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Hepatic Safety of Isavuconazole Compared with Voriconazole in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation Complicated by Invasive Mold Disease – a Post-Hoc Analysis from the SECURE Study

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ABSTRACT

Background: Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) often require mold-active antifungal treatment and are at increased risk of drug-related hepatotoxicity. We compared hepatic toxicity profiles of isavuconazole (ISAV) and voriconazole (VRC) in a post-hoc analysis of patients in the SECURE study with and without allogeneic HSCT.

Methods: Patients were randomized 1:1 to ISAV or VRC; allogeneic HSCT was a stratification factor. The number of patients with treatment-emergent adverse events (TEAEs) in the System Organ Class "Hepatobiliary disorders" (MedDRA v12.1) and alanine/aspartate aminotransferase (ALT/AST) and bilirubin elevation rates at the end of treatment were compared.

Results: Of 516 patients, 20% had allogeneic HSCT (ISAV n=54, VRC n=51). Hepatobiliary TEAEs and transaminase/bilirubin levels results are summarized in **Table A**. For ISAV the proportion of patients with or without allogeneic HSCT who experienced ≥1 hepatobiliary TEAE was comparable (P=0.6); this rate was higher for patients on VRC (P=0.056). Fewer patients experienced drug-related hepatobiliary TEAEs with ISAV than VRC, both in patients with and without allogeneic HSCT (P<0.01).

Table A

Parameter	Without allogeneic HSCT: ISAV n=203	VRC n=208	Difference[a] % (95% CI)	Relative risk[b]	With allogeneic HSCT: ISAV n=54	VRC n=51	Difference[a] % (95% CI)	Relative risk[b]
Patients with ≥1 hepatobiliary TEAE, n (%)								
Overall	17 (8)	29 (14)	−6 (−12, 1)	0.6	6 (11)	13 (25)	−14 (−31, 2)	0.4
Moderate/severe	13 (6)	20 (10)	−3 (−9, 3)	0.7	4 (7)	8 (16)	−8 (−23, 6)	0.5
Leading to permanent discontinuation	1 (0.5)	3 (1)	−1 (−3, 1)	0.3	0	3 (6)	−6 (−14, 3)	-
Drug-related	4 (2)	17 (8)	−6 (−11, −2)	0.2	1 (2)	9 (18)	−16 (−29, 3)	0.1
Serious	2 (1)	3 (1)	−1 (−3, 2)	0.7	1 (2)	3 (6)	−4 (−13, 5)	0.3
Transaminase elevations >3x ULN, n/N (%)								
ALT	6/196 (3)	10/205 (5)	−2 (−6, 3)	0.6	3/54 (6)	7/50 (14)	−8 (−22, 5)	0.4
ALT or AST	8/196 (4)	20/205 (10)	−6 (−11, 0)	0.4	3/54 (6)	7/50 (14)	−8 (−22, 5)	0.4
ALT or AST and bilirubin 2× ULN	0/195	2/205 (1)	−2 (−4, 1)	-	1/54 (2)	5/50 (10)	−6 (−17, 4)	0.2

[a](ISAV−VRC); [b](ISAV/VRC); ULN, upper limit of normal

Conclusions: In this analysis allogeneic HSCT recipients had an increased rate of hepatobiliary toxicity. ISAV had a favorable hepatic safety profile vs. VRC in patients with or without allogeneic HSCT, with a more pronounced safety benefit in patients after allogeneic HSCT.

INTRODUCTION

- Recipients of allogeneic hematopoietic stem cell transplantation (HSCT) are a high risk group for invasive fungal disease (IFD).[1]
  - Liver-related complications can affect up to 80% of allogeneic HSCT recipients and can include sinusoidal obstruction syndrome and graft vs. host disease early after transplantation, and infectious sequelae, cirrhosis and hepatic malignancies as late complications.[2]
  - Treatment in this patient group for IFD can be complicated due to an increased risk of drug-related hepatotoxicity.[3]
- Isavuconazole (ISAV), administered as the water-soluble prodrug isavuconazonium sulfate, is a broad-spectrum triazole antifungal agent.[4]
  - In the Phase 3 SECURE trial, ISAV was shown to be non-inferior to voriconazole (VRC) in the overall patient population for Day 42 all-cause mortality for the primary treatment of invasive aspergillosis (IA) and IFD caused by other filamentous fungi.[5]
  - ISAV-treated patients were observed to have a lower frequency of treatment-emergent hepatobiliary disorders (P=0.016) than VRC-treated patients.[5]
  - ISAV is approved by the US Food and Drug Administration for the treatment of adults with IA and invasive mucormycosis[4] and by the European Medicines Agency for the primary treatment of IA in adults, and for the treatment of mucormycosis in adults for whom treatment with amphotericin B is inappropriate.[6]
- We compared hepatic toxicity profiles of ISAV and VRC in a post-hoc analysis of patients in the SECURE Phase 3 trial with and without allogeneic HSCT.

METHODS

Study design

- SECURE (ClinicalTrials.gov identifier: NCT00412893) was a Phase 3, global multi-center, double-blind, parallel-group, non-inferiority trial that evaluated ISAV vs. VRC for the primary treatment of IFD caused by *Aspergillus* spp. and other filamentous fungi.[5]
- Patients with proven/probable/possible IFD (EORTC/MSG criteria[7]), ≥18 years of age were randomized to receive ISAV or VRC; allogeneic HSCT was a stratification factor.
- All patients who received at least one dose of the study drug were included in the safety analysis population.

Safety assessments

- The number of patients with treatment-emergent adverse events (TEAEs) in the System Organ Class "Hepatobiliary disorders" (MedDRA v12.1) were recorded.
- Alanine/aspartate aminotransferase (ALT/AST) and bilirubin elevation rates at the end of treatment were compared.

RESULTS

Patient characteristics

- Out of a total of 516 patients who received the study drug in the SECURE trial, 105 (20%) had allogeneic HSCT at baseline (ISAV n=54, VRC n=51) and 411 (80%) had no allogeneic HSCT at baseline (ISAV n=203, VRC n=208).
  - Baseline characteristics were similar between patients with allogeneic HSCT treated with either ISAV or VRC, although the VRC group had a higher proportion of male patients (**Table 1**).
  - The most common underlying disease in patients with and without allogeneic HSCT was acute myeloid leukemia (**Table 1**).
  - Transplant characteristics of patients between treatment groups were similar (**Table 2**).
- For the allogeneic HSCT recipients, the median (range) total duration of treatment was 38 (3–102) days in patients who received ISAV and 42 (5–88) days in patients who received VRC (difference not statistically significant) (**Table 3**).

Safety assessments

- Among patients treated with ISAV, the proportions with or without allogeneic HSCT who experienced ≥1 hepatobiliary TEAE were comparable (P=0.6) (**Figure 1A, B**).
  - In patients treated with VRC, a numerically higher proportion of patients with allogeneic HSCT than those without allogeneic HSCT experienced ≥1 hepatobiliary TEAE (P=0.056) (**Figure 1A, B**).
  - Significantly fewer patients experienced drug-related hepatobiliary TEAEs with ISAV than VRC, both in patients with and without allogeneic HSCT (P<0.01) (**Figure 1A, B**).
- Irrespective of treatment assignment, more patients with than without HSCT had increases in levels of ALT or AST >3× the upper limit of normal (ULN) and bilirubin >2× ULN (P=0.0013) (**Figure 2A, B**).

Table 1. Characteristics of patients with and without allogeneic HSCT

Parameter	Patients with allogeneic HSCT: ISAV (n=54)	VRC (n=51)	Patients without allogeneic HSCT: ISAV (n=203)	VRC (n=208)
Age [years], median (range)	51 (18–73)	44 (21–69)	56 (17–82)	55 (18–87)
Gender, n (%)				
Male	30 (55)	41 (80)	115 (57)	122 (59)
Race, n (%)				
White	45 (83)	42 (82)	166 (82)	149 (72)
Other[a]	9 (17)	9 (18)	37 (18)	58 (28)
Risk factor for IFD, n (%)				
Uncontrolled malignancy[b]	24 (44)	25 (49)	149 (73)	162 (78)
Neutropenia[c]	26 (48)	22 (43)	137 (67)	153 (74)
Hematological malignancy	51 (94)	50 (98)	160 (80)	172 (83)
Use of corticosteroid	16 (30)	18 (35)	32 (16)	21 (10)
Use of T-cell immunosuppressant	40 (74)	40 (78)	71 (35)	69 (33)
Underlying disease, n (%)				
Acute myeloid leukemia	19 (35)	19 (37)	80 (39)	107 (52)
Acute lymphocytic leukemia	11 (20)	9 (18)	19 (9)	15 (7)
Chronic lymphocytic leukemia	3 (6)	6 (12)	7 (3)	7 (3)
Other	21 (39)	17 (33)	93 (46)	75 (36)

[a]Other includes Black or African American and Asian
[b]Patients with malignancy diagnosis and new/active disease or relapse
[c]Absolute neutrophil count <0.5 x 10^9/L at baseline
HSCT, hematopoietic stem cell transplant; IFD, invasive fungal disease; ISAV, isavuconazole; VRC, voriconazole

Table 2. Transplant characteristics of patients

Parameter, n (%)	Patients with allogeneic HSCT: ISAV (n=54)	VRC (n=51)
Type of transplant		
Autologous	3 (6)	3 (6)
Allogeneic	54 (100)	51 (100)
Type of cells		
Bone marrow cells	14 (26)	17 (33)
Peripheral stem cells	38 (70)	34 (67)
Cord blood cells	1 (2)	2 (4)
Graft vs. host disease		
Graft vs. host disease grade		
I	4 (7)	10 (20)
II	5 (9)	9 (18)
III	8 (15)	6 (12)
IV	1 (2)	1 (2)
Missing	2 (4)	0

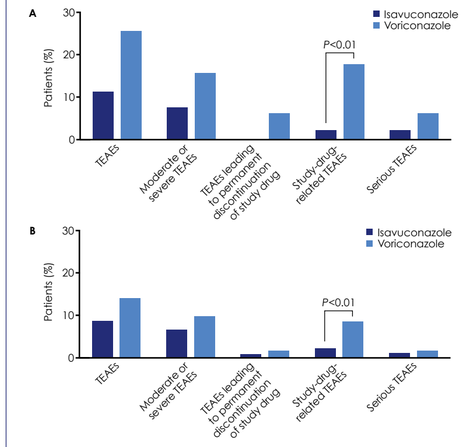
HSCT, hematopoietic stem cell transplant; ISAV, isavuconazole; VRC, voriconazole

Table 3. Study drug exposure

Parameter [days], median (range)	Patients with allogeneic HSCT: ISAV (n=54)	VRC (n=51)
Total duration	38 (3–102)	42 (5–88)
Duration of IV dosing only	8 (2–84)	7 (3–63)
Duration of oral dosing only	48 (1–100)	47 (1–83)

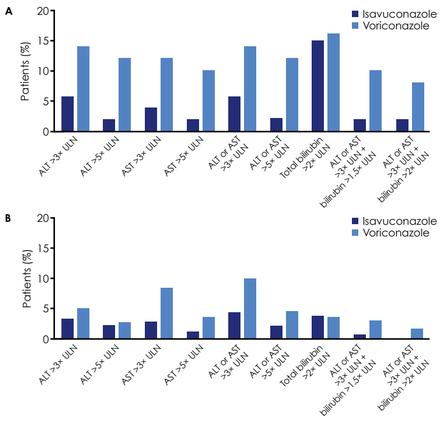
HSCT, hematopoietic stem cell transplant; ISAV, isavuconazole; IV, intravenous; VRC, voriconazole

Figure 1. Percent of patients with ≥1 hepatobiliary TEAE among those with (A) or without (B) allogeneic HSCT



HSCT, hematopoietic stem cell transplant; TEAE, treatment-emergent adverse event

Figure 2. Percent of patients with increases from baseline in liver enzyme and bilirubin levels among those with (A) or without (B) allogeneic HSCT



ALT, alanine transaminase; AST, aspartate transaminase; HSCT, hematopoietic stem cell transplant; ULN, upper limit of normal

CONCLUSIONS

- In this analysis, allogeneic HSCT recipients had an increased rate of elevations of hepatic enzymes and bilirubin compared with patients without allogeneic HSCT.
  - This is consistent with the known hepatic complications that accompany HSCT[2] and hepatic effects of antifungal treatments.[3]
- Unlike treatment with VRC, treatment with ISAV was not associated with an increased number of patients with vs. without allogeneic HSCT who experienced hepatic TEAEs.
  - Fewer ISAV-treated patients than VRC-treated patients had elevated levels of liver enzymes.
- Taken together, these observations suggest that ISAV had a favorable hepatic safety profile vs. VRC in patients with or without allogeneic HSCT with a more pronounced hepatic safety benefit in patients after allogeneic HSCT.

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