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A Single-Center, Open-Label Trial of Isavuconazole Prophylaxis against Invasive Fungal Infection in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Isavuconazole is a broad-spectrum triazole approved for treatment of invasive fungal infections (IFIs). In this open-label, single-arm study, we evaluated isavuconazole for antifungal prophylaxis after allogeneic hematopoietic cell transplantation (HCT). Adult patients admitted for first HCT received micafungin 150 mg i.v. daily from admission through day +7 (D+7) post-transplantation (±2 days) followed by isavuconazole prophylaxis (i.v./p.o. 372 mg every 8 hours for 6 doses and then 372 mg daily) through maximum D+98 post-HCT. Patients were followed through D+182. The primary endpoint was prophylaxis failure, defined as discontinuation of prophylaxis for proven/probable IFI; systemic antifungal therapy for >14 days for suspected IFI; toxicity leading to discontinuation; or an adverse event. Between June 2017 and October 2018, 99 patients were enrolled in the study, of whom 95 were included in our analysis. The median patient age was 57 years (interquartile range [IQR], 50 to 66 years). Sixty-four (67%) patients received peripheral blood, 17(18%) received bone marrow, and 14 (15%) received a cord blood allograft for acute leukemia (55%), lymphoma (17%), myelodysplastic syndrome (16%), or another hematologic disease (14%). One-third (n = 31; 33%) of patients underwent $CD34^+$-selected HCT. Isavuconazole prophylaxis was given for a median of 90 days (IQR, 87 to 91 days). Ten patients (10.7%) met the primary endpoint. Candidemia occurred in 3 patients (3.1%), 1 of whom had grade III skin acute graft-versus-host disease (GVHD). Toxicity leading to discontinuation occurred in 7 patients (7.4%). The most common toxicity was liver function abnormalities in 5 patients, including grade 1 transaminitis in 2 patients and grade 3 hyperbilirubinemia in 3 patients. Four patients (4.2%) had early discontinuation of isavuconazole for reasons not meeting the primary study endpoint. Six patients died during the study period, including 3 during prophylaxis and 3 during follow-up. No deaths were attributed to isavuconazole. The majority (85%) of allogeneic HCT recipients completed isavuconazole prophylaxis according to protocol. The rate of breakthrough candidemia was 3.1%, and there were no invasive mold infections. Our data support the utility of isavuconazole for antifungal prophylaxis after HCT.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is associated with a high risk of invasive fungal infections (IFIs). Fluconazole is approved in the United States for *Candida* prophylaxis during HCT, but it does not provide coverage against molds [1]. Voriconazole, a broad-spectrum triazole active against *Candida* and *Aspergillus* species, has been increasingly used for antifungal prophylaxis in patients undergoing high-risk HCT, such as cord blood HCT and ex vivo T cell-depleted HCT recipients [2-4]. In a randomized trial of voriconazole versus fluconazole prophylaxis in standard-risk HCT recipients, the overall rates of IFI and fungal infection-free survival at 6 and 12 months were similar in the 2 arms, but there was a significant decrease in infections caused by *Aspergillus* in the voriconazole arm at 6 months [5].

The utility of voriconazole is limited by drug-drug interactions (especially with immunosuppressants), variations in metabolism due to CYP2C19 polymorphisms, and adverse events (AEs), including hepatotoxicity, QT prolongation, reversible central nervous system (CNS) effects, and increased risk of skin neoplasms with long-term use. In clinical trials of voriconazole for the

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treatment of invasive aspergillosis (IA), transaminase elevations were observed in up to 19% of patients, with 4% being serious hepatic AEs. In a retrospective study of 200 HCT recipients who received voriconazole prophylaxis between 2005 and 2007 at one center, elevation in liver function tests occurred in 68 patients (34%), and 17 patients (8.5%) developed clinical hepatotoxicity. Voriconazole was discontinued in approximately one-half of all patients with hepatotoxicity [6]. In a more recent study, voriconazole was discontinued prematurely in 45% of HCT recipients (n = 147) due to intolerance, toxicity, or drug interactions [7]. Posaconazole, another mold-active triazole, has been approved for antifungal prophylaxis in HCT recipients with graft-versus-host disease (GVHD) based on a study showing noninferiority compared with fluconazole or itraconazole in this population [8]. Posaconazole has a relatively favorable safety profile but is associated with QT prolongation and drug-drug interactions [9,10].

Isavuconazonium sulfate (Cresemba) [11] is the prodrug of isavuconazole, a broad-spectrum triazole that demonstrated potent activity in animal models of IA, mucormycosis, and invasive candidiasis [12]. Isavuconazole was approved in 2015 by the US Food and Drug Administration for the treatment of IA and invasive mucormycosis. In a large randomized study of isavuconazole versus voriconazole for treatment of IA and other filamentous fungi (SECURE trial), isavuconazole was noninferior to voriconazole in terms of fungal-free survival and overall response, but had better tolerability and safety profile. Of the drug-related hepatobiliary AEs reported in the study, 16% (n = 42) were noted in the voriconazole group, compared with 9% (n = 23) in the isavuconazole group. Furthermore, key AEs known to be related to voriconazole (including eye, hepatic, and skin disorders) and discontinuations due to AE were significantly less common among isavuconazole-treated patients [13]. Isavuconazole is associated with fewer drug interactions compared with voriconazole and itraconazole, because it is a weaker inhibitor of CYP3A4 [14], thereby easing administration in patients receiving immunosuppressive therapy. Interestingly, in contrast to other triazoles, isavuconazole shortens the QTc interval in a concentration-related manner [11]. QTc shortening was also observed during administration of the currently approved dose in clinical trials and real-world studies of isavuconazole [13,15-17].

There are limited data on the use of isavuconazole as prophylaxis in HCT recipients [18]. We conducted a prospective single-center, open-label, single-arm study of isavuconazole for antifungal prophylaxis through week 14 post-HCT. Our objectives were to evaluate the safety, tolerability, and effectiveness of isavuconazole prophylaxis for IFI prevention in allogeneic HCT recipients.

METHODS

Patients and Study Design

We recruited subjects aged ≥18 years who received a first peripheral blood, marrow, or cord blood transplant for a hematologic malignancy. Patients were excluded if they had one of the following: proven or probable mold infection or deep mycoses, including hepatosplenic candidiasis, <60 days from the first dose of isavuconazole; history of allergy or intolerance to isavuconazole; clinically significant elevation of liver function tests (LFTs), at the discretion of the treating physician; or familial short QT syndrome.

In accordance with the institutional standard of care, HCT recipients received antifungal prophylaxis with micafungin 150 mg i.v. once daily from the day of admission for HCT until day +7 post-transplantation (D+7) [19,20]. The dose of micafungin was chosen based on early studies suggesting administration of high doses of micafungin when used for antimold prophylaxis [21,22]. On D+7 (±2 days), micafungin was discontinued, and isavuconazole was started at 372 mg every 8 hours for 6 doses, followed by 372 mg once daily. Isavuconazole was administered p.o. or i.v. until patients could receive oral medication, at the discretion of the treating physician. Patients who met all eligibility criteria but had a contraindication to starting isavuconazole on D+9 were permitted to start isavuconazole later than D+9 after review and approval by the study's primary investigator.

The maximum duration of isavuconazole prophylaxis on the study was through week +14 (D+98). Recipients of conventional peripheral blood or marrow allografts with no GVHD were permitted to discontinue prophylaxis as early as D+60 at the discretion of the clinician. Interruption of isavuconazole prophylaxis was permitted during IFI workup, during which patients received other empiric antifungal therapy according to the institutional standard of care. If an IFI diagnosis was not confirmed and the patient had received ≤14 days of systemic antifungal therapy, isavuconazole prophylaxis was resumed. If IFI was confirmed or patients received >14 days of systemic antifungal therapy, isavuconazole prophylaxis was permanently discontinued. Any IFI occurring during prophylaxis was classified according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions [23]. Interruption of isavuconazole for ≤14 days was permitted for evaluation of possible toxicity. If toxicity was deemed unrelated to isavuconazole, prophylaxis was resumed. Patients were followed through week +26 post-HCT for overall survival and occurrence of IFI. A study schema is provided in Supplementary Figure S1.

Post-Transplantation Immunosuppression

Recipients of ex vivo T cell-depleted (TCD) allografts did not receive any additional pharmacologic GVHD prophylaxis [24]. Recipients of unmodified peripheral blood or marrow HCT received tacrolimus-based immunosuppression, except for haploidentical transplant recipients, who were given cyclophosphamide post-HCT. Recipients of cord blood transplants received a calcineurin inhibitor (predominantly cyclosporine A) and mycophenolate mofetil [25-27].

Study Assessments

During the HCT admission, patients were monitored as inpatients. After discharge, they were monitored at the outpatient clinic at least weekly through D+60, at least every 2 weeks through D+98, and at least every 4 weeks through week +26. LFT parameters, including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin, were assessed during study visits. Serum isavuconazole levels were measured using reversed-phase ultra-performance liquid chromatography tandem mass spectrometry (Viracor-Eurofins, Lee's Summit, MO). Isavuconazole level was assessed once after patients had been receiving a steady dose of oral isavuconazole for 10 to 14 days. In addition, in the subgroup of patients with grade ≥II or higher acute GVHD of the gastrointestinal (GI) tract, serum levels of isavuconazole were obtained at diagnosis of GVHD and again at 2 weeks after starting treatment for GVHD. The clinical workup for suspected IFI included serum fungal markers galactomannan and [1,3]-beta-D-glucan and computed tomography (CT) scans of the chest, brain, sinus, or abdomen/pelvis as clinically indicated. In addition, bronchoscopy or other procedures for tissue sampling were performed based on clinical indication and feasibility. Acute GVHD was graded by standard criteria [28].

Study Endpoints

The primary endpoint was clinical failure by week +14 post-HCT. Clinical failure was defined as any of the following: receipt of systemic antifungal therapy for suspected fungal infection for >14 consecutive days, breakthrough proven or probable IFI during the prophylaxis phase, toxicity of isavuconazole leading to permanent discontinuation of prophylaxis, and any AE necessitating permanent discontinuation of isavuconazole regardless of attribution. The prophylaxis phase was defined as the period from the first dose of isavuconazole through 7 days after discontinuation.

Secondary endpoints included description of reasons for discontinuation of isavuconazole prophylaxis, number and type of probable or proven breakthrough IFIs by the end of the study (week +26), overall survival at week +26, and assessment of isavuconazole serum level in all patients and in patients with or without grade ≥II acute GVHD of the GI tract. AEs leading to discontinuation of isavuconazole were reported and graded according to the Common Terminology Criteria for Adverse Events version 5.0 [29], and the relationships of the AEs to isavuconazole were assessed.

Statistical Analysis

Patients who received >2 doses of isavuconazole were considered evaluable and included in our analyses. The incidence of clinical failure was estimated using the cumulative incidence function. Relapse or death were treated as competing risks.

Based on a previous multicenter, randomized prophylactic trial of voriconazole, the rate of clinical failure for voriconazole was estimated at 40% to 50% [5]. We estimated the rate of clinical failure in our historical control to be 50%; therefore, we considered isavuconazole prophylaxis promising and worthy of future investigation at clinical failure rate of ≤36%. Using these rates, a single-stage exact design was implemented. We planned to include a total of 85 evaluable patients in the primary endpoint and aimed to accrue

100 subjects to ensure at least 85 evaluable patients. Type I and type II errors were both set at .10.

The Mann-Whitney *U*test was used to assess serum levels of isavuconazole in patients with and without grade ≥II acute GVHD of the GI tract. We estimated the incidence of probable or proven breakthrough IFI with isavuconazole prophylaxis at the end of the study (week +26) using cumulative incidence functions. Death in the absence of IFI was considered a competing event for this analysis. Kaplan-Meier analysis was used to estimate overall survival at week +26.

Study Oversight

The study was funded through an investigator-initiated grant from Astellas Pharma Global Development, Inc. The Memorial Sloan Kettering Cancer Center Institutional Review Board reviewed and approved the study. All patients provided signed written informed consent before undergoing any study-specific procedures.

RESULTS

Between June 1, 2017, and October 31, 2018, a total of 99 patients were enrolled on the study. Four patients had LFT abnormalities precluding azole administration in the predefined window for isavuconazole initiation and thus were not included in our analysis. Ninety-five patients received more than 2 doses of isavuconazole and were included in the analysis (Figure 1). Demographic and clinical characteristics are summarized in Table 1. Sixty-four patients (67%) received peripheral blood stem cells, 17 (18%) received bone marrow, and 14 received (15%) cord blood allograft for acute leukemia (55%), lymphoma (17%), myelodysplastic syndrome (16%), or other hematologic diseases (14%). Thirty-one patients (33%) underwent $CD34^{+}$-selected HCT. The median time from HCT to engraftment was 12 days (IQR, 11 to 19 days). Fifty-four patients (57%) developed acute GVHD (grade I in 11 patients, grade II in 37, and grade III-IV in 6 patients).

Isavuconazole Administration

Isavuconazole prophylaxis was started at a median of 7 days after HCT (IQR, 7 to 8 days; range, 5 to 11 days) and continued according to protocol for a median of 90 days (IQR, 87 to 91 days; range, 1 to 93 days). Fifty-five patients (58%) continued isavuconazole prophylaxis beyond D+98 for a median of 10 additional days (IQR, 4 to 51 days) at the discretion of the clinicians.

Most patients (58; 61%) started prophylaxis with i.v. isavuconazole, with the majority (n = 55) later switching to the oral formulation after a median of 9 days (IQR, 6 to 14 days; range, 2 to 34 days). Thirty-seven patients (39%) started prophylaxis with oral isavuconazole and of these, 8 were later switched to the i.v. formulation due to issues with oral medication tolerability. Thirteen patients (14%) had interruptions in isavuconazole administration lasting <14 days (range, 1 to 13 days; median, 6 days). The reasons for temporary discontinuation of isavuconazole included transient LFT abnormalities in 5

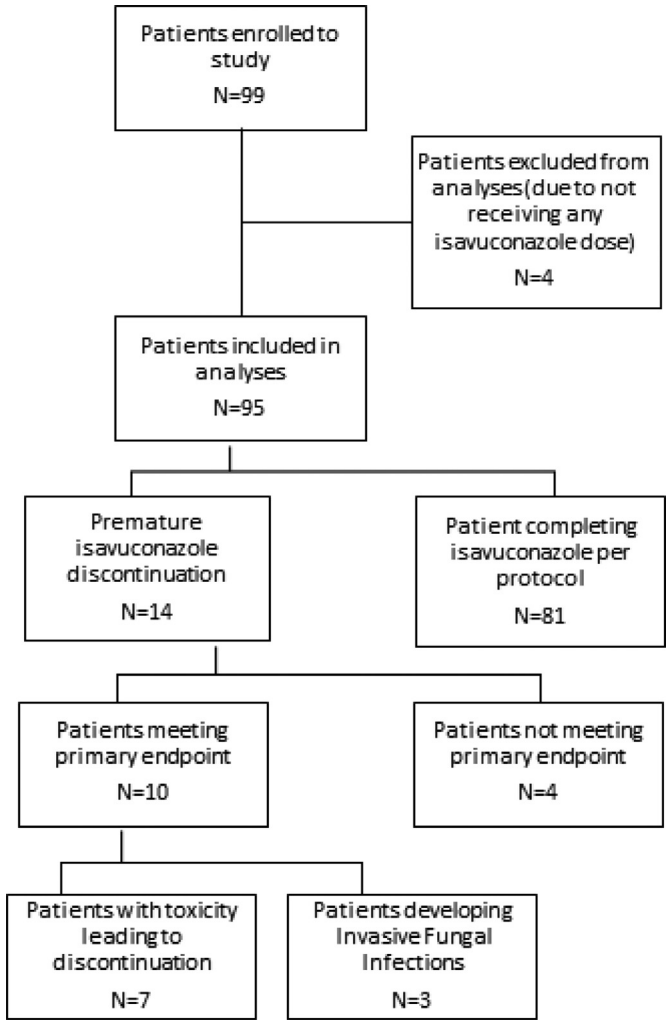


Figure 1. Study CONSORT flow chart.

Table 1
Patient Characteristics

Characteristic	Value
Age, yr, median (range)	57 (26-78)
Sex	
Female	31 (33)
Male	64 (67)
Underlying disease	
Leukemia	51 (53)
Myelodysplastic syndrome	15 (16)
Lymphoma	16 (17)
Other hematologic malignancy	13 (14)
Graft manipulation: ex vivo T cell depletion ($CD4^+$-selected)	31 (33)
Donor type	
Matched related	19 (20)
Matched unrelated	36 (38)
Mismatched related/unrelated	26 (27)
Haploidentical	14 (15)
HCT graft source	
Peripheral blood stem cells	64 (67)
Bone marrow	17 (18)
Cord blood	14 (15)
Conditioning	
Myeloablative	53 (56)
Nonmyeloablative	13 (14)
Reduced intensity	29 (30)
GVHD prophylaxis	
Tacrolimus + methotrexate*	26
Cyclosporine + mycophenolate mofetil†	16
Tacrolimus + mycophenolate mofetil	2
Cyclophosphamide + mycophenolate mofetil + tacrolimus or sirolimus‡	22
Ex vivo T cell depletion	29

* Seven patients also received sirolimus in addition to tacrolimus and methotrexate.
† Eleven patients received tocilizumab in addition to cyclosporine + mycophenolate mofetil.
‡ Cyclophosphamide was administered post-HCT. Tacrolimus (19 patients); Sirolimus (3 patients).

patients, other suspected toxicity in 2 patients, logistical issues leading to delay in medication procurement in 2 patients, and not documented in 4 patients.

Primary Endpoint

Ten patients met the primary endpoint of prophylaxis failure. Of these, 7 patients discontinued prophylaxis due to toxicity and 3 patients discontinued prophylaxis due to breakthrough IFI (Figure 1). The cumulative incidence of prophylaxis failure was 10.7% (Figure 2).

Secondary Endpoints

Reasons for Isavuconazole Discontinuation

Eighty-one patients (85%) completed isavuconazole prophylaxis according to protocol. Fourteen patients (15%) discontinued isavuconazole prematurely. Of these 14 patients, 10 met the primary endpoint and 4 discontinued prophylaxis for other reasons. Reasons for premature discontinuation of prophylaxis are shown on Table 2.

Toxicity leading to isavuconazole discontinuation included anemia in 1 patient, rash and nausea in 1 patient, and LFT abnormalities in 5 patients (2 with grade one transaminitis and 3 with grade three hyperbilirubinemia) (Table 3). Breakthrough candidemia occurred in 3 patients.

Four patients discontinued isavuconazole prophylaxis for other reasons. One patient had suspected esophageal candidiasis based on visual inspection during upper endoscopy (but no cultures). Based on this finding, isavuconazole prophylaxis was discontinued on D+36, and antifungal therapy with voriconazole and micafungin was started. One patient was empirically switched to voriconazole on D+97 due to a lung mass that was later diagnosed as nocardiosis, 1 patient was switched from isavuconazole to micafungin on D+19 due to low tacrolimus levels and concern for drug-drug interactions, and 1 patient had isavuconazole withheld on D+92 due to concern for interaction with antituberculosis medications (Table 2).

IFIs

Three patients developed breakthrough IFI while under isavuconazole prophylaxis. All 3 IFIs were candidemias, including 2 cases of *Candida parapsilosis* diagnosed at D+14 and D+47 and 1 case of *Candida glabrata* diagnosed on D+84. Both *C parapsilosis* strains were sensitive to fluconazole, with a minimal inhibitory concentration of 1 and 2 μg/mL, respectively. Isavuconazole sensitivity testing was not done. An isavuconazole level of 1.4 μg/mL was measured at IFI diagnosis in 1 patient. Antifungal sensitivity data were not available for *C glabrata* because culture results arrived after the patient had died. An isavuconazole level of 4.2 μg/mL was measured at 1 week before the onset of candidemia.

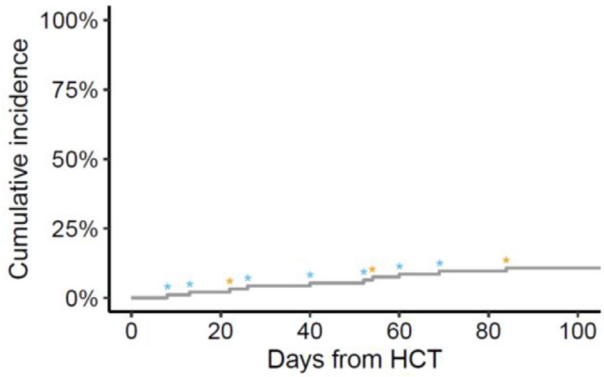
There were no cases of proven or probable invasive mold infection. Thirty-two patients underwent chest CT scan between D+1 and D+98 post-HCT for clinical indications. Four patients had radiographic findings consistent with possible IFI according to EORTC/MSG criteria, including 2 patients with clinical conditions that could explain the CT findings (1 with concurrent candidemia, 1 with pulmonary nocardiosis), 1 patient underwent lung biopsy that was nondiagnostic, and 1 patient had a lung nodule with a halo sign that was not evaluated further. No additional proven or probable IFI cases occurred during the follow-up period (up to week +26).

Overall Survival

A total of 6 patients (6.3%) died during the study, 3 during the prophylaxis phase and 3 during the follow-up phase. The causes of death included candidemia in 2 patients (1 with concomitant persistent vancomycin-resistant *Enterococcus faecium* bacteremia), GVHD in 2 patients, graft failure in 1 patient, and respiratory failure attributed to *Pneumocystits jirovecii* or bronchiolitis obliterans in 1 patient (Table 4).

Isavuconazole Levels

One hundred and ten serum samples for isavuconazole measurement were obtained from 92 patients. Ninety-two (84%) of the samples were obtained for routine drug levels according to protocol. Eighteen patients had multiple measurements (13 due to GI tract GVHD, 1 due to LFT abnormality, 3 due to suspected IFI, and 1 for an unknown reason). One hundred and four (94%) samples were obtained while the patient was on oral isavuconazole, 5 were drawn while the patient was on an I.V. formulation, and 1 sample was obtained after isavuconazole discontinuation in a patient with hyperbilirubinemia. The median isavuconazole level was 3 μg/mL (IQR, 2.2 to 4.2; range, .7 to 10). Four patients had levels exceeding 7 μg/mL, of whom 3 had GI GVHD. No patients experienced toxicity leading to discontinuation. Two of these patients had a repeat level within the acceptable range (4.4



Median (IQR)	Cumulative incidence	# of events/ # of patients
46 (23-59)	10.7%	10/95

Figure 2. Cumulative incidence of isavuconazole antifungal prophylaxis failure.

Ten patients (10.7%) met the primary endpoint of isavuconazole antifungal prophylaxis failure, including 7 patients with toxicity causing early isavuconazole discontinuation (marked with red stars) and 3 patients with breakthrough invasive fungal infection (marked with blue stars).

Table 2
Reasons for Early Isavuconazole Discontinuation (N = 14)

Reason for Discontinuation	Number
Primary endpoint achieved	10
Toxicity	
All	7
Liver function abnormalities	5
Rash and nausea	1
Anemia	1
Breakthrough IFI: candidemia*	3
Not meeting primary endpoint	4
Lung lesion suspected as IFI, eventually diagnosed as nocardia infection	1
Suspected drug-drug interaction with tacrolimus	1
Suspected esophageal candidiasis by endoscopy	1
Concern about drug-drug interaction with antituberculosis medications	1

* *C parapsilosis* in 2 patients and *C glabrata* in 1 patient.

μg/mL for both). No significant difference in isavuconazole level was found between patients with grade ≥II GI acute GVHD (n= 27; median, 2.7 μg/mL) and patients without GI GVHD (n = 62; median, 3.25 μg/mL; $P = .12$) (Figure 3). For the 13 patients who developed GI GVHD and had a second isavuconazole level drawn, no difference was found between the first and repeated isavuconazole levels (median, 2.3 μg/mL and 2.4 μg/mL, respectively; $P = .8$).

DISCUSSION

HCT recipients are at increased risk for IFI. The risk for IFI is dependent on the duration and severity of neutropenia, extent of GVHD and immunosuppressant therapy, and HCT characteristics, such as the degree of transplant matching. The Transplant-Associated Infection Surveillance Network database reported a cumulative annual IFI incidence of 5.8 to 8.1 per 100 allogeneic HCTs [30]. Accordingly, the Infectious Disease Society of America guidelines recommend antifungal prophylaxis in all patients following HCT, with antimold coverage in a subset of high-risk patients with previous invasive aspergillosis, anticipated prolonged neutropenic periods of at least 2 weeks, or a prolonged period of neutropenia immediately before HCT [31]. The acceptable prophylactic options include the triazoles (eg, fluconazole, itraconazole, voriconazole, posaconazole) and echinocandins (eg, micafungin, caspofungin). At our institution, patients are given micafungin from admission for HCT through D+7 to allow for stable calcineurin inhibitor dosing and to avoid possible drug interactions between azoles and conditioning agents, followed by voriconazole for up to D+75 to D+100 [20]. Voriconazole administration presents several challenges in HCT recipients. Owing to the variable pharmacokinetics and narrow therapeutic window, a considerable proportion of patients are either underdosed or experience AEs due to toxic levels [6,32]. Furthermore, voriconazole has drug interactions with many compounds, including drugs commonly used for GVHD prophylaxis [33]. Finally, administration of the i.v. formulation of voriconazole may be limited in patients with renal impairment due to its cyclodextrin content. In a retrospective study from our center, voriconazole antifungal prophylaxis was discontinued prematurely in 45% of HCT recipients due to intolerance, toxicity, or drug interaction [7].

In this first prospective study to evaluate the use of isavuconazole for the prevention of invasive fungal infections following HCT, 84% of patients completed antifungal prophylaxis according to the protocol. Seven patients (7.4%) discontinued isavuconazole due to toxicity, of which 5 patients (5.3%) discontinued isavuconazole due to LFT abnormalities. These figures are consistent with previous clinical trials showing a favorable safety and tolerability profile for isavuconazole [13]. In a dose-escalation study of isavuconazole for antifungal prophylaxis in patients with acute myelogenous leukemia and neutropenia, AEs were reported in 45.5% of patients in the low-dose cohort and in 66.7% of patients in the high-dose cohort, but these were mostly mild to moderate in severity, most commonly rash and headache [34].

Isavuconazole displays excellent bioavailability (~98%) after oral administration without any clinically relevant food restrictions [35]. However, the absorption of oral medications may be impaired in patients with significant mucositis or GI tract GVHD. Our patients had a median isavuconazole level of 3 μg/mL, which correlates with levels reported in other clinical trials [36,37]. We

Table 3
Characteristics of Liver Function Abnormalities

Patient	Reason for Isavuconazole Discontinuation	Days of Isavuconazole	Maximum AST/ALT, U/L	Maximum Total Bilirubin, mg/dL	AFP Given Following Isavuconazole	Other Concomitant Liver Disease
1	Transaminitis	19	287/536	1.2	Micafungin	None
2	Mild transaminitis	53	59/85	0.8	Posaconazole	Concomitant medications (fibrates)
3	Hyperbilirubinemia	35	55/36	2.5	Micafungin	Suspected VOD
4	Hyperbilirubinemia	1	11/9	29.1	Micafungin	VOD/liver GVHD
5	Hyperbilirubinemia	4	25/27	6.4	Micafungin => fluconazole	Concomitant medications (methotrexate)

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; AFP, antifungal prophylaxis; VOD, veno-occlusive disease.

Table 4
Time to Death Post-HCT and Causes of Death for Patients Who Expired During the Study

Death (Day Post-HCT)		Primary Cause of Death	Secondary Cause of Death	IFI Present at Time of Death
Death during isavuconazole prophylaxis				
1	D+36)	Relapse of leukemia	Infection (*C parapsilosis* BSI)	Yes
2	(D+57)	GVHD		No
3	(D+84)	Relapse of leukemia	Infection (*C. glabrata* + VRE BSI)	Yes
Death during follow-up period				
4	(D+103)	Respiratory failure	*Pneumocystits jirovecii* pneumonia vs bronchiolitis obliterans	No
5	(D+103)	GVHD		Yes
6	(D+177)	Graft failure	EBV PTLD	No

BSI indicates bloodstream infection; VRE, vancomycin-resistant enterococcus; EBV, Epstein-Barr virus; PTLD, post-transplantation lymphoproliferative disorder.

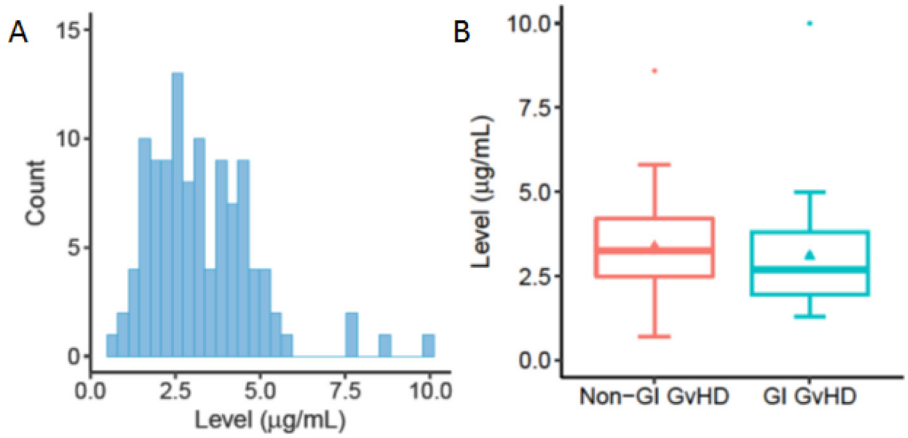


Figure 3. (A) Distribution of isavuconazole levels. Isavuconazole plasma concentrations in 104 samples obtained during oral isavuconazole therapy. The median concentration was 3 µg/mL (IQR, 2.2 to 4.2 µg/mL). (B) Boxplots of isavuconazole plasma concentrations in patients with grade ≥II GI GVHD (n = 27; median, 2.7 µg/mL) and patients without grade ≥II GI GVHD (n = 62; median, 3.25 µg/mL; *P* = .12). The horizontal line represents the median; boxes, IQR; whiskers, range.

used reversed-phase ultra-performance liquid chromatography tandem mass spectrometry for therapeutic drug monitoring, which has not yet been approved for diagnostic use by the Food and Drug Administration and may be associated with higher drug levels compared with highly sensitive assays. The clinical justification and the accuracy of this assay for therapeutic drug monitoring of isavuconazole remain to be determined. Nevertheless, the fact that no significant difference in isavuconazole levels was found between patients with and those without grade ≥II GI acute GVHD is reassuring and is consistent with previous evidence showing that mucositis might not preclude the use of oral isavuconazole [38].

In the early peritransplantation period, patients may be unable to tolerate oral medications due to mucositis, severe GVHD, or GI infectious complications. In contrast to voriconazole and posaconazole, the i.v. formulation of isavuconazole does not contain cyclodextrin and thus does not carry the risk of nephrotoxicity associated with these drugs [12].

Three patients (3.2%) from our cohort developed breakthrough IFI. This rate is comparable to breakthrough IFI rates reported in other studies of antifungal prophylaxis in patients following HCT [8,20,39]. Similar breakthrough IFI rates were previously reported in HCT recipients from our center treated with voriconazole for antifungal prophylaxis (13 of 327; 4%) [7]. Interestingly, all IFI cases in our cohort were candidemias, and none were invasive mold infections. The major risk factor for IA is prolonged neutropenia. In our study, the duration of neutropenia was relatively short, with a median time to engraftment of 12 days. Furthermore, high-risk patients with a previous history of mold infection were excluded, thereby selecting for patients with a lower risk of developing mold infection.

Isavuconazole displays in vitro broad activity against *Candida* and most *Aspergillus* species, similar to voriconazole [40], as well as variable activity against mucorales and other rare molds [41]. In the phase 3 SECURE trial, isavuconazole demonstrated noninferiority compared with voriconazole in treatment of invasive mold infections [13]. However, breakthrough IFIs have been reported with isavuconazole in the real-world setting [42]. In a retrospective trial of isavuconazole primary prophylaxis in 145 high-risk patients with hematologic malignancies or HCT, isavuconazole showed a trend toward higher rates of breakthrough IFIs compared with posaconazole and voriconazole [18]. Most IFI cases in that trial were invasive pulmonary aspergillosis, with only 1 case of *Candida* bloodstream infection described. Of note, only 32% of participants in this study were HCT recipients, and only 1 out of 12 breakthrough IFIs occurred in an HCT recipient [18]. In another study comprising 100 leukemia patients treated with isavuconazole for AFP, 13 patients had breakthrough IFI, 7 with *Candida* infections [43]. Breakthrough *Candida* infection was associated with profound neutropenia. In our study, however, 1 patient developed breakthrough candidemia while neutropenic, whereas in the other 2 patients it developed postengraftment. In the phase III clinical ACTIVE trial including patients with proven candidemia or invasive candidiasis, isavuconazole failed to demonstrate noninferiority compared with caspofungin but did show similar overall success at the end of treatment [44]. Of note, the minimum inhibitory concentration of specific *Candida* species (specifically *C glabrata, C krusei*, and *C guilliermondii*) has been shown to be higher for triazoles, including isavuconazole, compared with echinocandins [45]. More studies are needed to clarify whether isavuconazole provides sufficient protection against *Candida* infections post-HCT.

Our study has several limitations inherent to its design. As an open-label study, physicians were aware that patients were receiving a mold-active azole, and this knowledge may have influenced treatment decisions regarding empiric therapy or workup of pulmonary lesions. Because of the lack of a comparator arm, a head-to-head comparison with other antifungal agents was not possible. All patients received micafungin from admission through D+5 to D+9 post-HCT; thus, our study evaluates the efficacy of the strategy of sequential prophylaxis with micafungin and isavuconazole in the 14 weeks post-HCT. By including only proven and probable IFI cases as our endpoint definitions, we might have missed some cases of pulmonary IA that did not meet the strict EORTC/MSG definitions. A thorough review of all chest CT scans done from isavuconazole initiation to D+98 revealed 2 additional patients who might qualify as having possible IFI. However, in both cases, further investigation into the clinical course and associated workup suggested that a diagnosis of IFI was unlikely.

While acknowledging these limitations, our study has several strengths. We evaluated isavuconazole as primary prophylaxis in a contemporary cohort of HCT recipients at a large tertiary center. We found that isavuconazole was well tolerated and effective as prophylaxis in different HCT types, including cord blood and haploidentical HCT. Our data support adequate exposure and similar plasma concentrations of isavuconazole in patients with GI GVHD. Importantly, the rate of discontinuation due to hepatotoxicity was only 5%, much lower than that in historical controls from our center.

In summary, isavuconazole as primary prophylaxis in the first 100 days after allogeneic HCT was safe and effective in our study cohort. Our data show that isavuconazole is a suitable alternative to other currently available options for antifungal prophylaxis.

CONCLUSIONS

In this first prospective trial of isavuconazole prophylaxis in patients following HCT, isavuconazole was found to be safe and tolerable. The rate of premature discontinuation was lower with isavuconazole compared with the reported rate with voriconazole, and the rate of breakthrough IFI was comparable to that seen with alternative agents. More studies are needed to ensure the efficacy of isavuconazole in the prevention of *Candida* infections following HCT.

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Conflict of interest statement: G.A.P. has been an investigator and has received funding and consulting fees from Merck, Chimerix, Shire, and Astellas. M.A.P. reports honoraria from Abbvie, Bellicum, Celgene, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on data and safety monitoring boards for Cidara Therapeutics, Servier, and Medigene and on scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead, and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy and Be The Match, as well as on the Center for International Blood & Marrow Transplant Research Cellular Immunotherapy Data Resource Committee.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2020.02.009.

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