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Mucormycosis Treated with Isavuconazole: A Matched-Pair Analysis from the FungiScope® Registry

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Background

- Mucormycosis is a rare invasive fungal disease, typically occurring in patients with compromised immune systems; it may also affect immunocompetent patients after traumatic injuries or burns.
- Increasing incidences have been reported from several countries, because of advances in diagnostics and increased awareness for such emerging fungal infections as well as the increasing number of patients at risk (1–3).
- Mucormycosis is difficult to treat because of *in vitro* resistance to several antifungal drugs. As limited therapeutic options are available (4), mortality remains high for this disease (3).
- Isavuconazole is a novel, broad-spectrum triazole antifungal, available as both intravenous and oral formulations, for the treatment of adult patients with invasive aspergillosis and mucormycosis.
- Isavuconazole was first approved for mucormycosis in 2015 based on data from 37 patients enrolled in a single-arm open-label trial (VITAL study) and 33 matched control cases from the FungiScope® registry (5).
- In a retrospective case collection study, we compared outcomes for patients with invasive mucormycosis treated with isavuconazole versus other systemic antifungal therapies, in order to provide evidence of the real-world effectiveness of isavuconazole.

Methods

- Clinical data of proven and probable mucormycosis cases were collected in the ongoing global FungiScope® registry of rare fungal infections (NCT01731353) (6). Case enrolment requires cultural, histological, or molecular evidence of infection with non-endemic fungi. Data collected for each case include demographics, underlying conditions, immunosuppressive medications, clinical signs and symptoms, sites of infection, results from diagnostic tests, pathogen identification, antifungal treatments, and outcome.
- Cases treated with at least four consecutive days of isavuconazole between 2016 and 2019 were matched with control cases receiving lipid formulations of amphotericin B or posaconazole as first-line treatment between 2011 and 2019.
- Case-matching criteria were consistent with the VITAL study (5) and included disease severity, presence of hematological malignancy or allogeneic stem cell transplantation, and surgical treatment.
- Baseline patient variables, disease classification according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group 2008 criteria, all-cause mortality, and key outcomes of clinical response were compared descriptively.

Results

Case disposition and antifungal treatment

- As of June 2020, 144 mucormycosis cases treated with antifungal medications were identified in the FungiScope® registry that matched the criteria for a matched-pair analysis.
- Of **35 cases treated with isavuconazole**, 30 (22 proven, 8 probable) contained sufficient information to perform a matched-case analysis to a total of 69 (48 proven, 21 probable) control cases.
- **Each of the 30 isavuconazole cases was matched to 1–3 controls**, including 25 isavuconazole cases each matched to 2 or 3 controls.
- Median observation time (time between first fungal infection and last contact) was 238 (range 10–1053) days for isavuconazole cases and 60 (range 4–1189) days for control cases.

Table 1 Demographic and clinical characteristics

	Isavuconazole (N=30)	Control (N=69)
Median (range) age at diagnosis (years)	55.5 (8–77)	49 (0–85)
Male sex	22 (73.3%)	43 (62.3%)
Race/Ethnicity		
Caucasian	25 (83.3%)	60 (87.0%)
Hispanic or Latino	3 (10.0%)	2 (2.9%)
Asian	1 (3.3%)	5 (7.2%)
Unknown	1 (3.3%)	2 (2.9%)
Geographical region		
Europe	25 (83.3%)	41 (59.4%)
North America	5 (16.7%)	2 (2.9%)
Asia/Other	0	26 (37.7%)
Underlying conditions		
Hematological/Oncological disease	17 (56.7%)	44 (63.8%)
Acute leukemia	11 (36.7%)	24 (34.8%)
Lymphoma	0	6 (8.7%)
Chronic leukemia	1 (3.3%)	4 (5.8%)
Solid tumor	1 (3.3%)	3 (4.3%)
Myelodysplastic syndrome	2 (6.7%)	1 (1.4%)
Other	2 (6.7%)	6 (8.7%)
Chemotherapy	16 (53.3%)	37 (53.6%)
Neutropenia	12 (40.0%)	37 (53.6%)
Diabetes mellitus	6 (20.0%)	9 (13.0%)
Allogeneic HSCT	4 (13.3%)	10 (14.5%)
Site of infection		
Disseminated/CNS disease	12 (40.0%)	26 (37.7%)
Pulmonary only	15 (50.0%)	34 (49.3%)
Other (localized, not CNS, not pulmonary)	3 (10.0%)	9 (13.0%)
IFI-related surgery	21 (70.0%)	34 (49.3%)
EORTC/MSG disease classification		
Proven	22 (73.3%)	48 (69.6%)
Probable	8 (26.7%)	21 (30.4%)

All values are n (%) unless otherwise stated.
EORTC/MSG, European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG); CNS, central nervous system; HSCT, allogeneic hematopoietic stem cell transplant; IFI, invasive fungal infection.

- In most cases (n=21, 70.0%), isavuconazole was administered as a treatment for invasive mucormycosis in patients who had received prior lipid formulations of amphotericin B, alone (n=18) or in combination with posaconazole (n=3).
- In the remaining cases, isavuconazole was administered after prior voriconazole treatment (n=2) or as first-line treatment (n=7).
- In all control cases, lipid formulation of amphotericin B, posaconazole, or both had been given as first-line treatment.

Demographics, clinical characteristics and fungal pathogens

- Demographics, and clinical characteristics (**Table 1**) and causative fungal pathogens (**Table 2**) were generally similar between isavuconazole-treated cases and control cases. No significant difference between groups was identified (Fisher's exact test or Pearson Chi-squared test; data not shown).
  - There were fewer females among isavuconazole cases compared with control cases.
  - All isavuconazole cases were from Europe or North America, whereas 37.7% of control cases came from Asia (30.4%) or other regions (7.2%).
  - In both treatment arms, hematological/oncological disease, chemotherapy, neutropenia, and diabetes mellitus were the most common underlying conditions.
  - A similar proportion of the isavuconazole cases (13.3%) had received allogeneic hematopoietic stem cell transplantation compared with control cases (14.5%).
  - Causative pathogens were identified to the species level for most isavuconazole cases (93.3%), but were not determined for 12 (17.4%) control cases.

Efficacy outcomes

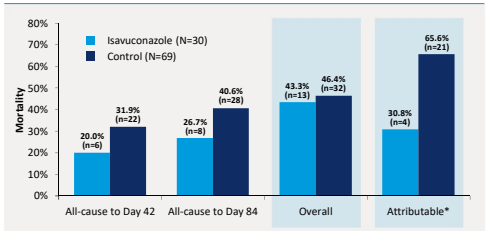
- All-cause mortality at any time was 43.3% for isavuconazole cases and 46.4% for control cases; mortality attributable to invasive fungal infection was 30.8% in isavuconazole cases compared to 65.6% in control cases, *P*=0.049 (**Figure 1**).
- Complete or partial response rates at final assessment were 50.0% for isavuconazole cases and 50.7% for control cases. Complete or partial response or stable disease rates at final assessment were 70.0% for isavuconazole cases and 59.4% for control cases (**Figure 2**).

Table 2 Fungal pathogens*

	Isavuconazole (N=30)	Control (N=69)
Rhizopus spp.	14 (46.7%)	28 (40.6%)
Mucor spp.	7 (23.3%)	15 (21.7%)
Lichtheimia spp.	4 (13.3%)	12 (17.4%)
Rhizomucor spp.	4 (13.3%)	2 (2.9%)
Cunninghamella spp.	1 (3.3%)	2 (2.9%)
Mucorales not otherwise specified	1 (3.3%)	9 (13.0%)
Other*	1 (3.3%)	1 (1.4%)

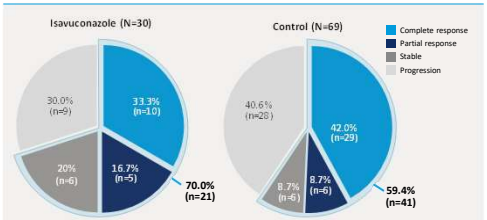
*Isavuconazole: 1 *Apophysomyces* spp.; control: 1 *Apophysomyces* spp.

Figure 1 Mortality rates



*Attributable to invasive fungal infection.

Figure 2 Response rates at final assessment



Safety outcomes

- Drug-related adverse events in either group were as follows:
  - Isavuconazole: Nausea/vomiting (n=1) and deterioration of renal function (n=1).
  - Lipid formulations of amphotericin B: Deterioration of renal function (n=12), renal failure (n=1), exanthematous rash over trunk and limbs (n=1), fever (n=1), hypokalemia (n=1), nausea and vomiting (n=1), and thrombocytopenia (n=1).
  - Posaconazole: Giddiness (n=1), hepatic toxicity (n=1), QTc prolongation (n=1), and deterioration of renal function (n=1).

Conclusion

- **In this analysis from the FungiScope® registry, isavuconazole showed similar overall treatment response and all-cause mortality rates, lower mortality attributable to invasive fungal infection, and lower rates of drug-related adverse events, as compared to lipid formulations of amphotericin B or posaconazole.**

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