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MAJOR ARTICLE

SUBA-Itraconazole for Primary Antifungal Prophylaxis After Allogeneic Hematopoietic Cell Transplantation

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Background. Itraconazole (ITZ) is an effective agent when used as primary invasive fungal disease (IFD) prophylaxis, but is limited by drug tolerability and variability in serum concentrations. A new formulation, SUBA-itraconazole (for "super bioavailability"; S-ITZ), addresses the limitations of conventional ITZ formulations.

Methods. We conducted a retrospective cohort study at 2 Australian centers to evaluate the safety, tolerability, and effectiveness of S-ITZ as primary antifungal prophylaxis in hematopoietic cell transplant (HCT) recipients without grade II–IV acute graft-vs-host disease, from day 1 until approximately day 100 (cohort A) or day 1 until neutrophil engraftment (cohort B). A total of 204 patients and 1410 trough plasma ITZ concentrations were assessed.

Results. The incidence of breakthrough proven/probable IFD at day 180 was 1.0% (95% confidence interval [CI], .2%–3.2%), with 1.6% in cohort A and 0% in cohort B, and overall fungal-free survival of proven/probable IFD was 82.9% (95% CI, 76.8%–87.4%). Preengraftment early permanent S-ITZ discontinuation was 3.4% overall, with no significant difference between cohorts. No patients required cessation due to gastrointestinal intolerance attributed to S-ITZ. The geometric mean trough plasma ITZ concentration was 1130 ng/mL (interquartile range, 566–1801 ng/mL; coefficient of variation, 56.57%) and the median time to achieve therapeutic levels was 10 days.

Conclusions. S-ITZ is a safe and well-tolerated oral formulation and is a novel alternative for primary IFD prophylaxis after HCT.

Keywords. allogeneic hematopoietic cell transplantation; antifungal prophylaxis; itraconazole; HCT; S-ITZ; SUBA-itraconazole.

Invasive fungal disease (IFD) in allogeneic hematopoietic cell transplant (HCT) recipients is associated with significant morbidity, mortality, and health care costs [1, 2]. Antifungal prophylaxis is known to prevent IFD in HCT, although the threshold for prophylaxis and agents of choice continue to evolve with progress in HCT and development of new antifungal agents and formulations [3–6]. There is no clear advantage between IFD prophylaxis agents that are routinely used in HCT in the absence of graft-vs-host disease (GVHD), particularly in regard to all-cause mortality [7]. Itraconazole (ITZ) has been demonstrated to be an effective primary prophylactic agent post-HCT in preventing the incidence of IFD in randomized controlled trials; however, because of consistent issues with gastrointestinal (GI) intolerance and compromised bioavailability, conventional ITZ has fallen out of favor in many HCT centers for newer triazoles such as voriconazole, posaconazole, and isavuconazole [8–12].

To address the limited bioavailability of, and intolerance to, conventional ITZ formulations, a novel formulation, SUBA ("super bioavailability") itraconazole (S-ITZ), was recently licensed by the Food and Drug Administration in the United States and the Therapeutic Goods Administration in Australia, but as yet, not the European Medicines Agency [13, 14]. S-ITZ is a formulation containing a solid dispersion of ITZ in a pH-dependent polymeric matrix to enhance intestinal

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absorption, therefore increasing bioavailability [15, 16]. The first study using this novel formulation for fungal prophylaxis compared conventional ITZ oral solution in patients undergoing HCT; [17] the S-ITZ capsule formulation was associated with more rapid attainment of therapeutic ITZ levels with less interpatient variability or GI intolerance, using the same initial dosage as the oral solution of 200 mg twice a day. However, the small sample size (n = 27) limited the study's findings, particularly the rate of IFD. In this multisite longitudinal cohort study, we report the use of S-ITZ prophylaxis after HCT in Australia.

METHODS

Study Design and Participants

This was a retrospective longitudinal cohort study of S-ITZ used as primary antifungal prophylaxis in HCT recipients at Royal North Shore Hospital (cohort A) and Royal Prince Alfred Hospital (cohort B) in Sydney, Australia, from June 2015 to January 2020. All consecutive patients undergoing HCT, without a documented prior IFD, were administered S-ITZ as primary antifungal prophylaxis. Patients were excluded if they had received secondary prophylaxis for a prior IFD, or if they were administered <5 uninterrupted days of S-ITZ. All patients were followed until death or at least 180 days post-HCT. Institutional databases were accessed, with a full chart review of each patient for details of antifungal prophylaxis, incidence of proven/probable and possible IFD according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the Mycoses Study Group Education and Research Consortium (EORTC/MSG ERC) definitions, or a suspected IFD by the treating clinician that did not meet EORTC/MSG ERC criteria for possible or proven/probable IFD [18], as well as HCT characteristics.

Primary Antifungal Prophylaxis and HCT Policies

S-ITZ was administered from day 1 of HCT except in haploidentical HCT where it was administered from day 5 due to a potential cytochrome P450 interaction with posttransplant cyclophosphamide. The initial dose was 200 mg twice a day (BID, every 12 hours) in both cohorts [19]. In cohort A, S-ITZ was administered as primary prophylaxis until weaning of immunosuppression at approximately day 100. In cohort B, S-ITZ was administered as primary prophylaxis only until neutrophil engraftment (Figure 1). In both cohorts, in the event of grade II–IV acute GVHD (aGVHD; defined by a modified Glucksberg criteria [20]), prophylaxis was switched to posaconazole as per national guidelines and continued for a duration specified by the treating physician [19]. Trough plasma ITZ concentrations were measured twice weekly aiming for a therapeutic range between 500 and 2000 ng/mL [21]. Hydroxyitraconazole levels were not measured as routine clinical practice and therefore were not

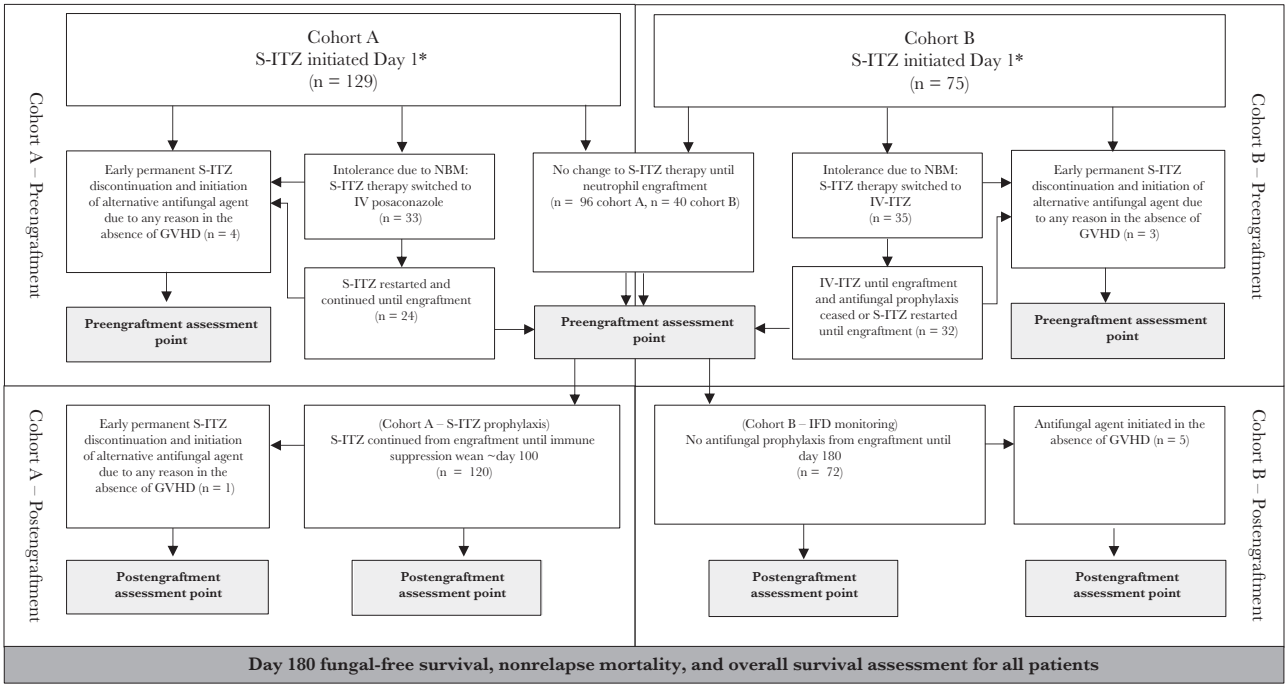

Figure 1. Study outline. If grade II–IV acute graft-vs-host disease was diagnosed at any timepoint, intravenous or oral posaconazole was initiated and the patient was censored at that timepoint for primary endpoint (SUBA-itraconazole [S-ITZ] breakthrough invasive fungal disease [IFD]); overall IFD, fungal-free survival, nonrelapse mortality, and overall survival continued to be measured for the entire cohorts. A minimum of 5 days of uninterrupted S-ITZ must have been given to meet inclusion criteria. *Initiated day 5 after posttransplant cyclophosphamide in haploidentical hematopoietic cell transplant. Abbreviations: GVHD, graft-vs-host disease; IFD, invasive fungal disease; IV-ITZ, intravenous itraconazole; NBM, nil by mouth; S-ITZ, SUBA-itraconazole.

reported. If trough ITZ concentrations were >2000 ng/mL, the dose was reduced by 50 mg/dose every week until steady-state concentrations returned to <2000 ng/mL; doses were not increased for subtherapeutic levels. If the patient was unable to tolerate any oral medication (nil by mouth), or the trough itraconazole level was <500 ng/mL after approximately 14 days of therapy, either intravenous (IV) posaconazole 300 mg daily (cohort A) or IV itraconazole 200 mg daily (cohort B) was given until the patient was able to take oral medication, at which point S-ITZ was restarted. Standard conditioning regimens were fludarabine-melphalan, fludarabine-busulfan, busulfan/cyclophosphamide, or cyclophosphamide/total body irradiation; standard GVHD prophylaxis consisted of cyclosporin and methotrexate, and all unrelated donors received thymoglobulin 4.5 mg/kg.

Safety and Tolerability

Microbiologic assessment, radiologic procedures, and other investigations such as *Aspergillus* galactomannan and *Aspergillus* polymerase chain reaction were undertaken throughout the study period as part of standard clinical practice only if prompted by fever not responding to empirical antibacterial therapy or for clinical suspicion of infection. Routine liver function tests were performed at least weekly and used to assess for drug-attributable hepatotoxicity. Moderate to severe liver injury defined as Drug-Induced Liver Injury Network (DILIN) grade 3+ liver injury [22] that was potentially attributable to S-ITZ required initiation of an alternative antifungal. Routine electrocardiography measurements were performed at the discretion of the treating clinician.

Study Endpoints

The primary endpoint was the incidence of breakthrough proven/probable IFD (bIFD) during administration or within 7 days of cessation of S-ITZ. Secondary endpoints included (1) the incidence of overall proven/probable IFD; (2) survival analyses including fungal-free survival (FFS; alive and free from proven/probable IFD), IFD attributable mortality, overall survival, and progression-free survival of malignant disease at 180 days post-HCT; and (3) early permanent S-ITZ discontinuation and/or initiation of alternative antifungal agent due to any reason, classified as a proven/probable IFD, a possible/suspected IFD, failure to achieve therapeutic serum concentrations after 14 days of therapy, an adverse drug reaction attributed to S-ITZ or intolerance to S-ITZ, or any other reason (Figure 1). Analysis of therapeutic drug levels were also performed, including the probability over time of attaining therapeutic ITZ serum concentrations defined as >500 ng/mL [21] and steady-state trough ITZ serum concentrations, which was defined by 14 days of uninterrupted therapy.

Endpoints were assessed over the preengraftment period from day 0 (day of stem cell infusion) until neutrophil recovery (>0.5 × 10^9/L absolute neutrophil count for 3 consecutive days) at the "engraftment assessment point," then through the postengraftment period until approximately day 180, at the "final assessment point" (Figure 1).

Statistical Analyses

Endpoints were assessed from day 0 of HCT until day 180 posttransplant. Cumulative incidence functions were used for bIFD, the early permanent S-ITZ discontinuation and/or initiation of alternative antifungal agent, and attainment of therapeutic drug levels, with death as a competing risk for all analyses and grade II–IV aGVHD as a competing risk for bIFD and S-ITZ discontinuation; relapse and nonrelapse mortality were competing risks for each other. The association of outcomes with pre- and posttransplant factors were analyzed using Fine-Gray competing risk regression [23]. Survival analyses were calculated using Kaplan-Meier and Fine-Gray proportional hazard regression analysis and groups compared with the log-rank test, with the impact of pretransplant factors and GVHD as a time-dependent posttransplant factor analyzed with Cox regression. Factors with a P value of < .10 on univariable analysis were included into multivariable models. Descriptive statistics were used for therapeutic drug levels of ITZ trough serum concentrations. As the maximum quantifiable ITZ level reported was 2000 ng/mL, any level >2000 ng/mL was considered 2000 ng/mL for the geometric mean. Statistical analyses were performed using R statistical software version 3.5.2 (R Core Development Team, Vienna, Austria) and EZR [24].

Patient Consent Statement

Institutional Human Ethics Committee approval was obtained with a patient waiver of consent (HREC/50095/PMCC-2019).

RESULTS

Demographics and Characteristics of S-ITZ Administration

A total of 204 patients met the inclusion criteria for study, 129 in cohort A, of which 27 have been previously described in a pilot study, [17] and 75 in cohort B, of which 6 were previously described [25]. Three additional patients were initiated on S-ITZ but did not meet inclusion criteria as they received <5 days of uninterrupted therapy. The median total days of S-ITZ therapy was 103 days (IQR, 58–133 days) in cohort A and 18 days (IQR, 13–21 days) in cohort B. Patient demographics and post-HCT parameters are shown in Table 1.

Incidence of IFD and FFS

The overall incidence of bIFD among patients receiving S-ITZ at day 180 posttransplant was 1.0% (95% confidence interval [CI], .2%–3.2%), with 1.6% (95% CI, .3%–5.0%) in cohort A and 0% in cohort B (P = .281) (Table 2 and Figure 2A and 2B).

The overall incidence of proven/probable IFD was 3.0% (95% CI, 1.2%–6.1%) with no significant difference between cohorts

Table 1. Cohort Demographics

Characteristic	Overall (N = 204)	Cohort A (n = 129)	Cohort B (n = 75)	*P* Value
Age, y, mean (SD)	51.13 (13.83)	53.70 (12.65)	46.72 (14.71)	<.001
Sex				
Female	85 (41.7)	55 (42.6)	30 (40.0)	.769
Male	119 (58.3)	74 (57.4)	45 (60.0)	
Primary disease				
Acute myeloid leukemia	85 (41.7)	57 (44.2)	28 (37.3)	.152
Myelodysplastic syndrome	33 (16.2)	22 (17.1)	11 (14.7)	
Acute lymphocytic leukemia	14 (6.9)	7 (5.4)	7 (9.3)	
Non-Hodgkin lymphoma	39 (19.1)	21 (16.3)	18 (24.0)	
Multiple myeloma	7 (3.4)	3 (2.3)	4 (5.3)	
Aplastic anemia	3 (1.5)	0 (0.0)	3 (4.0)	
Solid organ malignancy	1 (0.5)	0 (0.0)	1 (1.3)	
Other	22 (10.8)	19 (14.7)	3 (4.0)	
HCT conditioning				
Myeloablative	70 (34.3)	28 (21.7)	42 (56.0)	<.001
Reduced intensity	134 (65.7)	101 (78.3)	33 (44.0)	
HCT source				
Matched related donor	67 (32.8)	40 (31.0)	27 (36.0)	<.001
Unrelated donor	118 (57.8)	87 (67.4)	31 (41.3)	
Haploidentical	16 (7.8)	2 (1.6)	14 (18.7)	
Cord	3 (1.5)	0 (0.0)	3 (4.0)	
Unrelated donor HLA mismatch				
No (matched)	72 (61.0)	47 (54.0)	25 (80.6)	.010
Yes (mismatched)	46 (39.0)	40 (46.0)	6 (19.4)	
Antithymocyte globulin				
No	94 (46.1)	48 (37.2)	46 (61.3)	.001
Yes	110 (53.9)	81 (62.8)	29 (38.7)	
Post-HCT parameters				
Median days to engraftment	17	17	17	.796
Engraftment failure >30 d	2 (1.0)	0	2 (2.7)	NA
Relapse at day 180, % (95% CI)	14.5 (10.0–19.7)	13.4 (8.1–19.9)	16.4 (8.9–25.8)	.299
Grade II–IV aGVHD at day 100, % (95% CI)	22.6 (17.1–28.5)	17.8 (11.8–24.9)	30.7 (20.6–41.4)	.02

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: aGVHD, acute graft-vs-host disease; CI, confidence interval; HCT, hematopoietic cell transplant; NA, not applicable; SD, standard deviation.

A and B at 1.6% and 5.8%, respectively (P = .111). However, the overall incidence of proven/probable IFD combined with possible/suspected IFD was 5.4% (95% CI, 2.9%–9.2%), with a significantly higher rate in cohort B (12.2% [95% CI, 6.0%–20.9%]) compared to cohort A (1.6% [95% CI, .3%–5.0%]) (P = .002). When excluding patients who developed grade II–IV aGVHD, the overall incidence of proven/probable IFD was 2.0% (95% CI, .7%–4.7%) with no significant difference between cohorts A and B, at 1.6% and 3.0%, respectively (P = .551); and the incidence of proven/probable IFD combined with possible/suspected IFD was 3.5% (95% CI, 1.5%–6.7%) with a non–statistically significant trend between cohorts at 1.6% and 6.8%, respectively, (P = .053). On univariable analysis, only age was a risk factor for proven/probable IFD (Table 3).

FFS at day 180 was 82.9% (95% CI 76.8%–87.4%), with no significant difference between cohorts A and B at 85.2% and 78.6%, respectively (P = .139). On univariable and multivariable analysis, only the incidence of grade II–IV aGVHD was significantly associated with poorer FFS (Table 4; and Figure 3A and 3B).

Characteristics of IFD

There were 2 (2/204) bIFDs, both *Nakaseomyces glabrata (Candida glabrata)* fungemia and both in cohort A. The first bIFD was identified on day 12, with an ITZ trough serum concentration of 1607 ng/mL on day 13; antifungal sensitivities were not available for the isolate. The second bIFD was identified on day 15, after the patient achieved a ITZ trough serum concentration of 256 ng/mL on day 5, then was changed to IV posaconazole on day 12 due to nil by mouth; minimum inhibitory concentrations (MICs) of the isolate were 8.0 mg/L for ITZ and 2.0 mg/L for posaconazole. Both patients were successfully treated with anidulafungin (MIC = 0.060 mg/L for the second case). Four (4/202) other proven/probable IFDs were identified overall, all in cohort B after routine cessation of S-ITZ (postengraftment). These included 2 further *N glabrata* fungemias on day 90 post-HCT in remission and day 140 post-HCT after acute myeloid leukemia relapse, as well as 2 probable invasive pulmonary

Table 2. Cumulative Incidence of Breakthrough Invasive Fungal Disease (IFD), Fungal-Free Survival, Proven/Probable IFD, and Proven/Probable IFD Combined With Possible/Suspected IFD at 180 Days

Cohort	No.	Survival Rate/Cumulative Incidence, % (95% CI)	*P* Value
Breakthrough proven/probable IFD with competing risk of death			
Total	204	1.0 (.2–3.4)	
Cohort A	129	1.6 (.3–5.1)	.306
Cohort B	75	0	
Fungal-free survival (proven/probable)			
Total	204	83.1 (77.2–87.7)	
Cohort A	129	85.2 (77.7–90.3)	.057
Cohort B	75	79.7 (68.6–87.2)	
Proven/probable IFD with competing risk of death			
Total	204	3.0 (1.2–6.0)	
Cohort A	129	1.6 (.3–5.0)	.124
Cohort B	75	5.5 (1.7–12.4)	
Proven/probable IFD with competing risk of death and GVHD			
Total	204	2.0 (.7–4.7)	
Cohort A	129	1.6 (.3–5.0)	.563
Cohort B	75	2.9 (.5–9.0)	
Proven/probable IFD combined with possible/suspected IFD with competing risk of death			
Total	204	5.4 (2.9–9.2)	
Cohort A	129	1.6 (.3–5.0)	.002
Cohort B	75	12.2 (6.0–20.9)	
Proven/probable IFD combined with possible/suspected IFD with competing risk of death and GVHD			
Total	204	3.5 (1.5–6.7)	
Cohort A	129	1.6 (.3–5.0)	.053
Cohort B	75	6.8 (2.5–14.2)	

Abbreviations: CI, confidence interval; GVHD, graft-vs-host disease; IFD, invasive fungal disease.

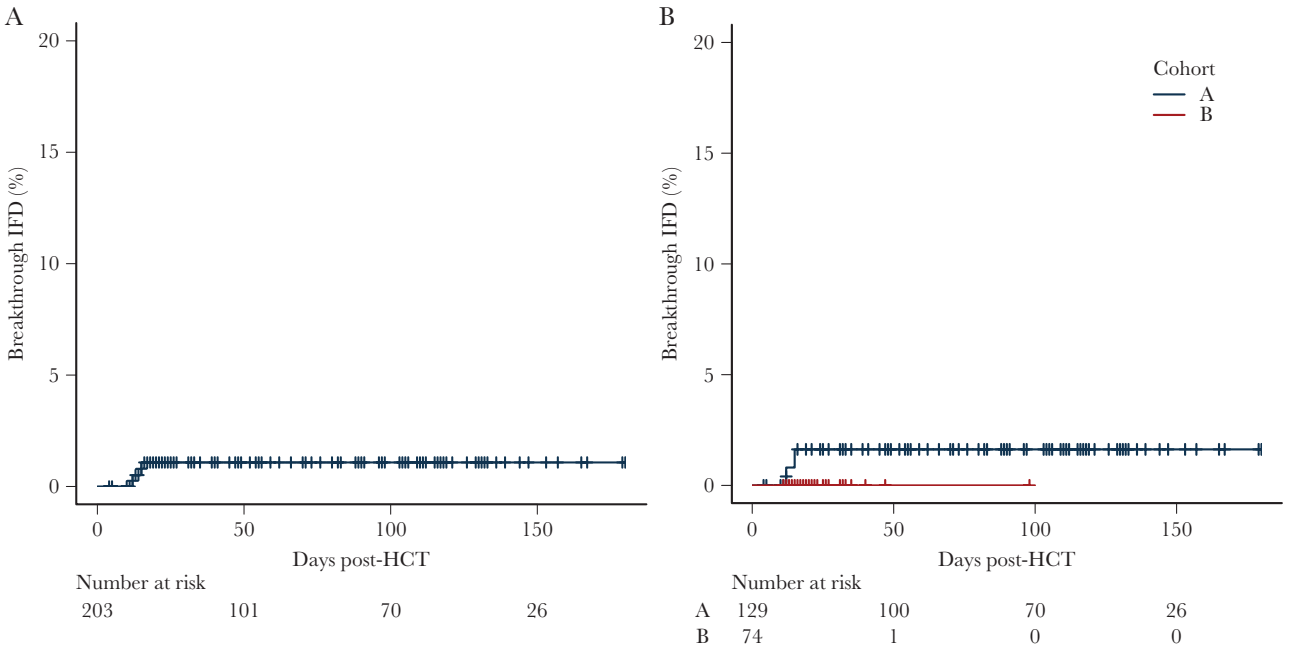

Figure 2. Breakthrough proven/probable invasive fungal disease for total patients (*A*) and by cohort (*B*). Abbreviations: HCT, hematopoietic cell transplant; IFD, invasive fungal disease.

Table 3. Univariable Analysis of Risk Factors for Proven/Probable Invasive Fungal Disease

	Univariable Analysis			
Variable	HR	Lower 95% CI	Upper 95% CI	*P* Value
Age	1.085	1.034	1.138	.001
Antithymocyte globulin	1.72	.3181	9.3	.529
Cohort B (vs A)	3.629	.648	20.33	.143
Male sex (vs female)	1.414	.26	7.686	.689
Conditioning: RIC (vs MAT)	1.041	.1921	5.643	.963
Donor source (vs MRD)				
Unrelated donor	1.135	.2104	6.123	.883
Haploidentical	0	NA	NA	NA
Cord	0	NA	NA	NA
Mismatch (vs matched)	0.63	.0727	5.459	.675
Primary disease (vs lymphoma)				
AML/MDS	1.533	.1732	13.57	.701
ALL	0	NA	NA	NA
Other	1.783	.1125	28.27	.6816
Grade II–IV aGVHD (time dependent)	1.164	.1249	10.84	.8942

Abbreviations: aGVHD, acute graft-vs-host disease; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; MAT, myeloablative conditioning; MDS, myelodysplastic syndrome; MRD, matched related donor; NA, not applicable; RIC, reduced intensity conditioning.

aspergilloses, identified on computed tomography, with positive galactomannan on bronchoalveolar lavage on days 69 and 82 post-HCT; 1 was in the context of grade II–IV aGVHD. No deaths were attributable to IFD.

Overall Survival, Progression-Free Survival, and Incidence of GVHD

The overall survival was 89.7% (95% CI, 84.6%–93.2%) at day 100, 84.6% (95% CI, 78.9%–88.9%) at day 180, and 74.9% (95% CI, 67.9%–80.6%) at 1 year. At day 180, cohorts A and B had similar rates of overall survival (85.2% vs 83.8%, $P = .187$), progression-free survival (76.5% vs 71.5%, $P = .141$), and nonrelapse mortality (10.1% vs 12.1%, $P = .464$). The incidence of grade II–IV aGVHD was 18.1% (95% CI, 13.2%–23.7%) at day 50 and 22.6% (95% CI, 17.1%–28.5%) at day 100, with a lower rate reported in cohort A compared to cohort B (14.0% vs 25.3% at day 50 and 17.8% vs 30.7% at day 100; $P = .018$).

Early Permanent Discontinuation of S-ITZ and/or Initiation of Alternative Antifungal Agent

Preengraftment early permanent S-ITZ discontinuation and initiation of an alternative antifungal agent in the absence of grade II–IV aGVHD was 3.4% (7/204; 95% CI, 1.5%–6.6%) overall,

Table 4. Univariable and Multivariable Analysis of Risk Factors for Fungal-Free Survival (Alive Without Proven/Probable Invasive Fungal Disease)

	Univariable				Multivariable			
Variable	HR	Lower 95% CI	Upper 95% CI	*P* Value	HR	Lower 95% CI	Upper 95% CI	*P* Value
Age	1.013	.993	1.033	.213	…	…	…	
Antithymocyte globulin	1.386	.826	2.327	.217	…	…	…	
Cohort B (vs A)	1.630	.981	2.708	.060	1.520	.868	2.663	.143
Male sex (vs female)	0.978	.585	1.634	.932	…	…	…	
Conditioning: RIC (vs MAT)	1.189	.689	2.050	.534	…	…	…	
Donor source (vs MRD)								
Unrelated donor	1.721	.946	3.132	.075	1.669	.912	3.052	.097
Haploidentical	1.589	.577	4.378	.370	1.558	.539	4.509	.413
Cord	2.416	.317	18.390	.394	1.954	.248	15.380	.525
Mismatch (vs matched)	1.154	.630	2.113	.643	…	…	…	
Primary disease (vs lymphoma)								
AML/MDS	1.596	.768	3.315	.210	1.567	.745	3.297	.236
ALL	1.666	.511	5.425	.397	1.497	.455	4.923	.507
Other	2.148	.890	5.185	.089	2.275	.924	5.601	.074
Grade II–IV GVHD (time dependent)	2.291	1.336	3.929	.003	2.035	1.155	3.587	.014

Outcome events: death or proven/probable invasive fungal disease.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; GVHD, acute graft-vs-host disease; HR, hazard ratio; MAT, myeloablative conditioning; MDS, myelodysplastic syndrome; MRD, matched related donor; RIC, reduced intensity conditioning.

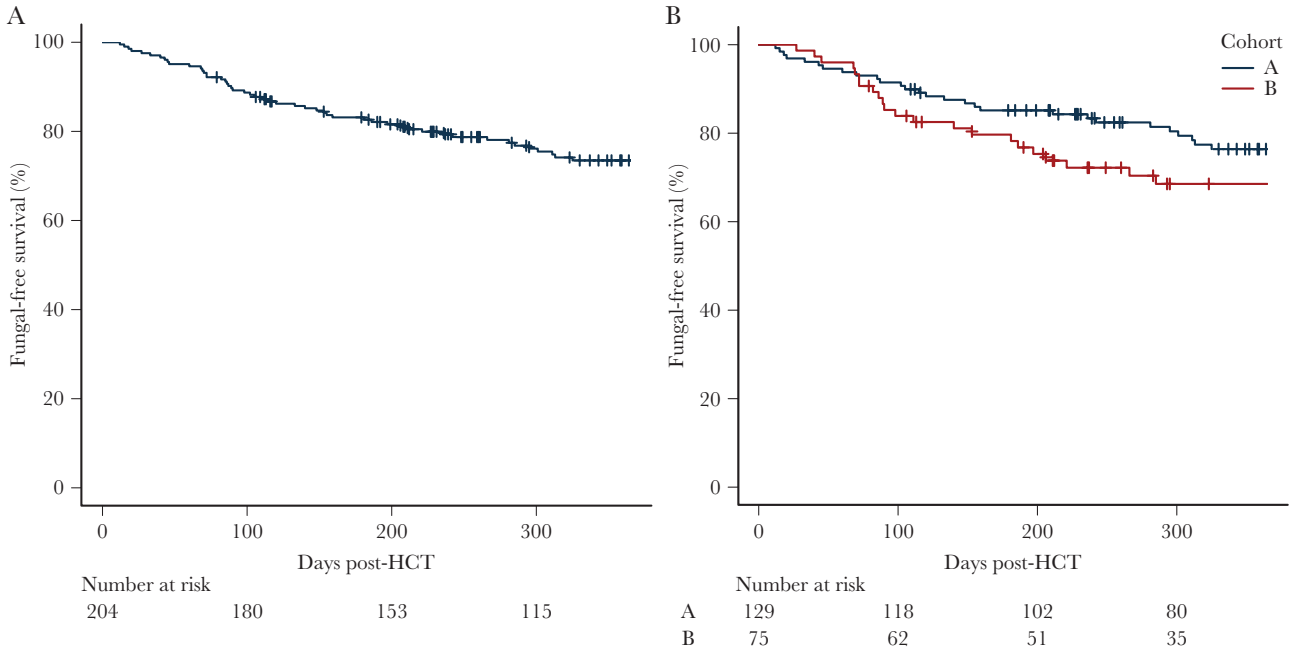

Figure 3. Fungal-free survival for total patients (*A*) and by cohort (*B*). Abbreviation: HCT, hematopoietic cell transplant.

with no significant difference between cohorts (Table 5 and Figure 4A). Reasons for overall preengraftment S-ITZ discontinuations are shown in Table 6.

Postengraftment early permanent S-ITZ discontinuation and/or the initiation of an alternative antifungal agent in the absence of grade II–IV aGVHD was 2.5% (6/197; 95% CI, 1.0%–5.5%) overall. In cohort A, where S-ITZ was used as primary prophylaxis until weaning of immunosuppression (~day 100), an alternative antifungal agent was initiated in 0.8% (1/125; 95% CI, .1%–4.0%) of patients. In cohort B, where no routine primary prophylaxis after engraftment was used, 7.1% (5/72; 95% CI, 2.6%–14.6%) of patients were initiated on an antifungal agent (P = .016) (Tables 5 and 6 and Figure 4B).

Table 5. Overall Early Permanent SUBA-Itraconazole Discontinuation and/or Initiation of Alternative Antifungal Agent for Any Reason in the Absence of Graft-vs-Host Disease

Cohort	No.	Cumulative Incidence, % (95% CI)	*P* Value
Preengraftment[a]			
Total	204	3.4 (1.5–6.6)	
Cohort A	129	3.1 (1.0–7.2)	.750
Cohort B	75	4.0 (1.1–10.3)	
Postengraftment[b]			
Total	197	2.5 (1.0–5.5)	
Cohort A	125	0.8 (.1–4.0)	.016
Cohort B	72	7.1 (2.6–14.6)	

Abbreviation: CI, confidence interval.

[a]Early permanent SUBA-itraconazole discontinuation and initiation of alternative antifungal.

[b]Early permanent SUBA-itraconazole discontinuation and initiation of alternative antifungal in cohort A and initiation of an antifungal agent in cohort B.

Safety and Tolerability

One patient (0.5%) developed DILIN grade 3+ liver injury potentially attributable to S-ITZ, no patients were reported having a prolonged QTc, and no patients required cessation due to GI intolerance attributed to S-ITZ.

Sixty-four patients (31%) required temporary substitution of an IV alternative antifungal as per institutional policy—22.4% (29/129) in cohort A to IV posaconazole, and 46.7% (35/75) in cohort B to IV itraconazole. The most common reason for temporary substitution was nil by mouth due to mucositis (92.2%), followed by nil by mouth due to any other reason (6.3%), liver dysfunction not attributed to S-ITZ (1.6%), or omitted in error (1.6%). The median day post-HCT for substitution was day 8 (range, 1–39). In cohort A, 82.7% (24/29) of patients restarted S-ITZ, with the remaining patients developing aGVHD and remaining on posaconazole. In cohort B, 40.0% (14/35) patients restarted S-ITZ; the remaining patients were discharged postengraftment without an antifungal or developed aGVHD and were changed to posaconazole as per policy. The median duration of substitution was 11 days (range, 5–25 days). The median day post-HCT for cohort B to cease S-ITZ on engraftment as per policy was 18 (range, 10–47).

Therapeutic Drug Levels of S-ITZ

A total of 1410 trough plasma ITZ concentrations from 193 (94.6%) patients are shown in Figure 5A. The geometric mean trough plasma concentration was 1130 ng/mL (IQR, 566–1801 ng/mL; coefficient of variation [CV], 56.57%). Therapeutic ITZ level attainment is shown in Figure 5B; the median time to achieve therapeutic levels was 10 days (95% CI, 10–11 days),

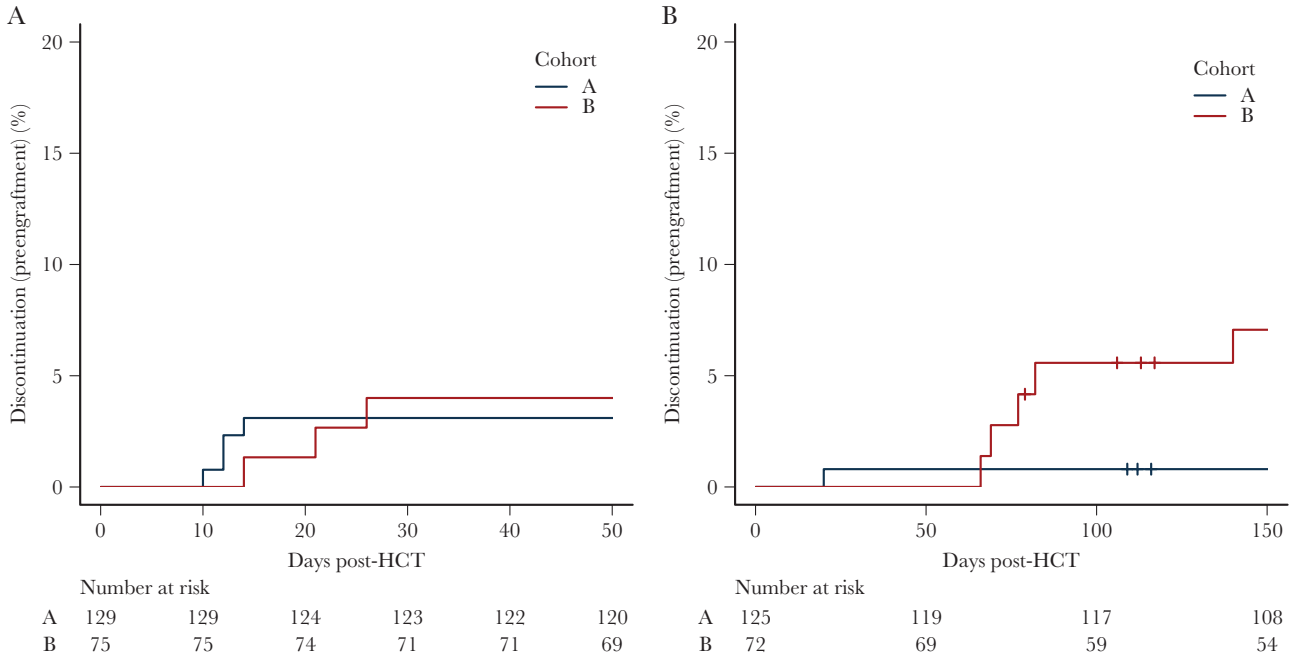

Figure 4. *A*, Preengraftment, early permanent SUBA-itraconazole (S-ITZ) discontinuation and initiation of alternative antifungal agent for any reason by cohort. *B*, Postengraftment, early permanent S-ITZ discontinuation, and initiation of alternative antifungal agent (cohort A) or initiation of an antifungal agent (cohort B). Abbreviation: HCT, hematopoietic cell transplant.

with no significant difference between cohorts ($P = .27$). By day 14 and day 21 of S-ITZ therapy, 75.8% (95% CI, 69.0%–82.0%) and 94.0% (95% CI, 89.3%–97.1%) of patients achieved therapeutic levels. Overall, the geometric mean of first ITZ trough concentration after steady state was 1037 ng/mL (range 248–2000 ng/mL; IQR, 651–1370 ng/mL; CV, 56.71%) and there was no significant difference between cohorts (Figure 5C).

A total of 119 patients in cohort A continued S-ITZ postengraftment without clinical failure. To maintain a therapeutic ITZ level between 1000 and 2000 ng/mL, 68 of these patients (57.1%) maintained a dose of 200 mg BID, 35 patients (29.4%) required a dose adjustment to 150 mg BID (median day post-HCT, 41 [range, 7–78]), and 15 of 32 patients required a further dose adjustment to 100 mg BID (median day post-HCT, 61 [range, 12–105]); the remaining 16 patients (13.4%) developed grade II–IV aGVHD and were changed to posaconazole.

DISCUSSION

In this multisite longitudinal cohort study, S-ITZ as primary IFD prophylaxis after HCT appeared effective and well tolerated, with low levels of bIFD or early discontinuations due to GI intolerability or adverse effects.

ITZ is well described as an effective primary IFD prophylaxis choice post-HCT; however, routine use has been limited by GI tolerability and variation in absorption and therefore has fallen out of favor in many HCT centers [10, 11, 26, 27]. In 2004, Marr et al demonstrated that ITZ oral solution 2.5 mg/kg 3 times daily showed no survival advantage over fluconazole despite being more effective in preventing molds in HCT recipients; however, 36% of patients were discontinued from ITZ because of toxicities or GI intolerance and approximately 20% of patients dose-reduced ITZ due to GI intolerance [10]. The largest randomized controlled trial in this setting using ITZ by Marks et al failed to demonstrate a survival or proven/probable IFD difference compared to voriconazole; however, early discontinuation of ITZ due to intolerance or adverse effects including vomiting, nausea, and diarrhea was significant [11]. With improvements to the formulation maximizing tolerability and absorption, S-ITZ may be a potentially advantageous choice of agent for primary IFD prophylaxis in HCT.

The utility of conventional ITZ for primary prophylaxis has also been restricted by high individual pharmacokinetic variability [21, 28, 29]. We found that therapeutic levels of S-ITZ were achieved at a median of 10 days, with 75% of patients achieving therapeutic levels by 14 days, and that the overall mean S-ITZ level was 1130 ng/mL. Serum ITZ trough concentrations <1000 ng/mL are predictive of therapeutic failure, with individuals with concentrations <500 ng/mL significantly more likely to develop IFD [21, 29]. With the achievement of higher serum trough levels than previous studies of conventional formulations [10, 11], and improved tolerability, S-ITZ may also be a potentially useful agent for primary IFD prophylaxis during GVHD, with further studies using the S-ITZ formulation in this population warranted [27]. Recently, there has been a report of using a 3-day loading dose to achieve therapeutic levels more

Table 6. Early Permanent SUBA-Itraconazole Discontinuation and/or Initiation of Alternative Antifungal Agent for Any Reason in the Absence of Graft-vs-Host Disease by Numbers of Patients

Cohort	Preengraftment[a]	Postengraftment[b]
Total	204	197
Cohort A	129	125
Cohort B	75	72
Proven/probable IFD		
Total	2 (1.0)	3 (1.5)
Cohort A	2 (1.6)	0
Cohort B	0	3 (2.4)
Possible/suspected IFD		
Total	2 (1.0)	3 (1.5)
Cohort A	0	1 (0.8)
Cohort B	2 (2.7)	2 (2.8)
Failure to achieve therapeutic serum ITZ concentrations after 14 d of therapy		
Total	1 (0.5)	0
Cohort A	1 (0.8)	0
Cohort B	0	NA
Adverse drug reactions attributed to S-ITZ		
Total	1 (0.5)	0
Cohort A	0	0
Cohort B	1 (1.3)	NA
Intolerance to S-ITZ		
Total	0	0
Cohort A	0	0
Cohort B	0	NA
Any other reason		
Total	1 (0.5)	0
Cohort A	1 (0.8)	0
Cohort B	0	NA

Data are presented as No. (%).

Abbreviations: IFD, invasive fungal disease; ITZ, itraconazole; NA, not applicable; S-ITZ, SUBA-itraconazole.

[a]Early permanent S-ITZ discontinuation and initiation of alternative antifungal.

[b]Early permanent S-ITZ discontinuation and initiation of alternative antifungal in cohort A and initiation of an antifungal agent in cohort B.

rapidly, which may be a potential strategy to further improve its use in clinical practice [16].

Despite achieving higher trough ITZ serum concentrations than previous studies, we did not identify any safety issues. Documented toxicity was minimal, with 1 patient demonstrating liver injury potentially attributable to S-ITZ and no patients reported to have a prolonged QTc or GI intolerance; however, routine QTc measurements were at the discretion of the treating physician only.

Drug–drug interactions are a major consideration with the use of triazole antifungals for antifungal prophylaxis in HCT [30–32]. Many centers that use triazoles as standard prophylaxis have specific dosing and therapeutic drug monitoring protocols for concomitant drugs such as calcineurin inhibitors, taking into consideration these interactions. One advantage of continuing prophylaxis with a triazole until weaning of immunosuppression, such as the cohort A policy, is the stable CYP3A4 inhibition throughout the first 100 days post-HCT, which leads to less variation in calcineurin or mTOR inhibitor levels, which could potentially impact toxicity or rates of GVHD. S-ITZ also has the advantage of less interpatient variability in trough serum levels compared to other formulations of ITZ, which in turn results in more stable CYP3A4 inhibition [13, 17].

The results of this study are limited by the retrospective, noninterventional design. In addition, the study included 2 antifungal prophylaxis strategies, with differing durations of S-ITZ therapy. We did not demonstrate a significant difference in survival or proven/probable IFD but noted there were more cases of possible/suspected IFD combined with proven/probable IFD after engraftment in cohort B with a shorter duration of prophylaxis; however, as addressed above, this result was not statistically significant in the absence of GVHD. There is currently no consensus for the duration or agent of choice for primary antifungal prophylaxis after HCT in the absence of GVHD [5]. Local prevalence of IFD, drug–drug interactions, tolerability, and the cost-to-benefit ratio result in varied practices. In low-IFD-risk, non-GVHD HCT recipients, *Candida* prophylaxis alone with fluconazole is used in centers with historically low rates of mold infections, whereas mold-active agents such as voriconazole, posaconazole, and isavuconazole are also often chosen [5, 33]. Mold-active prophylaxis has been reported to be marginally more effective for preventing IFD compared to empiric or preemptive therapy, but at a higher cost [34]. Further studies assessing the most appropriate postengraftment antifungal strategy are therefore warranted.

Overall, this study has demonstrated that S-ITZ is a safe and well-tolerated formulation and overcomes many of the limitations seen with the older oral ITZ formulation. It is a novel alternative for primary IFD prophylaxis after HCT.

Notes

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Potential conflicts of interest. J. L. has served on advisory boards for Mayne Pharma, Merck Sharp & Dohme (MSD), Amgen, and Bristol-Myers Squibb. D. C. M. K. has served on advisory boards for Becton Dickinson and MSD, and has received financial support from MSD and F2G, all unrelated to the current work. S. A. P. receives research support from Global Life Technologies; participated in research trials with Chimerix and Merck & Co; and participated in a clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (grant number U01-AI132004). All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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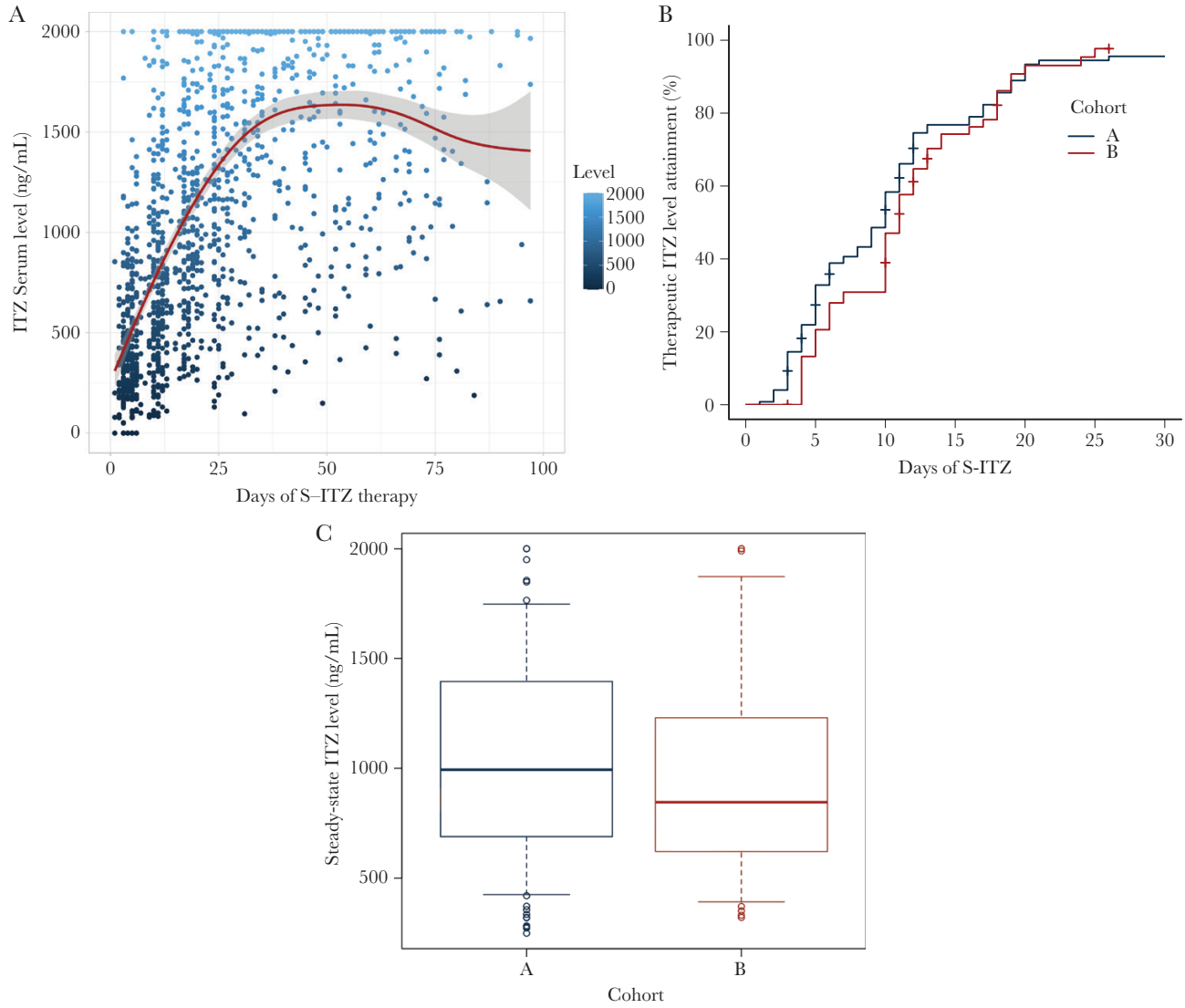

Figure 5. SUBA-itraconazole (S-ITZ) levels among study cohorts. *A*, Total S-ITZ levels with mean and 95% confidence interval indicated (n = 1414). *B*, Proportion of patients to attain therapeutic itraconazole (ITZ) levels (defined by >500 ng/mL; cohort A, n = 124; cohort B, n = 69). *C*, Steady-state levels (defined by first level taken >14 days of S-ITZ; cohort A, n = 99; cohort B, n = 33).

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