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Efficacy and safety of isavuconazole compared with voriconazole as primary antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients

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Abstract

Voriconazole is frequently discontinued prematurely as primary antifungal prophylaxis (AFP) in allogeneic hematopoietic cell transplant (HCT) recipients due to adverse events. Limited data exists for isavuconazole as AFP. We analyzed adult HCT recipients who received voriconazole or isavuconazole AFP to estimate rate of premature AFP discontinuation, identify risk factors for premature AFP discontinuation, and compare incidence of invasive fungal infection (IFI) and survival at day + 180 post-HCT between patients who received voriconazole/isavuconazole-AFP. This was a propensity score matched cohort analysis of 210 HCT-recipients who received voriconazole-AFP (9/1/2014-12/31/2016; voriconazole-cohort), and 95 HCT-recipients who received isavuconazole-AFP (5/1/2017-10/31/2018; isavuconazole-cohort). AFP discontinuation for any reason prior to completion was defined as "premature". Median (interquartile range, IQR) duration of AFP was longer in the isavuconazole-cohort (94 days, 87–100) vs. the voriconazole-cohort (76 days, 23–94; *P*-value < 0.0001). Premature AFP discontinuation was more frequent in the voriconazole-cohort (92/210, 43.8%) vs. the isavuconazole-cohort (14/95, 14.7%; *P*-value < 0.0001). The most common reason for premature discontinuation was biochemical hepatotoxicity (voriconazole-cohort: 48/210, 22.8% vs. isavuconazole-cohort: 5/95, 5.26%; *P*-value $= 0.0002$). Transaminase values between baseline and end-of-treatment (EOT) and up to 14 days post-EOT significantly increased in the voriconazole-cohort, but remained unchanged in the isavuconazole-cohort. The incidence of IFI at day + 180 was 2.9% (6/210) and 3.2% (3/95) in the voriconazole-cohort and isavuconazole-cohort, respectively (*P*-value $= 0.881$). All-cause mortality at day + 180 was 2.4% (5/210) and 6.3% (6/95) in the voriconazole-cohort and isavuconazole-cohort, respectively (*P*-value $= 0.089$). When compared to voriconazole, isavuconazole was a safer and as effective primary AFP during the first 3 months after HCT.

Lay Summary

When compared to voriconazole, isavuconazole is a safer and as effective primary antifungal prophylaxis during the first 3 months after allogeneic hematopoietic cell transplant, with lower rates of hepatotoxicity, and similar rates of fungal infections and all-cause mortality.

Key words: Isavuconazole, voriconazole, prophylaxis, invasive fungal infections, allogeneic hematopoietic cell transplant.

Introduction

Voriconazole is commonly used as primary antifungal prophylaxis (AFP) after allogeneic hematopoietic cell transplant (HCT) based on a randomized clinical trial and consensus guidelines.[1–3] However, premature discontinuation of voriconazole AFP occurs in up to 40% of patients due to adverse events (AE), predominately voriconazole-associated hepatotoxicity.[4,5] Isavuconazole is a broad-spectrum azole approved for treatment of infections by *Aspergillus* species and other non-*Aspergillus* molds. In a phase III randomized controlled trial, AE including hepatobiliary, skin, and eye disorders were reported less frequently in the isavuconazole compared with the voriconazole arm.[6] Limited, mainly retrospective, data exist on the safety and efficacy of isavuconazole as AFP in patients with hematologic malignancies, with breakthrough invasive fungal infection (bIFI) rates ranging between 0 and 18.5%.[7–10] However, few allogeneic HCT recipients were included in these studies.[7,10] Considering its broad spectrum of activity, established efficacy as treatment for invasive aspergillosis, and relatively benign AE-profile, isavuconazole appears as a desirable alternative for primary AFP in high-risk patients.[6–8,11,12]

At our Institution, voriconazole is used as AFP per standard of care[5] except between July 1, 2017 and October 31, 2018 when we conducted a single center, open-label trial of isavuconazole prophylaxis (ClinicalTrials.gov NCT03149055).[13] In this study, isavuconazole AFP was discontinued prematurely in 15% of patients, mainly due to an AE (7%) or a bIFI (3%).[13] The objectives of the present study are to (i) compare tolerability of voriconazole and isavuconazole as AFP; (ii) identify risk factors for premature AFP discontinuation and (iii) compare the incidence of IFI and overall survival by day + 180 post-HCT between patients who received voriconazole and isavuconazole AFP.

Methods

Study design

This is a frequency matched cohort analysis of adult (age ≥ 18 years) allogeneic HCT recipients at Memorial Sloan Kettering Cancer Center (MSKCC). The isavuconazole-cohort consists of 95 patients enrolled in an open-label trial of isavuconazole prophylaxis conducted from May 1, 2017 to October 31, 2018 (ClinicalTrials.gov NCT03149055).[13] The voriconazole-cohort consists of 210 patients who received voriconazole AFP between September 1, 2014 and December 31, 2016, matched to the isavuconazole-cohort using propensity score analysis (details in Statistical analysis). The study was approved by the MSKCC Institutional Review Board.

Standards of care

Graft manipulation and conditioning regimens were provided in accordance with institutional guidelines and as previously described.[14] Per our Institutional algorithm, patients with acute leukemia in first complete remission and patients with myelodysplastic syndrome received *ex vivo* T-cell depleted/CD34$^+$- selected HCT unless deemed ineligible. T-cell depletion was performed with the CliniMACS CD34 + reagent system (Miltenyi Biotec, Gladbach, Germany). Recipients of unmodified marrow or peripheral blood HCT received graft-versus- host disease (GvHD) prophylaxis, including tacrolimus and/or sirolimus and mycophenolate mofetil with or without methotrexate[15]; or post HCT cyclophosphamide for recipients of haploidentical donor allografts.[16] Cord blood HCT received cyclosporin and mycophenolate mofetil as GvHD prophylaxis.[17] Bacterial and viral prophylaxis was administered as previously described.[18]

Antifungal prophylaxis strategy

Antifungal prophylactic strategies at our institution have been described.[5] All patients received micafungin 150 mg IV q24 from day-2 through day+7 (±2 days) post-HCT followed by either voriconazole (voriconazole-cohort) or isavuconazole (isavuconazole-cohort). Overall, voriconazole was administered at a dose of 4 mg/kg twice daily IV or 200 mg twice daily PO, after a loading dose of 6 mg/kg twice daily for the first day. Isavuconazole was administered at a dose of 372 mg once daily (IV or PO) after a loading dose of 372 mg three times daily for the first two days in all patients. The duration of prophylaxis was based on IFI risk. Low-risk patients, defined as recipients of unmodified allografts without GvHD, discontinued AFP at cessation of immunosuppression, typically around day + 75 (±7 days) post-HCT. High-risk patients continued AFP beyond 100 days post-HCT. High-risk patients with premature discontinuation of voriconazole or isavuconazole AFP were placed on alternative antifungal prophylaxis at clinicians' discretion. For the purposes of this study, data on AFP were collected up to 100 days from AFP initiation. Voriconazole therapeutic drug monitoring and dose adjustments were at clinicians' discretion.[5] In the isavuconazole-cohort, serum isavuconazole levels were obtained once after patients had received 10–14 days of a steady oral dose of isavuconazole; no dose adjustments were made based on results. The diagnostic protocol in case of neutropenic fever or suspicion for an IFI remained the same during both the isavuconazole and voriconazole studies.

Data collection

The following data were collected: (i) demographics, (ii) underlying hematologic malignancy, (iii) HCT-related variables: type of transplant (unmodified vs. T-cell depleted), stem cell source (bone marrow vs. peripheral blood stem cells vs. cord blood), donor-recipient matching, and conditioning regimen, (iv) AFP-related variables: voriconazole/isavuconazole administration details, including AE and reasons of discontinuation, (v) outcome-related

variables: probable or proven IFI from Day 0 until day + 180 post-HCT and all-cause mortality, and (vi) liver function tests: alanine transaminase (ALT), aspartate aminotransferase (AST), and total bilirubin at baseline, end-of-treatment (EOT), and 7 and 14 days after EOT.

Definitions

In this study, duration of AFP refers to voriconazole/isavuconazole AFP up to 100 days from HCT regardless whether the patients received alternative AFP after premature discontinuation of voriconazole/isavuconazole. Premature AFP-discontinuation was defined as discontinuation for any reason prior to clinically indicated completion of AFP. There was no predetermined threshold of transaminase values for AFP discontinuation, in patients whose AFP was discontinued for elevated liver function tests. Discontinuation of AFP was at physicians' discretion. Invasive fungal infections were defined based on consensus guidelines.[19] Breakthrough IFI were defined as a diagnosis of an IFI on the assigned AFP after a minimum of 7 days of administration of active AFP.[9,20] Acute GvHD (aGvHD) scoring was based on established guidelines.[21]

Statistical analysis

Patients in the voriconazole-cohort were selected from a previous cohort of 327 consecutive HCT recipients from September 1, 2014 and December 31, 2016, who received voriconazole AFP as described previously.[5] Patients in the voriconazole-cohort were matched to the isavuconazole-cohort using frequency matching based on nearest neighbor propensity score for the following variables: age (18–39 vs. 40–64 vs. > 64 years), gender (female vs. male), underlying disease (leukemia vs. lymphoma vs. myelodysplastic syndrome vs. other), conditioning regimen intensity (myeloablative vs. reduced intensity/non-myeloablative), donor type (matched vs. mismatched), stem cell source (bone marrow vs. peripheral blood stem cells vs. cord blood), and GvHD prophylaxis (tacrolimus/sirolimus and mycophenolate mofetil vs. cyclosporin and mycophenolate mofetil vs. $CD34^+$ selection). Categorical variables were compared by chi-square or Fisher's tests, and continuous variables were compared by t-tests, Wilcoxon rank-sum tests, paired t-tests, or Wilcoxon signed-rank tests, as appropriate. The rates of discontinuation of AFP were estimated using multi-state models, including transitions from HCT to initiation of AFP, premature discontinuation of AFP and completion of AFP. The rate of IFI was estimated using Gray's method, considering death as competing risk. Mortality was estimated using Kaplan-Meier estimates and compared using logrank test between isavuconazole-cohort and voriconazole-cohort. Risk factors for premature discontinuation of AFP were explored using multi-state models. Potential risk factors included baseline (age, gender, and race) and transplant characteristics (underlying disease, conditioning regimen intensity, donor type, stem cell source, GvHD prophylaxis, recipient CMV serostatus, donor CMV serostatus, aGvHD grade, and AFP). aGvHD was included as time-dependent covariate. Variables with P-value < 0.3 in the univariable model were selected in a full multivariable model, and those were further selected in the final multivariable model using forward selection according to Akaike information criterion statistic. Since drug type was the variable of interest, it was always in the final model regardless of significance. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated for binary outcome of premature discontinuation of AFP by 100 days post HCT to show the difference in hazards between the voriconazole-cohort and isavuconazole-cohort. All tests were two-sided. P-values of < 0.05 were considered significant. All analyses were performed by R, version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria).

Results

Patient population

A total of 305 allogeneic HCT recipients were analyzed including 210 patients in the voriconazole-cohort and 95 patients in the isavuconazole-cohort (Table 1). The two cohorts were sufficiently matched in terms of demographics, underlying disease, stem cell source, and GvHD prophylaxis. Due to evolving practices in HCT during the study period, the intensity of the conditioning regimens and proportion of haploidentical donor allografts differed between the two cohorts. More patients in the voriconazole-cohort received reduced intensity conditioning whereas more patients in the isavuconazole-cohort received either ablative or non-ablative conditioning regimens (P-value < 0.001). Haploidentical donor allografts comprised 3.8% of the voriconazole-cohort and 14.7% of the isavuconazole-cohort (P-value = 0.002). Time to neutrophil engraftment (median 12 days) and acute GvHD were similar for the two cohorts.

Administration of AFP

Both voriconazole and isavuconazole were started at a median of 7 days (interquartile range [IQR]: 7, 8) post-HCT. A loading dose was administered in 187 (89.0%) patients in the voriconazole-cohort and 95 (100.0%) in the isavuconazole-cohort (P-value = 0.0002). Duration of AFP was longer for isavuconazole (median: 94 days; IQR: 87, 100) compared with voriconazole (median: 76 days; IQR: 23, 94; P-value < 0.0001).

Discontinuation of AFP

Figure 1A shows the multi-state curves of time to initiation and discontinuation of AFP. Four and three patients

Table 1. Comparison of baseline and transplant characteristics for the voriconazole-cohort and isavuconazole-cohort.

Characteristic	Total	Voriconazole	Isavuconazole	*P*-value
	(n = 305)	(n = 210)	(n = 95)	
Age group, years				0.182
18—39	37 (12.1%)	30 (14.3%)	7 (7.4%)	
40—64	184 (60.3%)	126 (60.0%)	58 (61.1%)	
64+	84 (27.5%)	54 (25.7%)	30 (31.6%)	
Sex				0.283
Female	113 (37.0%)	82 (39.0%)	31 (32.6%)	
Male	192 (63.0%)	128 (61.0%)	64 (67.4%)	
Race				0.191
White	253 (83.0%)	172 (81.9%)	81 (85.3%)	
Black	21 (6.9%)	14 (6.7%)	7 (7.4%)	
Asian	16 (5.2%)	10 (4.8%)	6 (6.3%)	
Other	15 (4.9%)	14 (6.7%)	1 (1.1%)	
Underlying disease				0.589
Leukemia	151 (49.5%)	100 (47.6%)	51 (53.7%)	
Lymphoma	58 (19.0%)	42 (19.0%)	16 (16.8%)	
MDS	44 (14.4%)	29 (13.8%)	15 (15.8%)	
Other[1]	52 (17.0%)	39 (18.6%)	13 (13.7%)	
Conditioning intensity				0.0001
Ablative	146 (47.9%)	93 (44.3%)	53 (55.8%)	
Reduced	136 (44.6%)	108 (51.4%)	28 (29.5%)	
Non-ablative	23 (7.5%)	9 (4.3%)	14 (14.7%)	
Donor type				0.002
Matched	195 (67.2%)	150 (71.4%)	55 (57.9%)	
Mismatched	78 (25.6%)	52 (24.8%)	26 (27.4%)	
Haploidentical	22 (7.2%)	8 (3.8%)	14 (14.7%)	
Stem cell source				0.154
Marrow	38 (12.5%)	21 (10.0%)	17 (17.9%)	
Cord blood	48 (15.7%)	34 (16.2%)	14 (14.7%)	
Peripheral blood	219 (71.8%)	155 (73.8%)	64 (67.4%)	
GvHD prophylaxis				0.625
TAC or Sirolimus + MMF	148 (48.5%)	98 (46.7%)	50 (52.6%)	
Cyclosporin + MMF	48 (15.7%)	34 (16.2%)	14 (14.7%)	
$CD34^+$ selection	109 (35.7%)	78 (37.1%)	31 (32.6%)	
Recipient CMV serostatus				0.197
Negative[2]	147 (48.2%)	96 (45.7%)	51 (53.7%)	
Positive	158 (51.8%)	114 (54.3%)	44 (46.3%)	
Donor CMV serostatus				0.261
Negative[3]	175 (57.4%)	116 (55.2%)	59 (62.1%)	
Positive	130 (42.6%)	94 (44.8%)	36 (37.9%)	
Acute GvHD grade[4]				0.396
0—1	164 (54.1%)	116 (55.8%)	48 (50.5%)	
2—4	139 (45.9%)	92 (44.2%)	47 (49.5%)	

[1]Other included: multiple myeloma (n = 30), myeloproliferative disorder (n = 18), aplastic anemia (n = 3), and non-malignant hematologic disorders (n = 1).
[2]Including six patients with equivocal recipient CMV serostatus, four from voriconazole-cohort, and two from isavuconazole-cohort.
[3]Including eight patients with equivocal donor CMV serostatus from isavuconazole-cohort.
[4]Two patients with unknown acute GvHD grade were excluded from voriconazole group, and in total 303 patients were included for this comparison.
CMV: Cytomegalovirus; GvHD: Graft versus Host Disease; MDS: Myelodysplastic syndrome; MMF: Myophenolate mofetil; TAC: Tacrolimus.

in the voriconazole-cohort and isavuconazole-cohort respectively died before Day 100. Voriconazole was discontinued earlier and more frequently compared with isavuconazole (*P*-value < 0.0001).

Premature discontinuation of AFP

Figure 1B shows the multi-state curves of time to initiation and premature discontinuation of AFP. Voriconazole was discontinued prematurely earlier and more frequently compared with

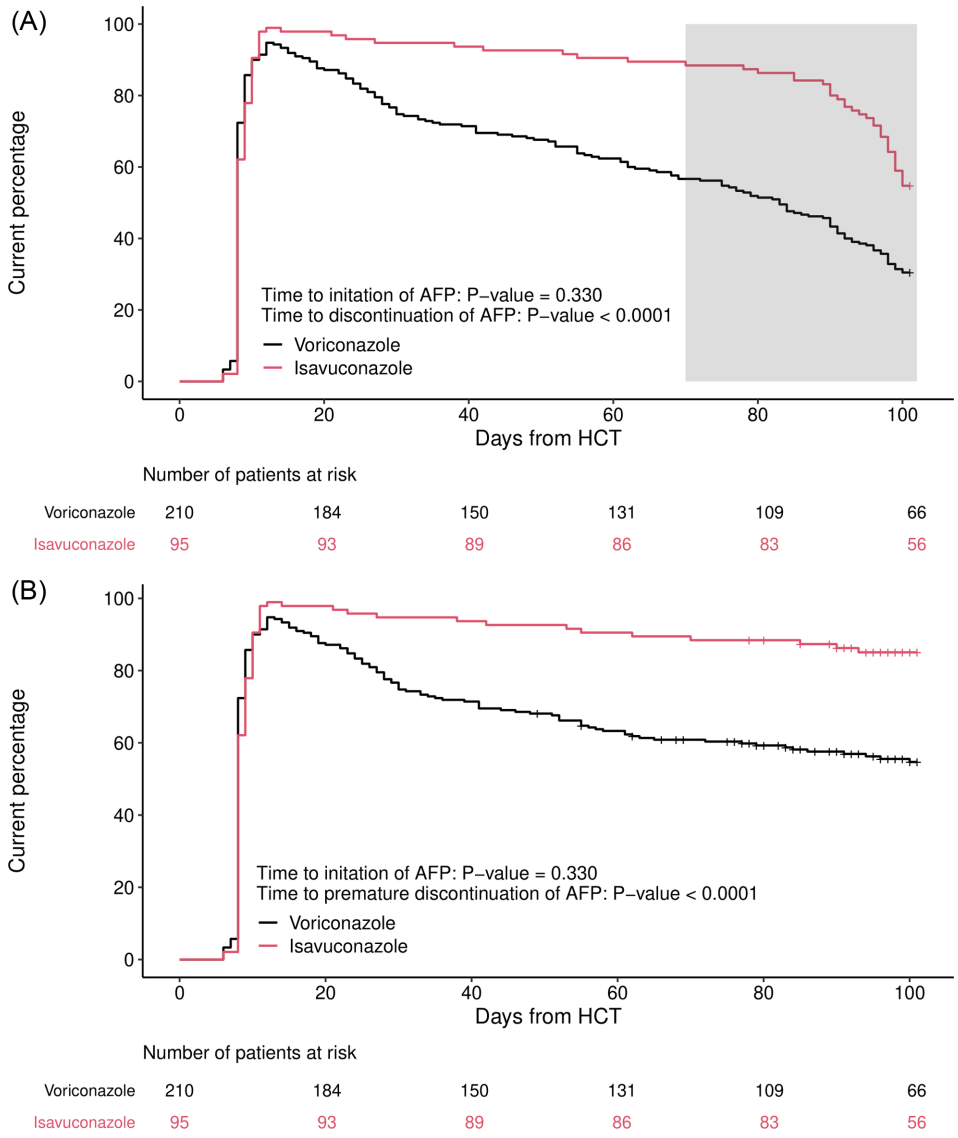

Figure 1. Multi-state curves of time to initiation and discontinuation (a) and time to initiation and premature discontinuation (b) of voriconazole and isavuconazole antifungal prophylaxis by day + 100 after allogeneic hematopoietic cell transplant. Shaded area represents the timeframe for discontinuation per standard of care for patients at low risk for an invasive fungal infection. Day 0 is the day of allogeneic hematopoietic cell transplant. Three patients in the isavuconazole-cohort and four patients in the voriconazole died before 100 days of HCT. Completion of AFP was considered as competing risk event in Fig. 1B. Patients were censored at the end of the study.

isavuconazole (*P*-value < 0.0001). By Day 100, voriconazole was discontinued prematurely in 92/210 (43.8%) compared to 14/95 (14.7%) with isavuconazole (*P*-value < 0.0001).

Reasons for premature discontinuation of voriconazole were: death (N: 2/92;2.2%), elevated liver function tests (N: 48/92, 52.2%), drug–drug interactions (N: 13/92, 14.1%), visual hallucinations (N: 8/92, 8.7%), vivid dreams (N: 3/92, 3.3%), subtherapeutic serum concentration (N: 3/92, 3.3%), photosensitivity/rash (N: 10/92, 10.8%), acute kidney injury (N: 2/92, 2.2%), gastrointestinal toxicity (N: 1/92, 1.1%); other (N: 2/92, 2.2%). Reasons for premature discontinuation of isavuconazole were: death (N: 1/14; 7.1%), elevated liver function tests (N: 5/14, 35.7%), bIFI (3/14, 21.4%), drug-drug interactions (N: 2/14, 14.3%), gastrointestinal toxicity (N: 2/14, 14.3%), and anemia (N: 1/14, 7.1%).

Predictors of premature AFP-discontinuation

AFP was entered as covariate in univariable and multivariable models to identify predictors for premature AFP discontinuation. Because all cord blood allograft recipients received cyclosporin with mycophenolate mofetil for GvHD prophylaxis and no other HCT-source allografts received this immunosuppression combination, there was multi-linearity between stem cell source, donor type, and GvHD prophylaxis. Since the distribution of matched vs. mismatched donor type was adjusted for

Table 2. Univariable and multivariable predictors for premature discontinuation of AFP after HCT (N = 303).[1]

	Univariable analysis			Multivariable analysis		
Predictor[2]	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age group, years						
18–39	Reference					
40–64	0.68	(0.39, 1.18)	0.170			
64+	0.87	(0.47, 1.59)	0.646			
Sex						
Female	Reference					
Male	0.73	(0.50, 1.08)	0.119			
Race						
White						
Black	1.74	(0.90, 3.37)	0.098			
Asian	2.21	(1.11, 4.41)	0.025			
Other	2.87	(1.44, 5.74)	0.003			
Donor type						
Matched	Reference					
Mismatched	1.67	(1.11, 2.52)	0.015			
Haploidentical	0.91	(0.39, 2.10)	0.818			
Stem cell source						
Marrow	Reference					
Cord blood	2.24	(1.07, 4.66)	0.031			
Peripheral blood	1.19	(0.61, 2.31)	0.613			
GvHD prophylaxis						
TAC or Sirolimus + MMF	Reference			Reference		
Cyclosporin + MMF	1.89	(1.16, 3.08)	0.011	1.94	(1.17, 3.21)	0.010
$CD34^+$ selection	0.95	(0.61, 1.49)	0.829	1.01	(0.64, 1.60)	0.954
Recipient CMV serostatus						
Negative	reference					
Positive	1.23	(0.83, 1.81)	0.298			
Donor CMV serostatus						
Negative	Reference			Reference		
Positive	1.29	(0.88, 1.90)	0.189	1.41	(0.95, 2.09)	0.093
aGvHD grade[3]						
0–1	Reference			Reference		
2–4	**1.63**	**(1.10, 2.40)**	**0.014**	1.62	(1.08, 2.45)	0.021
Antifungal prophylaxis						
Voriconazole	Reference			Reference		
Isavuconazole	0.27	(0.15, 0.48)	< 0.0001	0.26	(0.15, 0.46)	< 0.0001

[1]Two patients with unknown aGvHD grade were excluded.
[2]Variables with *P*-value < 0.3 in the univariable models are shown. Underlying disease and conditioning intensity were not included in the model.
[3]aGvHD was included as time-dependent covariate.
HCT: Hematopoietic cell transplant; HR: Hazard ratio, MDS: Myelodysplastic syndrome.

voriconazole-cohort and isavuconazole-cohort, and the effect of GvHD prophylaxis was clinically relevant, GvHD prophylaxis was selected in the final model. Variables included in the multivariable model are shown in Table 2. Isavuconazole-AFP was an independent predictor against premature AFP discontinuation when adjusting for GvHD prophylaxis, donor CMV serostatus, and acute GvHD (HR: 0.26, *P*-value < 0.0001). In addition, recipients of cyclosporin and mycophenolate mofetil as GvHD prophylaxis were 1.9 times more likely to have early AFP discontinuation as compared to recipients of tacrolimus/sirolimus and mycophenolate mofetil as GvHD prophylaxis, when adjusting for other covariates (*P*-value = 0.010). Finally, aGvHD ≥ grade 2 was a significant factor to predict AFP discontinuation (HR: 1.62, *P*-value: 0.02).

Discontinuation of AFP due to hepatotoxicity

Hepatotoxicity regardless of grade or causality was the most common reason for premature discontinuation of AFP. Hepatotoxicity leading to discontinuation was more frequent for voriconazole 48/210 (22.86%) compared with isavuconazole 5/95 (5.26%; *P*-value = 0.0002). Seven patients developed liver

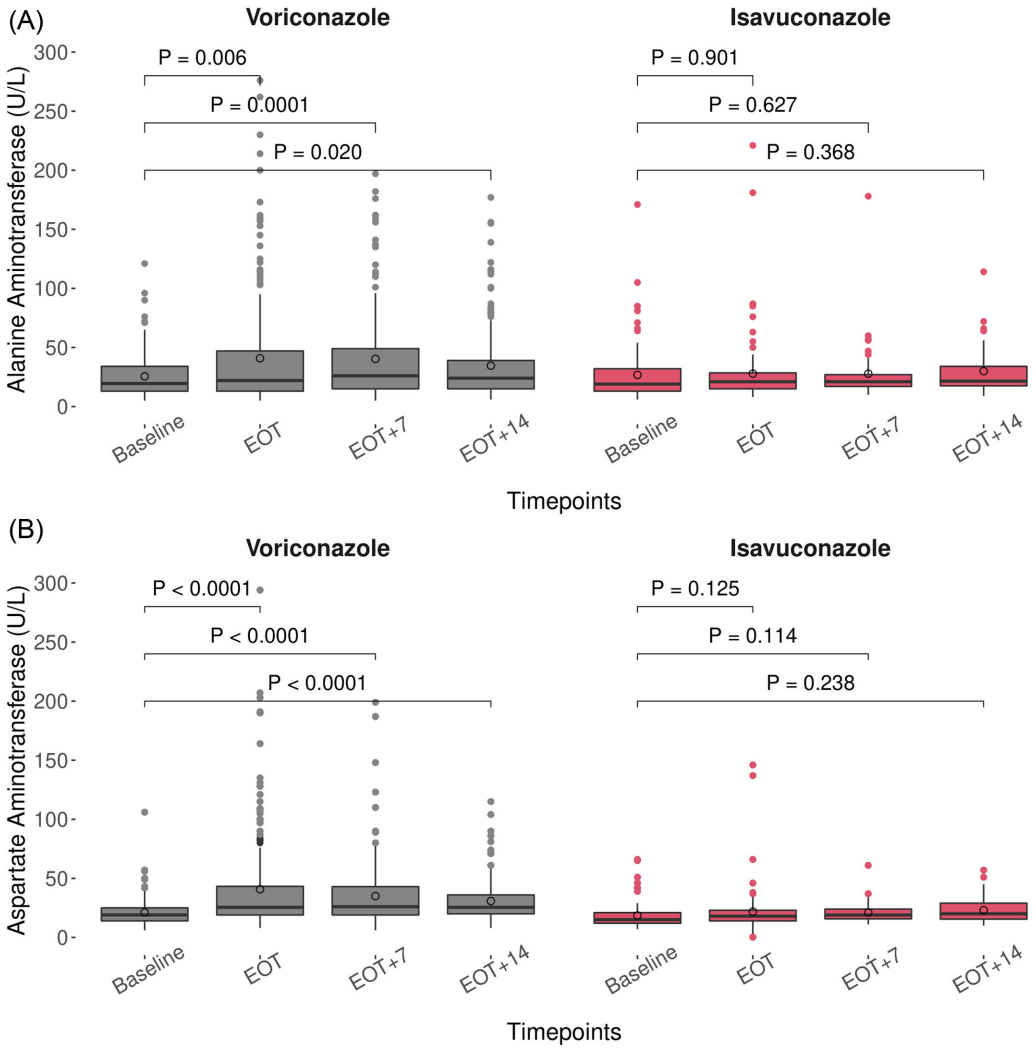

Figure 2. Boxplots for alanine aminotransferase (ALT) (a) and aspartate aminotransferase (AST) (b) at Day 0 (baseline), discontinuation of antifungal prophylaxis (end of treatment, EOT) and 7 and 14 days after EOT for the voriconazole-cohort and isavuconazole-cohort. Shaded areas (box) represent 25th and 75th percentiles. The horizontal bar and diamond within the box represent the median and mean values, respectively. The dots denote outliers below the 25th percentile or above 75th percentile. *P*-values were calculated using Wilcoxon signed-rank tests.

GvHD (stage ≥ 2) and all discontinued AFP prematurely: 6 (2.9%) patients in the voriconazole-cohort and one (1.1%) patient in the isavuconazole-cohort (with concomitant veno-occlusive disease; *P*-value = 0.44).

We compared ALT values between baseline, time of AFP discontinuation (EOT) and up to 14 days after EOT (Fig. 2A). For voriconazole, ALT increased a median of 1 U/l (IQR: -8, 23.5; *P*-value = 0.006) at EOT, 3 U/l (IQR: -6, 30; *P*-value = 0.0001) at EOT+7 days and 1 U/l (IQR: -8, 18; *P*-value = 0.020) at EOT + 14 days from baseline. The highest EOT ALT level observed among patients with premature drug discontinuation was 262 U/l in a patient in the voriconazole-cohort. In contrast, there were no significant changes observed in ALT between baseline and EOT, EOT + 7 days, and EOT + 14 days in the isavuconazole-cohort. We also compared AST values between baseline, time of AFP discontinuation (EOT), and up to 14 days after EOT (Fig. 2B). For voriconazole, AST increased a median of 7 U/l (IQR: -1, 25.75; *P*-value < 0.0001) at EOT, 7 U/l (IQR: -3, 21; *P*-value < 0.0001) at EOT + 7 days and 6 U/l (IQR: -3, 19; *P*-value < 0.0001) at EOT + 14 days from baseline. Similarly, there were no significant changes observed in AST between baseline and EOT, EOT + 7 days, and EOT + 14 days in the isavuconazole-cohort. There were no significant differences observed in total bilirubin between baseline and EOT + 14 days in both cohorts.

Incidence and types of IFI

A total of 9/305 (2.9%) patients developed probable or proven IFI by day + 180 post-HCT, including 6/210 (2.9%) patients in the voriconazole-cohort and 3/95 (3.2%) patients in the isavuconazole-cohort (*P*-value = 0.881; Fig. 3). Five of the nine IFI occurred after discontinuation of AFP, all in the

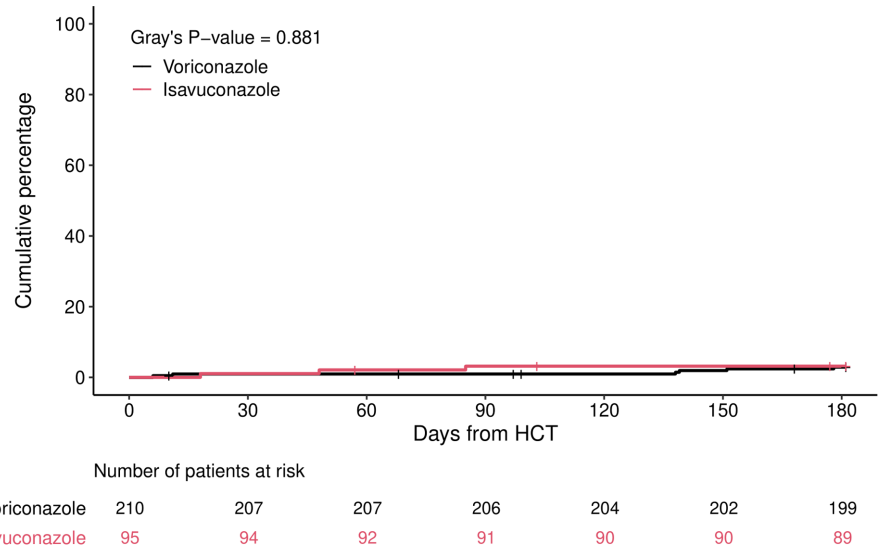

Figure 3. Cumulative incidence of proven and probable invasive fungal infections by day + 180 after allogeneic hematopoietic cell transplant for the voriconazole-cohort and isavuconazole-cohort. Death was considered as competing risk event. Patients were censored at end of the study.

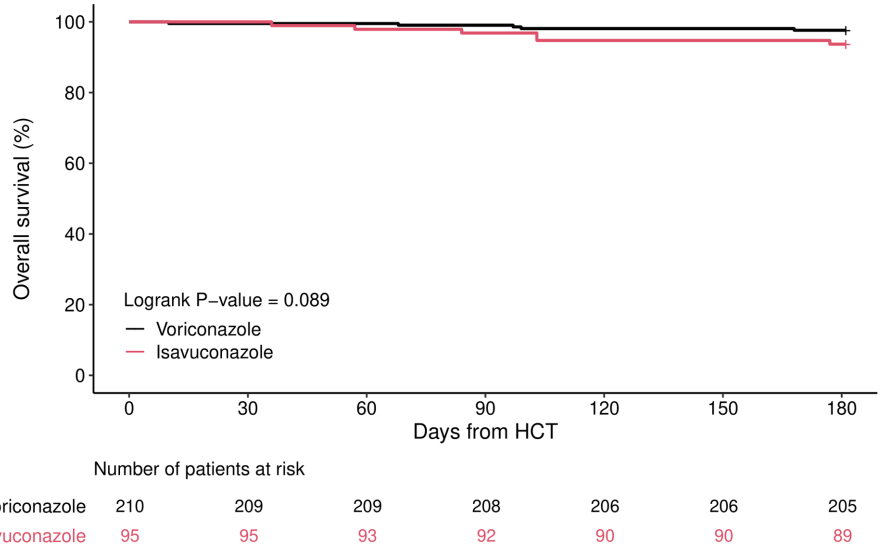

Figure 4. Kaplan-Meier survival analysis for overall survival by day + 180 after allogeneic hematopoietic cell transplant for the voriconazole-cohort and isavuconazole-cohort. Patients were censored at end of the study.

voriconazole-cohort. Four patients developed probable aspergillosis at a median of 85 days (IQR: 40, 138.75) post-HCT and one patient developed *C. glabrata* candidemia. In addition, one patient in the voriconazole cohort developed early probable invasive aspergillosis 3 days after initiation of voriconazole AFP.

Breakthrough IFI

In the voriconazole-cohort, no patient developed bIFI. In the isavuconazole-cohort, 3 (3.2%) patients developed candidemia at a median of 48 days post-HCT (IQR: 33–66.5) due to *C. parapsilosis* (in two patients; pre-engraftment in one patient) and *C. glabrata* (post-engraftment in setting of severe colitis due to GVHD. Both *C. parapsilosis* isolates were susceptible to fluconazole. Susceptibility testing was not performed for the *C. glabrata* isolate as the blood culture resulted postmortem. Isavuconazole susceptibility testing was performed in only one patient with *C. parapsilosis* and the minimal inhibitory concentration was ≤ 0.03.

Overall survival

By day + 180 post-HCT, 11 of 305 (3.6%) patients died, including 5/210 (2.4%) patients in the voriconazole-cohort and 6/95 (6.3%) patients in the isavuconazole-cohort (*P*-value = 0.089) (Fig. 4). The causes of death among the voriconazole-cohort were infection (bacterial sepsis 1, pneumonia 1), GvHD (1), disease progression (1), and multiorgan failure (1). The causes

of death among the isavuconazole-cohort were infection (candidemia with bacteremia 1, pneumonia 1), GvHD (2), relapse (1), and graft failure (1).

Discussion

In this matched cohort analysis of adult allogeneic HCT recipients, who received voriconazole and isavuconazole AFP in a single institution, we report less frequent premature discontinuation overall and due to hepatotoxicity and similar incidence of IFI in patients who received isavuconazole compared with voriconazole AFP. A trend for more bIFI, particularly candidemia, was observed in the isavuconazole-cohort, however the small number of patients with bIFI precluded formal comparisons.

Our data confirm previous observations that up to 40% of allogeneic HCT recipients may prematurely discontinue voriconazole as primary AFP.[4,5] This is, in part, due to biochemical hepatotoxicity and other AEs associated with voriconazole.[4,5] Our data suggest that AFP with isavuconazole may be better tolerated, with significantly fewer AEs, including hepatotoxicity. This is consistent with the results of the pivotal clinical trial, which compared isavuconazole with voriconazole for the treatment of invasive aspergillosis.[6] Significantly fewer hepatobiliary, eye and skin and soft tissue disorders were observed in the isavuconazole vs. the voriconazole arm. Similar observations have been made in real-life paradigms, where isavuconazole has been administered either as prophylaxis or treatment.[7,10,22,23] Furthermore, a decrease in transaminasenemia in leukemia patients who were switched from posaconazole to isavuconazole after experiencing hepatotoxicity while on posaconazole has been reported.[23] Notably, only moderate levels of hepatotoxicity were observed in our study, more likely representing the caution of clinicians, who tend to discontinue azole AFP even with moderate degree liver function test abnormalities. Nevertheless, we did observe that overall, the level of hepatotoxicity was higher in the voriconazole-cohort compared to the isavuconazole-cohort in patients who had early discontinuation of the study drug.

Currently, there are no prospective randomized clinical trials to assess the efficacy of isavuconazole as primary AFP in high-risk patients.[2,24,25] Our findings suggest that isavuconazole as primary AFP may be as effective as voriconazole. Overall, very low rates of IFI were observed, consistent with prior prophylaxis clinical trials in allogeneic HCT recipients.[2,25] Notably, there were only three bIFI observed in this study, all three candidemias (two due to *C. parapsilosis* and one due to *C. glabrata*) in the isavuconazole-cohort. Our observation of breakthrough candidemias on isavuconazole AFP is consistent with prior studies in patients with hematologic malignancies who receive isavuconazole prophylaxis.[7,9] Fontana et al. reported a bIFI rate of 10.2% in patients receiving isavuconazole prophylaxis versus 4.1% in patients receiving posaconazole, and only 1.1% in patients receiving voriconazole.[7] Similarly, data from MD Anderson suggest a bIFI rate of 13% (13/100) in high-risk hematologic patients receiving isavuconazole as primary/secondary prophylaxis or treatment, with the most common bIFIs being candidemias, due to non-*C. albicans* species.[9] The higher rates of breakthrough candidemia compared with our study could be at least partially due to higher numbers of patients with refractory leukemias and prolonged and profound neutropenia periods, suggesting potential selection biases.[7,9] Post-hoc analysis of the pivotal isavuconazole clinical trial suggested that isavuconazole may be less effective in patients with invasive aspergillosis and profound unresolved neutropenia.[26] Furthermore, a recently published clinical trial comparing isavuconazole to caspofungin for the treatment of invasive candidiasis did not demonstrate non-inferiority of isavuconazole.[27] Whether isavuconazole is less effective prophylaxis than voriconazole against *Candida* infections, particularly among patients with prolonged neutropenia, requires further studies. Notably, in contrast to previously published data, we did not observe any IFI caused by non-*Aspergillus* molds in our study.[7,10,27]

Tolerability and safety are important factors when deciding on a mold active azole AFP in the first 100 days post-HCT when patients are recovering from toxicities of HCT and are at risk for GvHD. In our multivariable model, isavuconazole AFP was protective against premature discontinuation of AFP. Patients on isavuconazole were 3.8 times less likely to discontinue AFP prematurely compared to voriconazole. Early AFP discontinuation was more common in recipients of cord blood transplants who received cyclosporin and mycophenolate mofetil as GvHD prophylaxis. Cyclosporin and mycophenolate mofetil for GvHD prophylaxis was an independent predictor for premature discontinuation of AFP. Cyclosporine therapy is associated with mild cholestatic liver enzyme elevations and occasional instances of cholestatic hepatitis while tacrolimus, sirolimus, and mycophenolate are not.[28] While cyclosporin levels were routinely monitored, mild cholestasis due to cyclosporin may at least in part accounted for higher rates of voriconazole AFP discontinuation in this patient group.

Our study has several limitations. While all patients were cared for at a single institution, the two cohorts were not contemporaneous; it is plausible that changes in HCT practices and supportive care between the two periods could not be accounted for and could potentially cause biases due to unbalanced characteristics. However, we did perform an intensive matching scheme in an effort to make the two cohorts as comparable as possible and multivariable modeling was also performed, to adjust for covariates when estimating association between outcome of interest and the two cohorts. Voriconazole was administered per standards of care as opposed to isavuconazole that was administered as in open-label, single arm trial; per protocol, however, clinicians were allowed to discontinue isavuconazole for any side effect if clinically indicated. Furthermore, objective measurements of transaminases up to 2 weeks post discontinuation of AFP were analyzed.

In conclusion, our data suggest that voriconazole remains an effective AFP in allogeneic HCT recipients, however, its use is hindered by high rates of discontinuation. In contrast, isavuconazole appears to be a safe and effective alternative for primary AFP in high-risk allogeneic HCT recipients. Early signals of lower efficacy of isavuconazole for the prevention of *Candida* infections, as previously reported, require further studies in the future.

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Authors contribution

Y.B., A.S., and Y.S. designed the research, analyzed data, and wrote the paper. Y.B., A.S., and Y.J.L. collected data. Y.J.L., S.K.S., B.S., and M.A.P provided critical review of the manuscript. G.A.P. and D.N. contributed to and supervised all aspects of the study.

Declaration of interest

Y.J.L. has received support for conducting industry-sponsored trials from Astellas Pharma.

M.A.P. reports receiving institutional research support for clinical trials from Incyte Corporation; honoraria from AbbVie, Bellicum, Bristol-Myers Squibb, Incyte Corporation, Merck, Novartis, Nektar Therapeutics, and Takeda; serving on data and safety monitoring boards for Servier and Medigene; and serving on scientific advisory boards for MolMed and NexImmune.

G.A.P. has been an investigator for Takeda, Merck & Co and Astellas, and has received consulting and other fees from ADMA biologics, Amplyx, Astellas Pharma Basilea, Cidara, Merck & Co, Octapharma, Partners Therapeutics, and Shionogi.

D.N. has received research support from MSD and Pfizer and has received consulting fees from MSD, Pfizer, Basilea, and Gilead.

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