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ORIGINAL RESEARCH

Effectiveness and Safety of Micafungin in Managing Invasive Fungal Infections among Patients in Greece with Hematologic Disorders: The ASPIRE Study

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ABSTRACT

Introduction: Invasive candidiasis (IC) can be a life-threatening infection in immunocompromised patients, particularly those with cancer, hematologic diseases and/or hematopoietic stem cell transplantation (HSCT) recipients. The objective of this study was to evaluate the effectiveness of micafungin in patients with hematologic malignancies or HSCT recipients, relevant to clinical presentation of IC, in real-life practice in Greece.

Methods: ASPIRE was a phase IV, multicenter, non-interventional, prospective cohort study, conducted at ten tertiary hospitals in Greece, in adults with hematologic disease. Micafungin treatment for IC or prophylaxis for *Candida* infection was administered per standard clinical practice until a clinical outcome (success or failure) was reached. Treatment success was defined by the EORTC/MSG criteria for invasive fungal infections (IFI) and was assessed by the

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investigator. Treatment discontinuation and safety were also evaluated.

Results: One hundred forty-three patients were enrolled. Median age was 62; 85 (59.4%) patients were male, and 133 (93.0%) had Greek ethnicity. One hundred twenty-six (88.1%) patients had hematologic malignancies, and 21 (14.7%) had received HSCT. Prophylaxis was administered to 74 (51.7%) patients [median (range) dose: 50 (50–150) mg/day] with no signs of IFI. Overall, 52 (36.4%) patients with possible IFI at baseline received micafungin treatment [100 (50–125) mg/day] versus 12 (17.2%) with probable [100 (75–150) mg/day] and 5 (3.5%) with confirmed [125 (100–150) mg/day] IFI. Treatment success was 91.6% (95% CI 85.80–95.59; $n = 131$) overall and 90.5% ($n = 67$) in patients receiving prophylaxis. Median time on treatment was 13 days. Treatment discontinuation ($n = 26$; 18.2%) was not related to adverse events. No treatment-related serious adverse events were reported.

Conclusion: Micafungin treatment for IC or prophylaxis for *Candida* infection was effective and well tolerated in patients with hematologic disorders in clinical practice in Greece. These results demonstrate that micafungin could be used more widely for prophylaxis. Further work is required to determine the efficacy and safety of micafungin for the management of IFIs in hematologic settings.

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Keywords: Antifungal; HSCT; Invasive candidiasis; Micafungin; Prophylaxis

INTRODUCTION

Invasive fungal infections (IFIs) are a major cause of nosocomial infections leading to morbidity and mortality. Immunocompromised patients, in particular those with cancer, hematologic diseases and/or hematopoietic stem cell transplantation (HSCT) recipients, carry a high risk of developing life-threatening opportunistic IFIs, such as invasive candidiasis (IC), aspergillosis and mucormycosis [1–3]. While advances such as organ transplantation, cancer therapies and intensive care unit interventions have improved the prognosis in these patients, these interventions have also increased susceptibility to IFIs [4, 5]. In patients with hematologic malignancies and IC, studies have reported an overall mortality risk of up to 38% with an attributable mortality of 19% [6]. Overall, IC is responsible for 2–3% of nosocomial infections in Europe [7].

Guidelines for the management of IC from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) strongly recommend an echinocandin (e.g., anidulafungin, caspofungin, micafungin) [6, 8, 9]. In adult patients with hematologic malignancies, guidelines only moderately support the use of liposomal amphotericin B and provide marginal support for fluconazole [6]. Of the recommended echinocandin therapies, micafungin is strongly recommended for both targeted therapy in patients with malignancies receiving allogeneic HSCT and for prophylaxis therapy in patients receiving allogeneic HSCT [6].

Micafungin inhibits the synthesis of 1, 3-β-D-glucan, an essential component of the fungal cell wall, leading to osmotic instability and eventual cell death [10, 11]. Several clinical trials involving micafungin have demonstrated its efficacy in IC, reporting response rates ranging from 71–90% [12–15]. Micafungin has also shown efficacy when used as a prophylactic agent for fungal infections in neutropenic patients [6, 16]. In addition, micafungin has a favorable safety and tolerability profile with a low potential for drug-drug interactions compared with caspofungin and fluconazole [17–19]. In addition, micafungin does not require a loading dose (unlike other echinocandins and azoles) and does not require dose adjustment in patients with renal or mild to moderate hepatic impairment [4, 10, 20].

Relatively few published data are available concerning current clinical practice patterns in Greece regarding fungal infections in patients with hematologic conditions and in HSCT recipients. Despite increasing interest in the clinical and therapeutic aspects of fungal infections in patients with hematologic disease, recent observational trials focus primarily on gathering evidence on prevalence and microbiologic characteristics [21–23]. To our

knowledge, there are no published data from prospective, multicenter, observational studies regarding treatment with new-generation antifungal agents in patients with hematologic disorders in real-life practice in Greece.

The aim of this multicenter, non-interventional, prospective study was to evaluate the effectiveness of micafungin administration in standard clinical practice among patients with hematologic malignancies, including patients who underwent HSCT. This article reports clinical presentation at treatment initiation, clinical outcomes, treatment duration and tolerability associated with micafungin treatment in Greece.

METHODS

Study Design and Treatment

The ASPIRE study (protocol: GR-MYC-NI-002) was a phase IV, multicenter, non-interventional, prospective cohort study conducted between June 2013 and March 2014 at ten tertiary hospitals in Greece. The study was designed to evaluate the efficacy of micafungin in standard clinical practice. Due to the non-interventional nature of this study, it was not registered in local or international clinical trial domains. The institutional review board or independent ethics committee of each participating hospital approved the study design, and the study was performed in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments, International Conference on Harmonisation Guidelines and local ethical and legal requirements. Informed consent was obtained prior to patients' participation in the study.

Inclusion criteria included being > 18 years of age and having a diagnosis of hematologic disease (including patients who underwent HSCT) with a performance status of 0–2 (on the Eastern Cooperative Oncology Group scale). Written informed consent was obtained from all patients or their legal representative(s). As micafungin is not recommended for use in patients with severe hepatic impairment, and caution is advised in those with renal impairment, patients with severe renal insufficiency (estimated creatinine clearance < 20 ml/min at baseline or likely to require dialysis during the study) and those with moderate or severe liver dysfunction at baseline [defined as aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase levels greater than two times the upper limit of normal (ULN) or a total bilirubin level greater than two times the ULN] were excluded from this trial.

Patients were classified (four levels) according to their clinical presentation at baseline, according to the investigator's discretion, using the revised European Organisation for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) criteria for IFI: no signs (at risk), possible, probably and proven [2]. For possible IFI, patients should have appropriate host factors (e.g., allogeneic HSCT) and clinical evidence of IFI, but no mycologic evidence. Cases of probable IFI require the presence of a host factor, together with clinical features and mycologic evidence. Proven IFI must be confirmed by microscopic analysis on sterile samples or recovery of yeast or mold by culture of blood or sterile samples [2]. Established risk factors for IFI were recorded for patients at treatment initiation [24–29]. Concomitant antineoplastic treatments received during the study period or during the 3-month period before study inclusion were recorded. In addition, for patients who did not receive micafungin as monotherapy to treat their IFI, the therapeutic agents included in the combination therapy were recorded.

The assignment of a patient to a particular therapeutic strategy was not decided in advance by the protocol. All patients received micafungin, administered at the discretion of the investigator, as per standard clinical practice in accordance with the approved prescribing information. Micafungin is approved in Europe as an intravenous infusion over approximately 1 h:100 mg/day for treatment and 50 mg/day for prophylaxis [20]. The observational period lasted until a clinical outcome (success or failure) was recorded.

Outcome Measures

The primary objective was treatment success, as assessed by investigators, relative to clinical presentation at baseline. Treatment success was defined by EORTC/MSG criteria and the daily clinical decision-making of investigators. Secondary objectives included describing the profile of clinical presentation on micafungin treatment initiation, the duration of micafungin treatment, micafungin discontinuation rate and safety. The latter included monitoring adverse drug reactions (ADRs), serious adverse events (SAEs) and clinical laboratory measurements (temperature; neutrophil count; liver and renal laboratory tests, including alkaline phosphatase, creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin and γ-glutamyl transferase). The average daily dose of micafungin was also recorded.

As this was an observational study performed under real-world clinical conditions, there was no schedule of procedures. Other than screening, all study assessments and follow-ups were performed at the discretion of the investigation in line with daily clinical practice at each center.

Statistical Analyses

The planned sample size, 108 patients, was calculated to provide an adequate precision level [95% confidence interval (CI) of ± 10%] for measuring clinical outcome (success versus failure), following a conservative statistical approach regarding the expected success rate (50%, as an expected success rate based on a previously published study could not be determined). Prior to study initiation, the protocol was amended to enroll 190 patients to increase precision; however, recruitment was not sufficient to complete enrollment within the planned study time lines. All patients were included in the analyses irrespective of study withdrawal.

Descriptive analyses are stratified by clinical presentation at baseline. Results are expressed as means ± standard deviation (SD) and median plus range for all continuous variables and as counts and proportions (along with Clopper-Pearson exact 95% CIs for categorical variables). Missing values were presented without imputation for all analyses. Statistical analysis was performed using SAS® 9.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient Disposition and Clinical Presentation at Baseline

A total of 143 patients were enrolled in the study to receive treatment with micafungin (Table 1). Fourteen patients (10%) did not complete the study because of lack of treatment availability at the treatment center's pharmacy ($n = 6$), death ($n = 5$), lack of efficacy ($n = 1$), adverse events (AEs) not related to micafungin ($n = 1$) and possible aspergillosis ($n = 1$). The most frequently observed comorbidities were related to cardiovascular (35.0%) and endocrine/metabolic (24.5%) systems. The median age of the study population was 62 (range: 22–89) years; 59.4% of patients were male, and the majority were of Greek ethnicity (93.0%).

At baseline, 74 (51.7%) patients received micafungin as prophylaxis (no signs of IFI), while 52 (36.4%), 12 (8.4%) and 5 (3.5%) patients received treatment for possible, probably and proven IFI, respectively (Fig. 1). Patients with proven IFI had *Candida albicans* recovered from their last cultures (urine culture $n = 2$; blood culture, sputum culture, tissue culture, each $n = 1$) prior to micafungin administration.

Overall, 122 (85.3%) patients had hematologic malignancies and 21 (14.7%) underwent HSCT. Of the HSCT recipients [12 (8.4%) autologous and 9 (6.3%) allogenic], 17 (11.9%) had hematologic malignancy and 4 (2.8%) underwent HSCT for other hematologic disorders (Table 1). Over half (51.0%) of patients were newly diagnosed and the most common hematologic disorder was acute myelogenous leukemia (40.6%). Three patients had Hodgkin's lymphoma; of these, two had hematologic disease, two had hematologic malignancy and possible IFI, and one had hematologic malignancy and HSCT. Common patient risk factors at baseline included systemic antibiotics

Table 1 Patient demographics and clinical presentation at baseline

	EORTC/MSG criteria				Total (N = 143)
	No signs of IFI[a] (n = 74)	Possible IFI (n = 52)	Probable IFI (n = 12)	Proven IFI (n = 5)	
Age, median (range)	62 (23–86)	58 (22–82)	69 (28–88)	74 (73–89)	62 (22–89)
Sex, *n* (%)					
Female	28 (37.8)	27 (51.9)	2 (16.7)	1 (20.0)	58 (40.6)
Male	46 (62.2)	25 (48.1)	10 (83.3)	4 (80.0)	85 (59.4)
Ethnic origin, *n* (%)					
Greek	69 (93.2)	49 (94.2)	10 (83.3)	5 (100.0)	133 (93.0)
Other	5 (6.8)	3 (5.8)	2 (16.7)	–	10 (7.0)
Underlying disease, *n* (%)					
Hematologic malignancy	58 (78.4)	48 (92.3)	11 (91.7)	5 (100.0)	122 (85.3)
HSCT	2 (2.7)	2 (3.8)	–	–	4 (2.8)[b]
Hematologic malignancy and HSCT	14 (18.9)	2 (3.8)	1 (8.3)	–	17 (11.9)
Primary hematologic disorder, *n* (%)					
Acute lymphoblastic leukemia	9 (12.2)	9 (17.3)	1 (8.3)	–	19 (13.3)
Acute myelogenous leukemia	38 (51.4)	14 (26.9)	4 (33.3)	2 (40.0)	58 (40.6)
Chronic lymphocytic leukemia	2 (2.7)	5 (9.6)	2 (16.7)	–	9 (6.3)
Chronic myelogenous leukemia	1 (1.4)	1 (1.9)	–	–	2 (1.4)
Chronic myeloproliferative disorder	1 (1.4)	–	–	–	1 (0.7)
Hodgkin's lymphoma	1 (1.4)	3 (5.8)	–	–	4 (2.8)
Multiple myeloma	7 (9.5)	4 (7.7)	2 (16.7)	1 (20.0)	14 (9.8)
Myelodysplastic	4 (5.4)	–	1 (8.3)	1 (20.0)	6 (4.2)
Non-Hodgkin's lymphoma	7 (9.5)	12 (23.1)	2 (16.7)	1 (20.0)	22 (15.4)
Other	4 (5.4)	4 (7.7)	–	–	8 (5.6)[c]
Disease stage of hematologic malignancy, *n* (%)	3 (4.1)	3 (5.8)	1 (8.3)	–	7 (4.9)
Chronic	3 (4.1)	3 (5.8)	1 (8.3)	–	7 (4.9)
First diagnosis	34 (45.9)	29 (55.8)	6 (50.0)	4 (80.0)	73 (51.0)
Other	4 (5.4)	1 (1.9)	–	–	5 (3.5)
Progressive disease	10 (13.5)	9 (17.3)	–	1 (20.0)	20 (14.0)
Relapse	13 (17.6)	5 (9.6)	3 (25.0)	–	21 (14.7)

Table 1 continued

	EORTC/MSG criteria				Total (N = 143)
	No signs of IFI[a] (n = 74)	Possible IFI (n = 52)	Probable IFI (n = 12)	Proven IFI (n = 5)	
Remission	10 (13.5)	5 (9.6)	2 (16.7)	–	17 (11.9)
Type of HSCT, n (%)					
Allogenic	8 (50.0)	1 (25.0)	–	–	9 (42.9)
Autologous	8 (50.0)	3 (75.0)	1 (100.0)	–	12 (57.1)

EORTC European Organisation for Research and Treatment of Cancer, *HSCT* hematopoietic stem cell transplantation, *IFI* invasive fungal infection, *MSG* Mycoses Study Group

[a] Patients with no signs of IFI at baseline received micafungin prophylaxis

[b] Multiple myeloma (n = 3); chronic myelogenous leukemia (n = 1)

[c] Acute promyelocytic leukemia (n = 1); idiopathic thrombocytopenic purpura (n = 1); myeloid sarcoma (n = 1); primary mediastinal B-cell lymphoma (n = 1); red cell aplasia (n = 1); T-cell large granular lymphocytic leukemia (n = 1); T-cell prolymphocytic leukemia (n = 1); aplastic anemia (n = 1)

(78.3%, n = 112), neutropenia (59.4%, n = 85) and fever (54.5%, n = 78) (Fig. 2). Mean temperature and neutrophil counts were 38.2 (SD ± 0.5) °C and 260.0 (SD ± 351.5) cells/mm^3, respectively. The mean number of risk factors per patient was 3.6 (SD ± 1.6) with over 25% of patients having five or more risk factors.

Treatment Exposure

The median duration of micafungin treatment for IC or prophylaxis for *Candida* infection was 13 [range: 0–77 (treatment was initiated on day 0)] days, and the mean average daily dose of micafungin per patient was 82.5 (SD ± 26.9) mg (Table 2). Seventy-four patients with no signs of IFI received micafungin as prophylactic therapy [mean average daily dose: 63.9 (SD ± 22.0)] mg. Micafungin was administered as monotherapy to 97.9% of patients and was first-line treatment in 75.5% of patients. In patients that received micafungin as second-line treatment (21.7%, n = 31), fluconazole was the most common first-line therapy (54.9%). Patients receiving combination antifungal therapy (2.1%; n = 3) received nystatin, posaconazole or amphotericin B in addition to micafungin.

Clinical Outcome

Overall, 91.6% (95% CI: 85.80–95.59; n = 131) of patients had treatment success with micafungin therapy (Table 3). Success rates between patients in each clinical presentation group were comparable. The highest success rate was observed in patients with proven IFI (100%; n = 5), followed by patients with possible (96.2%; n = 50), no signs of (90.5%; n = 67) and probable (75.0%, n = 9) IFI. Due to a lack of drug availability, an outcome could not be evaluated for five patients (3.5%). Only seven (4.9%) patients had treatment failure due to persistent febrile episodes and neutropenia (n = 1), no improvement in the patient's symptoms (n = 2), persistent fever with limited micafungin efficacy (n = 1), development of pleural effusion probably due to fungal infection (n = 1) or death due to lack of efficacy (n = 1).

Treatment Status on the Last Day of IC Therapy

On the last day of treatment, 26 (18.2%) patients had discontinued micafungin treatment and switched to another antifungal therapy. Common reasons for micafungin

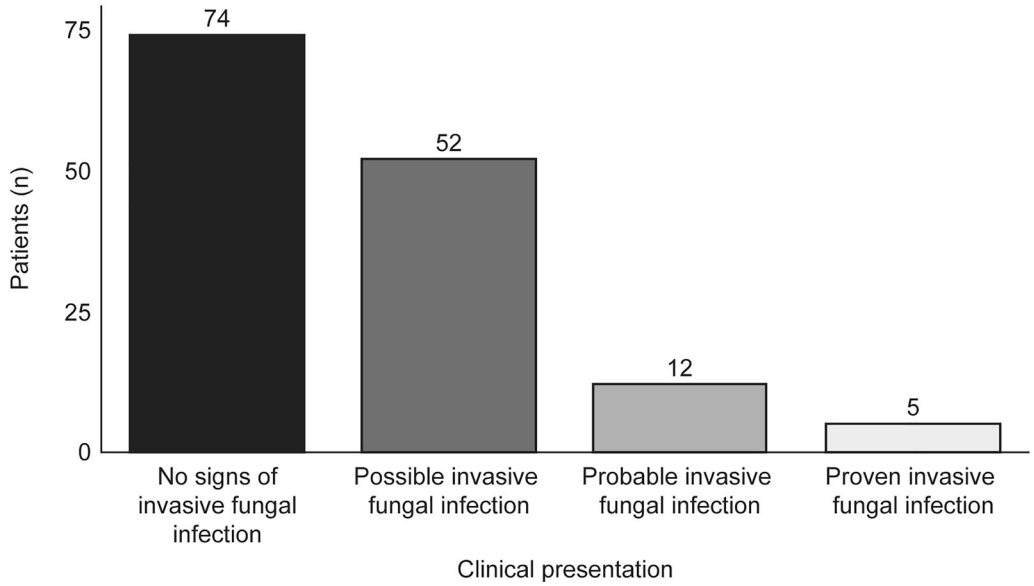

Fig. 1 Clinical presentation at baseline. Patients were classified according to their clinical presentation at baseline using the revised European Organisation for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) criteria for invasive fungal infections

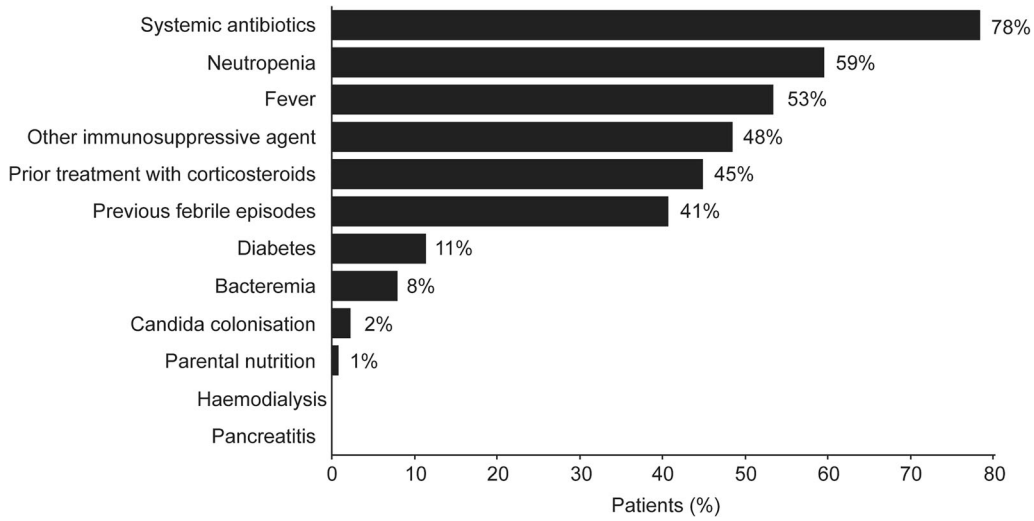

Fig. 2 Risk factors at baseline

treatment discontinuation included patient discharge ($n = 8$) and lack of drug availability ($n = 6$). Only one patient stopped therapy because of limited efficacy (Fig. 3).

Safety

Over the course of the study, events of interest were reported on ADR report forms for 22 (15.4%) patients and included off-label use ($n = 21$) and lack of drug efficacy ($n = 1$). Overall, eight deaths (all SAEs, not considered related to micafungin) occurred during the study; five during treatment with micafungin and three following the end of treatment. One case of lack of efficacy was reported and classified as serious; this included death but was not related to micafungin. The mean body temperature on

Table 2 Micafungin treatment exposure

	EORTC/MSG criteria				Total (N = 143)
	No signs of IFI (n = 74)	Possible IFI (n = 52)	Probable IFI (n = 12)	Proven IFI (n = 5)	
Monotherapy, n (%)	74 (100)	50 (96.2)	12 (100)	4 (80.0)	140 (97.9)
Line of treatment, n (%)					
First	68 (91.9)	29 (55.8)	6 (50.0)	5 (100.0)	108 (75.5)
Second	6 (8.1)	22 (42.3)	3 (25.0)	–	31 (21.7)
Third	–	1 (1.9)	3 (25.0)	–	4 (2.8)
Treatment duration, days					
Mean (SD)	14.1 (8.6)	14.2 (11.9)	13.8 (10.3)	17.6 (10.6)	14.2 (10.0)
Median (range)	14.0 (1.0–39.0)	11.0 (0–77.0)	13.0 (2.0–39.0)	16.0 (8.0–33.0)	13.0 (0.0–77.0)
Average daily dose, mg					
Mean (SD)	63.9 (22.0)	99.5 (9.2)	110.4 (22.5)	115.0 (22.4)	82.5 (26.9)
Median (range)	50.0 (50.0–125.0)	100.0 (50.0–125.0)	100.0 (75.0–150.0)	125.0 (100.0–150.0)	100.0 (50.0–150.0)

Patients with no signs of IFI at baseline received micafungin prophylaxis
EORTC European Organisation for Research and Treatment of Cancer, *IFI* invasive fungal infection, *MSG* Mycoses Study Group, *SD* standard deviation

Table 3 Clinical outcome based on clinical presentation

	EORTC/MSG criteria				Total	
	No signs of IFI* (n = 74)	Possible IFI (n = 52)	Probable IFI (n = 12)	Proven IFI (n = 5)	n (%) n = 143	95% CI
Success, n (%)	67 (90.5)	50 (96.2)	9 (75.0)	5 (100)	131 (91.6)	(85.80%–95.59%)
95% CI	81.48–96.11	86.79–99.53	42.81–94.51	47.82–100.00		
Failure, n (%)	5 (6.8)	1 (1.9)	1 (8.3)	–	7 (4.9)	(1.99%–9.83%)
95% CI	2.23–15.07	0.05–10.26	0.21–38.48	–		
Not available, n (%)	2 (2.7)	1 (1.9)	2 (16.7)	–	5 (3.5)	(1.14%–7.97)
95% CI	0.33–9.42	0.05–10.26	2.09–48.41	–		

Patients with no signs of IFI at baseline received micafungin prophylaxis
CI confidence interval, *EORTC* European Organisation for Research and Treatment of Cancer, *IFI* invasive fungal infection, *MSG* Mycoses Study Group

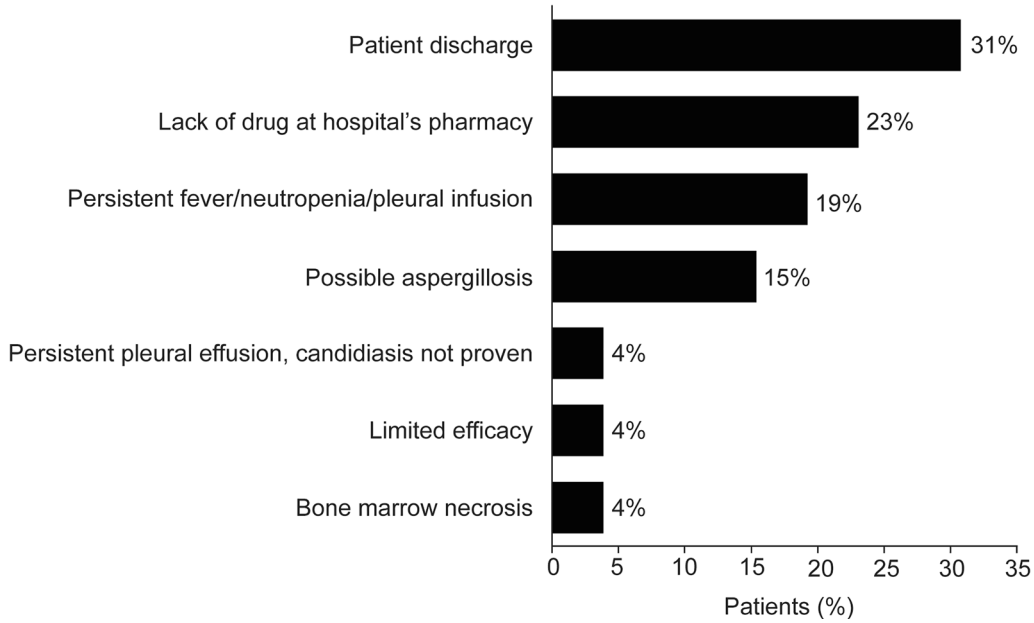

Fig. 3 Reasons for treatment discontinuation. Overall, 26 patients discontinued treatment

the last day of treatment was 36.9 (SD ± 0.8)°C, and the mean neutrophil count increased to 3901 (SD ± 6283) cells/mm^3. There were no notable changes in liver and renal function.

DISCUSSION

The study presented here demonstrated that micafungin is effective for the treatment of suspected and proven IC and as antifungal prophylaxis in patients with hematologic disease or in HSCT recipients in a clinical setting in Greece. Treatment success was observed in each patient group regardless of stratification by baseline clinical presentation or underlying disease. In addition, micafungin was well tolerated in these populations with no treatment-related SAEs reported.

The overall success rate (91.6%) in this study was higher than that observed in previous studies. In a prospective multicenter study conducted in Japan in patients with hematologic disorders and invasive aspergillosis and candidiasis, the total response rate to micafungin was 68.0% [30]. Similarly, as an empirical antifungal agent in febrile neutropenic patients, micafungin had a 61.7% and 64.4% success rate in an observational and randomized study, respectively [31, 32]. The higher success rate may be due to differences in the clinical profiles of patient populations, differences in the dosages administered or the use of micafungin in prophylaxis. In addition, our study only investigated candidiasis, as micafungin is not licensed for treatment of aspergillosis in Europe. Together, the overall success rates reported in these clinical and real-world studies support the ESCMID's recommendation for micafungin treatment in patients with hematologic disorders/HSCT [6].

As our study was observational, the assignment of a patient to a particular therapeutic strategy was not decided in advance by the protocol, and micafungin was administered according to the physician's decision, as well as per standard clinical practice according to its label. Given the high mortality in patients with IC, guidelines and the literature support prophylaxis for IFI as a rational strategy in high-risk patients, including those who are immunocompromised [33, 34]. In a meta-analysis of 38 trials including > 7000 patients, antifungal prophylaxis was associated with a treatment-related reduction in overall mortality among subgroups of high-risk patients with prolonged

neutropenia and in HSCT recipients, providing support for this approach [35].

Prophylaxis therapy is recommended for allogenic HSCT recipients who carry a particularly high risk of IFIs [6]. Although azoles are widely used for antifungal prophylaxis after HSCT, they are associated with hepatic toxicity and drug-drug interactions [36]. In addition, antifungal resistance has become a global problem, especially with *Candida glabrata*, which may be responsible for as many as 18.2% IC infections worldwide [37, 38]. Numerous trials have demonstrated the benefit of micafungin prophylaxis in HSCT recipients [16, 36, 39, 40]. In a prospective, randomized, double-blind comparative study of micafungin versus fluconazole, administered as antifungal prophylaxis during the neutropenic phase of HSCT, treatment success of micafungin was 80.0% versus 73.5% for fluconazole (95% CI: 0.9–12; $P = 0.03$) [36]. In HSCT recipients, prophylaxis with micafungin has also been shown to have similar efficacy to fluconazole [16]. In the current study, micafungin was effective for prophylaxis in patients at risk of IFI (90.5%). In agreement with our findings, recent studies have documented the benefit of micafungin prophylaxis in patients at high risk of IFI, regardless of HSCT [39–41].

In Europe, micafungin is licensed for prophylaxis in HSCT recipients and in patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/μl) for ≥ 10 days, at a dose of 50 mg/day (patients weighing $>$ 40 kg weight and aged ≥ 4 months) and at a dose of 100–200 mg for treatment of IC based on clinical response and body weight [20]. Among the patients in the 'no signs of IFI' group in ASPIRE, 52.7% had neutropenia at the onset of treatment, suggesting the presence of other risk factors. In ASPIRE, no controls were used for dose. The average dose administered to patients with no signs of IFI was 63.9 mg/day, with 15% of patients in this group receiving 100 mg/day. A retrospective study of micafungin prophylaxis prescribing practice in Germany found that 50% of physicians administered 50 mg/day and 50% administered 100 mg/day with success rates of 79.2% ($n = 42$) and 98.1% ($n = 52$), respectively [39]. Therefore, although clinical practice treatment indications for antifungals may deviate from the strict criteria used in clinical trials, additional benefits may also be observed.

In the present study, micafungin was shown to be well tolerated with no treatment-related SAEs reported. Liver injury or renal dysfunction was not observed during study monitoring. This is in agreement with previous studies including a retrospective observational study in patients with hematologic malignancies, where there was no evidence of liver or renal toxicity with micafungin prophylaxis at doses of up to 300 mg (2–3 doses per week) [40, 42]. However, cases of hepatic dysfunction with micafungin have been reported. Due to insufficient data available, micafungin is currently not recommended for patients with severe hepatic impairment [20]. In addition, although micafungin has demonstrated efficacy and safety at high doses, the potential emergence of echinocandin resistance should be considered in future clinical trials [43].

The primary reasons for treatment discontinuation were patient discharge and lack of drug availability; no treatment-related AEs leading to treatment discontinuation were recorded. In general, rates of discontinuation due to AEs are usually lower for echinocandins than azoles, with the exception of fluconazole [41].

The strengths of the ASPIRE study include a heterogeneous population with different underlying diseases, stratification of baseline characteristics and study data by clinical presentation at baseline (EORTC/MSG criteria), administration of micafungin monotherapy in the majority of patients (97.9%), administration of micafungin as both prophylaxis and targeted treatment, and a real-world setting. The study also has potential limitations. There was no standard definition of treatment success, which was assessed by the investigator, relative to clinical presentation at the start of treatment. In addition, clinical outcome was evaluated on the last day of study treatment with no further follow-up period after the end of study treatment and was defined by the investigators based on the EORTC/MSG criteria and their judgment as relevant for clinical decision-making. Other

limitations include low enrollment in the probable and proven IFI groups, low enrollment of patients with HSCT at baseline and monitoring of only SAEs and ADRs instead of all AEs. Finally, a combination of antifungal prophylaxis and treatment was used in this study.

CONCLUSION

In summary, in this multicenter study in Greece, micafungin was effective and well tolerated in clinical practice as prophylaxis and treatment for IC in patients with hematologic disease or with HSCT. This study demonstrates that micafungin could be more widely used for prophylaxis and provides evidence of micafungin use at doses up to 150 mg/day. However, further work is required to determine the efficacy and safety of micafungin for the management of IFI in a hematologic setting.

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Compliance with Ethics Guidelines. The institutional review board or independent ethics committee of each participating hospital approved the study design (University General Hospital "Attikon," Chaidari; 251 Airforce Hospital, Athens; General Hospital of Athens "Laikon," Athens; CTHP "Metaxa," Piraeus; University General Hospital of Heraklion, Heraklion; General Hospital of Athens "Euaggelismos," Athens; University General Hospital of Larissa, Larissa; University General Hospital of Patras, Patra; General Hospital of Athens "G. Gennimatas," Athens; General Hospital of Athens "Laikon," Athens). Informed consent was obtained prior to patients' participation in the study, according to the International Conference on Harmonisation (ICH) and good clinical practice and to the regulatory and legal requirements. The study was performed in

accordance with the principles of the 1964 Declaration of Helsinki and its later amendments, ICH Guidelines and local ethical and legal requirements.

Data Availability. Access to anonymized individual participant level data will not be provided for this trial as it meets one or more of the exceptions described on https://www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

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