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Health Economic Outcome Analysis of Patients Randomized in the SECURE Phase 3 Trial Comparing Isavuconazole to Voriconazole for Primary Treatment of Invasive Fungal Disease Caused by *Aspergillus* Species or Other Filamentous Fungi

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BACKGROUND

- Invasive fungal disease (IFD) caused by *Aspergillus* spp. and other filamentous fungi is a serious medical challenge in immunocompromised patients, such as those with malignancies, solid organ and hematopoietic stem cell transplants, and AIDS.[1–3]
- Patients with invasive aspergillosis have longer lengths of stay (LOS) in hospitals and higher cost of care compared with those without the disease.[4–6]
  - The hospital costs of patients with invasive aspergillosis vary widely depending on the severity of infection, especially in the context of comorbidities.[7]
- Despite improved treatment options and advances in diagnostic testing, patient outcomes remain suboptimal.
- Isavuconazole (ISA) is a broad-spectrum triazole antifungal, which has demonstrated potent *in vitro* activity against clinically relevant pathogens including *Aspergillus* spp., *Candida* spp., *Cryptococcus* spp., and Mucorales, as well as efficacy in animal models of invasive aspergillosis,[8] invasive candidiasis,[8] mucormycosis,[9] and cryptococcosis.[10]
- A large (N=516), Phase 3, randomized trial (SECURE) recently demonstrated non-inferiority of ISA compared with voriconazole (VRC; based on a non-inferiority margin of 10%) for Day 42 all-cause mortality for the primary treatment of IMD caused by *Aspergillus* spp. and other filamentous fungi.[11]

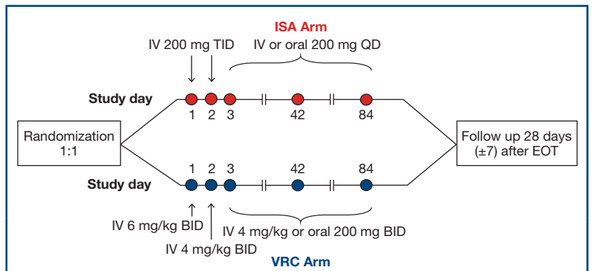
OBJECTIVES

- To compare the economic parameters that impacted the use of ISA and VRC in the SECURE trial by conducting a health economics and clinical outcomes research (HECOR) analysis.

METHODS

Study design and patient population

- SECURE was a global, Phase 3, multi-center, randomized, double-blind, parallel group, non-inferiority trial that evaluated ISA vs. VRC for the primary treatment of IFDs caused by *Aspergillus* spp. and other filamentous fungi.
- Patients, aged ≥18 years, with proven/probable/possible IFD (EORTC/MSG criteria) were randomized 1:1 to receive ISA or VRC (**Figure 1**).
- ISA 200 mg intravenous (IV) loading dose was administered 3 times daily (TID) on Days 1 and 2, followed by either IV or oral 200 mg once daily (QD) from Day 3 to end of treatment (EOT).
- VRC 6 mg/kg IV loading dose was administered twice daily (BID) on Day 1, followed by 4 mg/kg IV BID on Day 2, then either 4 mg/kg IV or 200 mg oral was administered BID from Day 3 to EOT.
- All patients who received at least 1 dose of the study drug were included in the intent-to-treat (ITT) population.
- The SECURE HECOR analysis plan was finalized prior to treatment unblinding.



ACM was assessed on Days 42 and 84
Overall response was assessed by the DRC on Day 42, 84, and EOT
The maximum duration of therapy was 84 days

Figure 1. Study design

Outcome measures

- The primary endpoint for this analysis was hospital LOS in patients who received ISA or VRC in the SECURE trial (ITT population).
  - Hospital LOS was defined as time (days) from beginning of randomized therapy (if admitted before randomization) to the date of discharge or death during the hospitalization, whichever happened first; if admitted after randomization, time from hospital admission to discharge or death during the hospitalization, whichever happened first.
- Other endpoints analyzed included:
  - 30-day all-cause hospital readmission rate, defined as at least 1 other hospital readmission within 30 days post-discharge date of initial hospitalization during which study drug was initiated.
  - Ratio of total days on IV over total number of days of IV + oral therapy for study drugs.
  - Total number of additional days on non-study antifungal drugs, for patients who switched from the study drugs to a potentially mold-active systemic antifungal therapy after end of study treatment, were also evaluated.

Subgroup analysis

- A pre-specified subgroup analysis assessing LOS in the following subgroups of clinical relevance was conducted using a Cox regression model:
  - Age (≤45, >45 to ≤65, and >65 years),
  - Body mass index (BMI; <25, ≥25 to <30, ≥30 kg/m^2), and
  - Renal impairment (estimated glomerular filtration rate-modification of diet in renal disease [eGFR-MDRD] category <60 mL/min/1.73 m^2).

RESULTS

Patients

- A total of 516 patients were included in the ITT population (ISA arm, n=258; VRC arm, n=258).

Outcomes

- The median LOS was found to be lower for patients in the ISA arm (13 days) vs. those in the VRC arm (15 days) (**Table 1**).
- The 30-day readmission rate was lower for ISA compared with VRC patients (18.3% vs. 24.4%, *P*=0.114) (**Table 1**).
- Ratios of days patients were on IV formulation to total days of IV + oral therapy were similar in both treatment arms (ISA 0.4 [standard deviation; SD 0.4]; VRC 0.4 [SD 0.4]) (**Table 1**).
- Median additional days patients were on potentially mold-active systemic antifungal therapy other than study drugs were comparable between the ISA and VRC arms (32 vs. 33 days).

Subgroup outcomes

- Median LOS was similar for most subgroups (**Figure 2**).
  - However, in patients >65 years of age and those with BMI ≥30 kg/m^2, LOS in the ISA arm was shorter than in the VRC arm (15 vs. 20 days) and (13.5 vs. 22.0 days), respectively.
  - LOS for patients with renal impairment was statistically significantly shorter in the ISA arm (9 days) compared with the VRC arm (19 days; *P*=0.0032).

Table 1. HECOR outcomes in the ITT population

Outcome	ISA (N=258)	VRC (N=258)
LOS [days], median (range)[a]	13 (1–371)	15 (2–118)
30-day readmission rate[a,b]		
Readmission rate, n/N (%)	45/246 (18.3)	62/254 (24.4)
Adjusted difference[c] (95% CI)	–6.0 (–1.3, 13.3)	
Treatment duration [days on IV], mean ± SD	8.1 ± 8.5	8.9 ± 9.6
Treatment duration [days on antifungals], mean ± SD	47.1 ± 32.4	46.4 ± 32.1
Ratio of days on IV vs. IV + oral therapy, mean ± SD	0.4 ± 0.4	0.4 ± 0.4

[a]For patients with sufficient hospitalization details. [b]Includes patients with a reported re-hospitalization or evidence of hospitalization reported as part of a serious adverse event. [c]Adjusted difference based on stratified Cox regression; geographical region, BMT/HSCT status, and uncontrolled malignancy were used for stratifying the study randomization. CI: confidence interval.

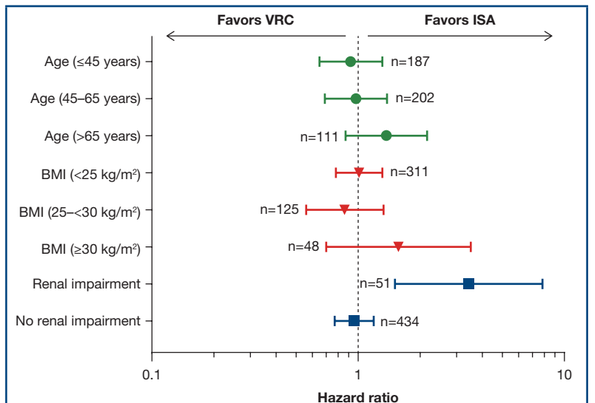


Figure 2. Comparison of median LOS (days) for ITT patients receiving ISA vs. VRC, by age, BMI, and renal impairment categories

CONCLUSIONS

HECOR analyses in the SECURE trial favored ISA compared with VRC:

- Patients treated with ISA showed shorter hospital LOS vs. those treated with VRC in the overall ITT study population; however, this difference was not statistically significant.
- Patients with renal impairment and receiving ISA had a statistically significantly shorter LOS compared with those receiving VRC, despite the small sample size.
- Patients aged >65 years and those with BMI ≥30 kg/m^2 also had shorter, but not statistically significant differences in LOS when treated with ISA vs. VRC.

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