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Original Research Article

Prescribing patterns of systemic antifungal medications in Indian patients with invasive fungal infections: a multicenter retrospective study

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ABSTRACT

Background: Objectives of the study was to describe the utilization pattern of systemic antifungal agents in Indian patients with invasive fungal infections (IFIs).
Methods: This real-world, multicenter (127 centers), retrospective analysis included data of patients receiving systemic antifungal medications at various centers across India. The study data was collected between April 2021 and March 2022.
Results: Data of a total of 323 patients was analyzed. The mean age of patients was 54±13.52 years. There was male preponderance seen in this study (72.4%). Diabetes was the most common comorbidity (36.8%) followed by concomitant diabetes and hypertension (31.9%), hypertension (9.6%) and hematological malignancies (9.6%). The most common indication occurring in >10% of the patients and for whom systemic antifungals were used included pulmonary mucormycosis (33.1%) followed by invasive candidiasis (16.1%), sepsis (13.3%) and fungal pneumonia (11.8%). In total 323 patients, the most common antifungal drug prescribed was posaconazole (38.6%) followed by anidulafungin (32.8%), caspofungin (10.5%), fluconazole (9.3%) and micafungin (8.7%). Posaconazole was most commonly used for pulmonary mucormycosis (84.8%), fluconazole for sepsis (33.3%), caspofungin for fungal pneumonia (23.5%) and anidulafungin (33.1%), and micafungin (39.3%) for invasive candidiasis.
Conclusions: This study provides real-world evidence on the demographics of Indian patients with IFIs and utilization pattern of systemic antifungals by health care physicians in clinical practice.

Keywords: Antifungal, Mucormycosis, Candida, Posaconazole, Caspofungin

INTRODUCTION

Fungal infections range from superficial, cutaneous and subcutaneous infections to systemic fungal infections.[1] These infections pose a serious threat to healthcare.[2] There has been a tremendous increase in the prevalence of IFIs in patients with acquired immunodeficiency syndrome (AIDS), those receiving immunosuppressive therapy, undergoing hematopoietic stem cell transplants (HSCT), cancers, elderly, and patients treated in critical care. *Candida* and *Aspergillus* spp. are the most commonly reported pathogens in fungal infections; *Zygomycetes*, *Fusarium*, *Scedosporium*, and black molds are also seen frequently.[3]

In India, the burden of IFIs has increased in the past few years. The possible factors responsible include the broad antibiotic usage and the fact that climatic diversity in India is suited for a wide variety of fungal infections. In India, however, the exact data on burden of fungal infections remains unclear.[4] Further, post-COVID-19, there was a huge surge in the incidence of IFIs in India, driven predominantly by mucormycosis.[5]

The standard of care for IFIs remains the systemic antifungal agents. Over the years, several new antifungal agents have been developed. Currently, available systemic anti-fungal agents include polyenes (amphotericin B), azoles (fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole), and echinocandins (micafungin, caspofungin and anidulafungin).[6,7]

Antifungal resistance represents a major clinical challenge in the treatment of IFIs. The problem of growing antifungal resistance is exacerbated by the emergence of resistant fungal species and a paucity of new antifungal agents in development that have unique mechanisms of action.[8] In addition, the utility of current antifungal drugs may be limited by drug–drug interactions and serious adverse effects/toxicities that prevent their prolonged use or dosage escalation. The data of systemic antifungal prescribing pattern in Indian patients is scarce. Hence, this study aimed to provide an input about the prescription patterns of systemic antifungals by health care physicians in Indian patients with IFIs.

METHODS

Study design

This retrospective analysis involved data of patients with fungal infections, who received treatment with systemic antifungal agents. The study was conducted at 127 centers across India. In this study, the data was collected between April 2021 and March 2022 on patients' demographic characteristics, as well as treatment utilization patterns. The characteristics including age, gender, type of infection and treatment-related parameters were collected.

Sample size and statistical analysis

This was a real-world study and data was collected retrospectively without any predetermined sample size. No hypothesis was tested in this study and only the observations from patient's records were collected and analyzed. Demographic and baseline characteristics were summarized using descriptive statistics. Categorical variables were summarized with frequency and percentage. Continuous variables were summarized with count, mean, standard deviation, etc. Statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., USA).

Ethics statement

The study protocol was approved by the ACEAS independent ethics committee, Ahmedabad, India. This study was performed in accordance with International Conference on Harmonisation- Good Clinical Practice (ICH GCP) and the ethical principles of the Declaration of Helsinki. As this study involved data retrieval from medical records only, an informed consent was not obtained.

RESULTS

Data of a total of 323 patients were analyzed. The mean age of patients was 54±13.52 years. There was male preponderance seen in this study (72.4%). Diabetes was the most common comorbidity (36.8%) followed by concomitant diabetes and hypertension (31.9%), hypertension (9.6%) and hematological malignancies (9.6%). Table 1 describes individual drug wise demographic characteristics of the study participants in detail.

Table 1: Demographic characteristics.

Variables	All patients (n=323)	Posaconazole (n=125)	Anidulafungin (n=106)	Caspofungin (n=34)	Fluconazole (n=30)	Micafungin (n=28)
Age (years), mean±SD	54±13.52	54.82±13.59	54.60±13.52	54.00±13.38	56.50±13.13	54.64±13.11
Gender, N (%)						
Male	234 (72.4)	94 (75.2)	81 (76.4)	21 (61.7)	20 (66.7)	18 (64.3)
Female	89 (27.5)	31 (24.8)	25 (23.6)	13 (38.2)	10 (33.3)	10 (35.7)
Comorbid conditions, N (%)						
Diabetes	119 (36.8)	62 (49.6)	28 (26.4)	11 (32.3)	8 (26.7)	10 (35.7)
Diabetes and hypertension	103 (31.9)	37 (29.6)	37 (34.9)	10 (29.4)	9 (30)	10 (35.7)
Hypertension	31 (9.6)	8 (6.4)	11 (10.4)	5 (14.7)	5 (16.7)	2 (7.1)
Hematological malignancy	31 (9.6)	13 (10.4)	8 (7.5)	3 (8.8)	3 (10)	4 (14.3)
No comorbidities	39 (12.1)	5 (4)	22 (20.7)	5 (14.7)	5 (16.7)	2 (7.1)

Indications

The most common indications for usage of the systemic antifungal agents were pulmonary mucormycosis (33.1%) followed by invasive candidiasis (16.1%), sepsis (13.3%) and fungal pneumonia (11.8%) (Figure 1).

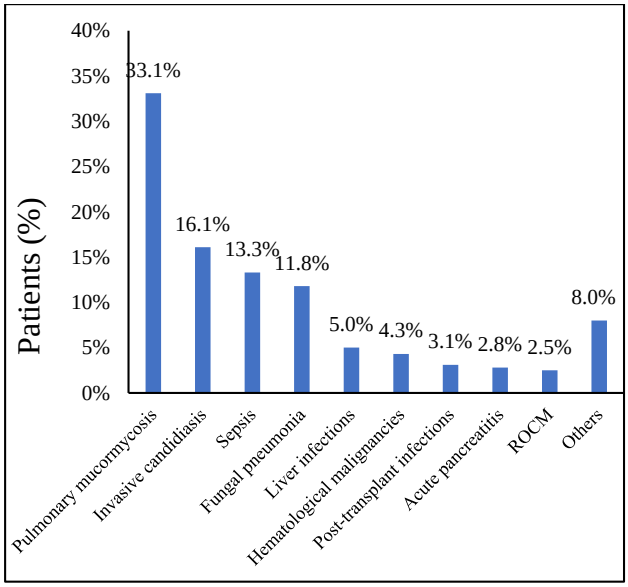

Figure 1: Most common indications.

ROCM-Rhino-orbital-cerebral mucormycosis.

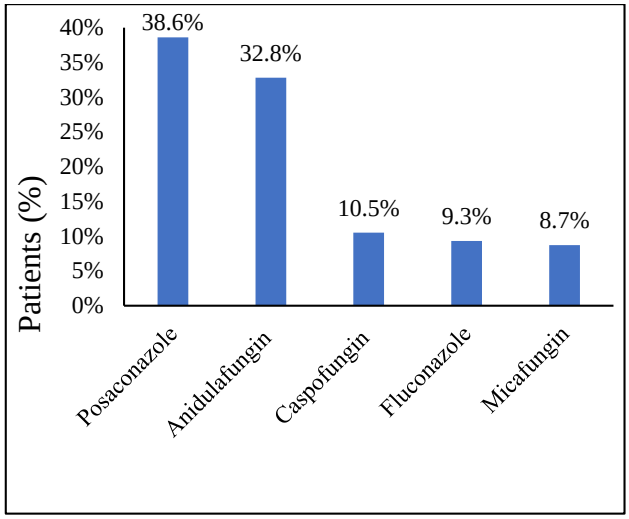

Figure 2: Anti-fungal agents.

Type of anti-fungal agents

The most common antifungal drug prescribed was posaconazole (38.6%) followed by anidulafungin (32.8%), caspofungin (10.5%), fluconazole (9.3%) and micafungin (8.7%).

Type of infection and anti-fungal agent

Posaconazole was most commonly used for pulmonary mucormycosis (84.8%), fluconazole for sepsis (33.3%), caspofungin for fungal pneumonia (23.5%), and anidulafungin (33.1%) and micafungin (39.3%) for invasive candidiasis. For mucormycosis, posaconazole used in combination with amphotericin B. Detailed breakup of various indications and antifungal therapy are described in Table 2.

Table 2: Indications and type of anti-fungal agents used.

Variables	All patients (n=323), (%)	Posaconazole (n=125), (%)	Anidulafungin (n=106), (%)	Caspofungin (n=34), (%)	Fluconazole (n=30), (%)	Micafungin (n=28), (%)
Pulmonary mucormycosis	107 (33.1)	106 (84.8)	-	-	-	1 (3.6)
ROCM	8 (2.5)	8 (6.4)	-	-	-	-
Hematological malignancies	14 (4.3)	7 (5.6)	2 (1.9)	2 (5.9)	3 (10)	-
Fungal pneumonia	38 (11.8)	4 (3.2)	15 (14.2)	8 (23.5)	8 (26.7)	3 (10.7)
Acute pancreatitis	9 (2.8)	-	5 (4.7)	4 (11.8)	-	-
Invasive candidiasis	52 (16.1)	-	33 (31.1)	7 (20.6)	1 (3.3)	11 (39.3)
Post-transplant infections	10 (3.1)	-	10 (9.4)	-	-	-
Sepsis	43 (13.3)	-	24 (22.6)	6 (17.6)	10 (33.3)	3 (10.7)
Liver infections	16 (5)	-	11 (10.4)	2 (5.9)	-	3 (10.7)
Others	26 (8)	-	6 (5.7)	5 (14.7)	8 (26.7)	7 (25)

ROCM-Rhino-orbital-cerebral mucormycosis. Hematological malignancies included acute myeloid leukemia, acute lymphocytic lymphoma, and myelodysplastic syndrome.

DISCUSSION

This retrospective study provides an assessment of the real-world utilization patterns of antifungal agents used by health care practitioners in India. This report provides an insight into the demographics and characteristics of patients with various IFIs at multiple centers across India and the utilization patterns of various systemic antifungal agents in these patients. The mean age of patients was 54 years, consistent with a study by Kongkookum et al.[9] There was a male preponderance reported in this study, which is in line with the previous reports.[6,10]

Fungal infections are common in patients with comorbidities.[11] In our study, diabetes, hypertension and hematological malignancies were the most common comorbidities.

The most common indications reported in this study were pulmonary mucormycosis (33.1%) followed by invasive candidiasis (16.1%), sepsis (13.3%) and fungal pneumonia (11.8%). In patients with pulmonary mucormycosis, posaconazole with amphotericin B was most commonly used. As per the European Society of Clinical Microbiology and Infectious Diseases fungal infection study group; European Confederation of Medical Mycology (ESCMID/ECMM) guidelines, liposomal amphotericin B (≥5 mg/kg/day) is the drug of choice for initial treatment of mucormycosis, and posaconazole or lipid-based amphotericin ± caspofungin are the alternatives agents.[12] Our study included data from patients receiving antifungal agents even during the COVID times. For the treatment of mucormycosis in COVID-19 patients, liposomal amphotericin B is used and after favorable response is achieved, treatment with posaconazole or isavuconazole is recommended.[13]

In patients with invasive candidiasis in our study, micafungin, anidulafungin and caspofungin were the most commonly used antifungal agents. The echinocandins (i.e., caspofungin, micafungin, and anidulafungin) impairs the cell walls of candida species. In an individual patient-level quantitative review of 7 randomized, double-blind trials for treatment of invasive candidiasis (n=1915) with 3 different classes of treatment, liposomal amphotericin B; echinocandins (anidulafungin, caspofungin, micafungin); and azoles (fluconazole, voriconazole) demonstrated that treatment with an echinocandin was associated with a significant decrease in the mortality by 35% and increased treatment success rate by 133%.[14] Further, the Infectious Diseases Society of America (IDSA) guidelines recommend an echinocandin [caspofungin, micafungin or anidulafungin] as initial therapy for the treatment of candidemia.[15]

In the current study, 4.3% of the patients were prescribed systemic antifungals for IFIs in patients with hematological malignancies. In these patients, posaconazole was the most commonly used agent. According to the IDSA guidelines, posaconazole is the first choice for prophylaxis of IFIs in patients with malignancies.[16] As per the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO), the treatment of any infx depends on the identification of pathogen.[17] Current study findings interpretation require consideration in view of certain limitations, which include missing data, potential inconsistency in data entry as multiple study centers involved.

CONCLUSIONS

This retrospective, observational study reports that the utilization of antifungal drugs in our study was consistent to the trends reported globally and in line with the guideline recommendations in general. Pulmonary mucormycosis was the most common fungal infection reported in our study. Posaconazole was the most common antifungal drug prescribed in our study cohort.

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Conflict of interest: Dr. Deepak Bunger, Dr. Lav Patel, and Shreekant Sharma are employees of Intas Pharmaceuticals Limited, Ahmedabad, Gujarat, India
Ethical approval: The study was approved by the ACEAS Independent Ethics Committee, Ahmedabad, India

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