IFI had achieved CR, in contrast to 6 of 8 patients who were alive at day 42 (Table 3).

Two additional patients developed b-IFIs within 30 days following the discontinuation of ISAV PAP. One patient who had stopped ISAV upon investigator decision had a subsequent chest CT consistent with fungal lung infection during the follow-up period (possible IFI). A second patient developed a fungal gluteal abscess due to *Candida glabrata*. The isolate was susceptible to echinocandins (minimum inhibitory concentration [MIC] of micafungin, 0.008 µg/mL) and amphotericin B (1 µg/mL) and had dose-dependent susceptibility to fluconazole (4 µg/mL), whereas the MICs of itraconazole, posaconazole, voriconazole, and ISAV were 0.25 µg/mL, 0.5 µg/mL, 0.12 µg/mL, and 1 µg/mL, respectively (Clinical and Laboratory Standards Institute M27, fourth edition). The IFI classification of another patient was upgraded

Table 2. Summary of Reasons for Isavuconazole Discontinuation and Invasive Fungal Infection Outcomes After the 30-Day Follow-up Period

	Total	IFI Outcome 30 d After the Last Dose of ISAV			
Reason for Discontinuation of ISAV	No. (%)	No IFI	Possible IFI	Probable IFI	Proven IFI
Completed 12 wk of ISAV	9 (14)	9	0	0	0
Achieved CR/CRi + ANC > 0.5	37 (57)	36	0	0	**1**
Investigator decision	7 (11)	6	**1**	0	0
Death, not IFI-related	2 (3)	NA (2)	NA	NA	NA
Possible IFI	8 (12)	0	7	**1**	0
Probable IFI	2 (3)	0	0	2	0
All patients, no. (%)	…	53 (82)	8 (12)	3 (5)	1 (2)

Patients with a change in their IFI classification during the follow-up period are highlighted in bold.

Abbreviations: ANC, absolute neutrophil count; CR/CRi, complete remission with our without complete count recovery; IFI, invasive fungal infection; ISAV, isavuconazole; NA, not applicable.

Table 3. Characteristics of the 10 Patients Who Developed Breakthrough Invasive Fungal Infections While on Isavuconazole Prophylaxis

Age/Sex	Diagnosis	Remission-induction Chemotherapy	IFI[a] (EORTC/MSG Criteria)	ISAV Serum Concentration Day 8/15, μg/mL	Days on ISAV Prophylaxis	Initial Antifungal Treatment of b-IFI	ANC at the Time of IFI Diagnosis	CR Status at the Time of IFI Diagnosis	CR Status/Alive at 42 d After IFI Diagnosis
44/M	AML	CLIA	Possible	4.49/6.96	19	LipoAMB (7 d) + PCZ → PCZ	0.01	Not in CR	CR/Yes
63/M	AML	CLIA	Possible	4.60/6.99	15	LipoAMB (7 d) + VRC → VRC	0.00	Not in CR	Deceased
42/F	AML	CLIA	Possible	NA/NA	53	LipoAMB (21 d) + PCZ → PCZ	0.13	Not in CR	Not in CR/Yes
67/M	AML	Decitabine + venetoclax	Possible	5.77/3.67	23	LipoAMB (4 d) + PCZ → PCZ	0.00	Not in CR	CR/Yes
72/F	AML	Decitabine + venetoclax	Possible	3.81/5.52	21	LipoAMB (3 d) + PCZ → PCZ	0.00	Not in CR	CR/Yes
64/M	AML	Decitabine + venetoclax	Probable BAL GM 1.14	4.01/4.53	29	LipoAMB (14 d) + PCZ (16 d) → VRC	0.00	Not in CR	CR/Yes
43/M	MDS	CLIA	Possible	2.90/Discontinued	10	LipoAMB (4 d) + PCZ → PCZ	0.03	Not in CR	Not in CR/Yes
71/M	AML	Decitabine + venetoclax	Possible	3.27/4.83	57	PCZ + CAS → PCZ + CAS + LipoAMB	0.00	Not in CR	Deceased
66/M	AML	FLAG + GO	Probable BAL GM 0.81	2.37/Discontinued	8	PCZ	0.00	Not in CR	CR/Yes
79/F	AML	Decitabine + venetoclax	Possible[b]	5.62/5.36	26	PCZ + CAS → PCZ	0.00	Not in CR	CR/Yes

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; b-IFI, breakthrough fungal infection; CAS, caspofungin; CLIA, cladribine, idarubicin, cytarabine; CR, complete remission; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group–National Institute of Allergy and Infectious Diseases Mycoses Study Group; FLAG + GO, fludarabine, cytarabine, granulocyte colony-stimulating factor + gemtuzumab-ozogamicin; GM, Aspergillus galactomannan; IFI, invasive fungal infection; ISAV, isavuconazole; LipoAMB, liposomal formulation of amphotericin B; MDS, myelodysplastic syndrome; NA, not available; PCZ, posaconazole; VRC, voriconazole.

[a]All b-IFIs during ISAV primary antifungal prophylaxis were lung infections.

[b]Patient was upgraded from possible to probable IFI during the follow-up period due to a positive *Aspergillus* serum antigen assay.

from possible (while on ISAV) to probable IFI during the 30-day follow-up period due to a positive *Aspergillus* serum antigen assay. Collectively, 4 probable or proven (6%) and 8 possible (12%) IFI cases were seen during ISAV PAP and the 30-day follow-up period (Figure 1 and Table 2).

ISAV trough serum concentrations were available in 57 patients on day 8 (median, 3.37 μg/mL [range, 1.81–7.65]) and 54 patients on day 15 (median, 3.95 μg/mL [range, 1.56–9.25]). Day 15 serum ISAV levels were significantly higher ($P = .035$; Figure 2A). ISAV concentrations had very low intrapatient variability, with only 2 patients showing a ≥3 μg/mL change in serum concentrations between day 8 and day 15 (Figure 2B). Among patients who had their ISAV levels checked, no difference in day 8 ISAV trough concentrations were seen between

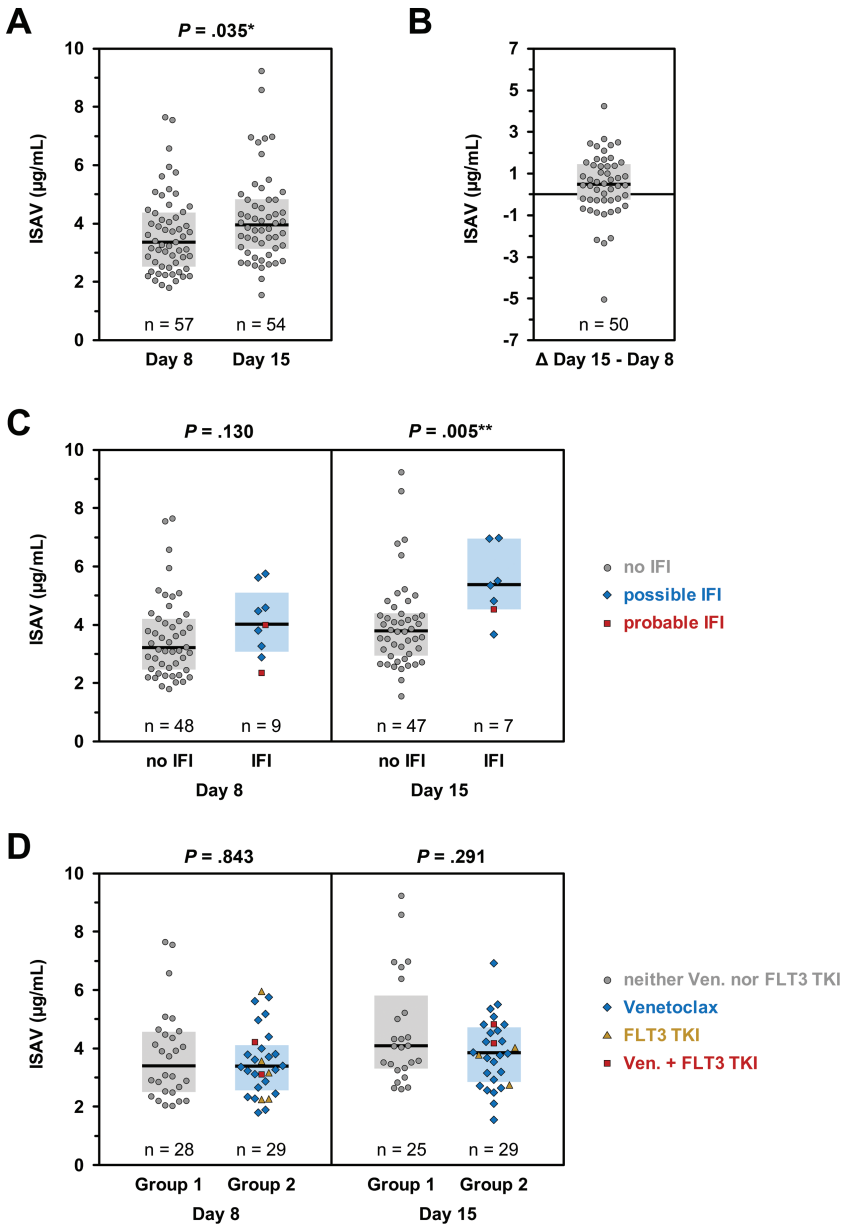

Figure 2. Isavuconazole (ISAV) trough concentrations on day 8 and day 15. ISAV trough concentrations were measured on days 8 and 15 using a validated liquid chromatography–tandem mass spectrometry assay [16]. *A*, Trough concentrations were available from 57 patients on day 8 and 54 patients on day 15. *B*, Matched pairs of day 8 and day 15 ISAV trough concentrations were available in 50 patients. The difference between serum concentrations on day 15 minus day 8 is plotted to document the intraindividual stability of ISAV serum levels. *C*, Comparison of ISAV trough concentrations on days 8 and 15 relative to the invasive fungal infection status at the time of ISAV discontinuation. *D*, Comparison of ISAV trough concentrations depending on the patients' chemotherapy regimen. Group 1: patients receiving neither venetoclax nor FLT3 tyrosine kinase inhibitors (gray circles). Group 2: patients receiving venetoclax (blue diamonds), FLT3 tyrosine kinase inhibitors (golden triangles), or both (red squares). For all panels, individual values, median (horizontal bars), and interquartile range (colored boxes) are shown. *A*, *C*, and *D*, Mann-Whitney *U* test. Significance levels are denoted by asterisks: **P* < .05, ***P* < .01. Abbreviations: IFI, invasive fungal infection; TKI, tyrosine kinase inhibitor; Ven., venetoclax.

those who developed b-IFIs (possible/probable) while on ISAV and those without b-IFIs, whereas, unexpectedly, day 15 concentrations tended to be higher in patients with b-IFIs (Figure 2C). Importantly, there were no differences in ISAV levels between patients who received venetoclax, FLT3 TKIs, or combinations thereof and those who did not (Figure 2D).

Finally, tolerability of ISAV was excellent, with grade 1 transaminitis, possibly attributable to ISAV, reported in only 2 patients (alanine aminotransferase [ALT] 85 U/L, aspartate aminotransferase 64 U/L in 1 patient, ALT 100 U/L in another one) who had normal liver function tests at baseline. In addition, 1 possibly ISAV-related case of elevated total bilirubin (2.9 mg/dL, grade 2) was seen. No patient experienced QTc prolongation while on ISAV. The median QTc times at baseline and on day 10 of ISAV were 404 and 402 ms, respectively.

DISCUSSION

This is the first prospective study of ISAV as PAP in patients with newly diagnosed AML/MDS undergoing RIC. Overall, we found that ISAV PAP is a safe and effective alternative in this patient cohort. ISAV absorption was excellent, and ISAV levels were higher on day 15, consistent with the fact that it takes 10–14 days for ISAV to reach steady-state levels [17]. However, on both day 8 and day 15, serum ISAV levels in all patients were above the proposed breakpoints (1 μg/mL) for *Aspergillus* [18], the most common causative agent of IFI in patients with hematological malignancies [19].

The (proven/probable) breakthrough IFI rate was 3% (15% if adding possible cases) during ISAV PAP and 6% (18% including possible cases) by the end of the 30-day follow-up period. Although comparable, the incidence of b-IFIs appears to be slightly higher in the present study than in randomized controlled [3] and real-life [20] studies of posaconazole as PAP as well as our own historical data [21]. One possible explanation could be that our patients were older, with a median age of 67 years vs 49 years in the randomized registration trial of posaconazole [3]. Older age (> 60 years) is a well-established risk factor for severe infections including IFI and inferior outcome during RIC in AML [22, 23]. Our patients also had a longer mean duration of severe neutropenia than in the posaconazole registration trial (32 days vs 25 days). In prior reports, ISAV has been associated with b-IFIs, mostly in patients with refractory leukemia and prolonged cytopenia [24]. There is a possibility that ISAV might be inferior to other triazoles in the setting of protracted neutropenia and lack of neutrophil recovery [25] and therefore may be prudent to avoid ISAV in heavily pretreated patients where marrow recovery might be delayed.

Among the patients who developed b-IFIs, nearly all received either venetoclax-based regimens or CLIA, agents/regimens associated with high efficacy but severe immunosuppression in patients with AML [26, 27]. Specifically, venectoclax is associated with prolonged and profound neutropenia [27, 28], a risk factor for IFI, as mature neutrophils depend on the antiapoptotic function of BCL-2 for survival. A recent study found prolonged neutropenia and thrombocytopenia in patients receiving venetoclax in combination with triazoles [29]. Although ISAV is a less potent CYP3A4 inhibitor compared with posaconazole [11] and venetoclax was dose-reduced by 50% in patients receiving ISAV following the recommendations in the venetoclax US label [30], ISAV may still lead to increased venetoclax serum concentrations, thereby potentiating the myelosuppressive effect [28, 29, 31]. However, therapeutic drug monitoring is not currently available for this newly approved BCL-2 antagonist to test this hypothesis. Therefore, further studies would be warranted to define the comparative impact of different triazoles on the duration and intensity of chemotherapy-induced cytopenia, especially in combination with venetoclax or other CYP3A4 substrates.

Importantly, the short-term survival of patients with b-IFIs was excellent in our study, and associated with subsequent achievement of CR. This, along with the fact that b-IFIs were not associated with low serum ISAV levels, underscores the importance of host-related factors to both the risk and outcomes of b-IFIs during RIC in the era of potent mold active triazoles such as posaconazole, voriconazole, and ISAV. Interestingly, outcomes were good in patients who developed b-IFIs while on ISAV prophylaxis and received treatment with other triazoles, consistent with anecdotal published experience [32].

ISAV toxicity was minimal and much less compared to our historical controls with posaconazole used as PAP [21]. Although the incorporation of "real-world" data in the study by Tverdek et al [21] could explain the excess toxicities of posaconazole when used as PAP, ISAV appears to be less toxic [33] and a good alternative in patients with posaconazole-associated toxicities [34]. In particular, no increased incidence of ISAV-associated side effects was seen and ISAV serum levels were adequate in patents given venetoclax and/or FLT3 TKIs as part of their RIC. Despite the inclusion of older subjects in our study, patients in general and specifically those who received either venetoclax, a FTL3 TKI, or both, achieved high CR rates and had excellent survival. This underscores the importance of the ability to incorporate the most potent molecularly targeted agents into RIC regimens, which is facilitated by the use of ISAV as PAP. As more novel targeted antileukemia agents (eg, mutant isocitrate dehydrogenase inhibitors and newer-generation, potent FLT3 TKIs [gilteritinib, quizartinib, and crenolanib]) continue to be studied as frontline AML therapies with promising results [35], the strategy of personalizing PAP—for example, studying these agents in combination with ISAV—has merit and deserves further evaluation.

Despite its strength as a prospective and detailed study of a relatively homogeneous neutropenic patient cohort naive to prior antifungals, there are limitations of our single-institution, unblinded, nonrandomized study. Importantly, our

experience cannot be extrapolated to patients receiving secondary antifungal prophylaxis (ie, patients who had received prior posaconazole or voriconazole or those with prior IFI), or to patients with relapsed or refractory leukemia. The choice of PAP in the frontline setting might be different compared to PAP in the setting of salvage chemotherapy, and factors such as prolonged cumulative immunosuppression, comorbidities, use of QTc-prolonging agents, local epidemiology, and sequential exposures to antifungals (and hence, concerns of selection of antifungal resistance) need to be considered. In addition, trials of ISAV PAP would be warranted during RIC in acute lymphocytic leukemia, a disease with a high background rate of IFIs [36]. As echinocandins have been shown to be inferior to triazoles as PAP in AML in some [37] but not all studies [38], the role of echinocandins as PAP in patients receiving molecularly targeted therapies in acute leukemia also needs to be revisited. Finally, as b-IFIs have been reported in high-risk hematology patients on prophylaxis with all the major triazoles (voriconazole, posaconazole, ISAV) [39], it would be important to study the comparative effectiveness of these agents and their long-term tolerability in the context of the changing landscape of acute leukemia treatment [40]. Well-conducted prospective comparative trials of each triazole used as PAP or, more realistically, well-constructed multi-institutional registries would be important.

Notes

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