Diagnostic Microbiology and Infectious Disease 94 (2019) 268–273

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Micafungin prophylaxis in routine medical practice in adult and pediatric patients with hematological malignancy: a prospective, observational study in France

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ARTICLE INFO

Article history:
Received 17 October 2018
Received in revised form 16 January 2019
Accepted 21 January 2019
Available online 26 January 2019

Keywords:
Invasive fungal infection
Prophylaxis
Micafungin, hematology
Prospective, observational, multicenter study

ABSTRACT

This prospective, observational, multicenter study evaluated the real-world incidence of invasive fungal infection (IFI) during and after micafungin prophylaxis in France. Patients with a hematological malignancy/solid tumor received micafungin prophylaxis according to usual clinical practice and were followed for 3 months. Primary endpoint was breakthrough IFI incidence during prophylaxis. Secondary endpoints included the identification of IFI risk factors, IFI incidence during follow-up, and adverse events (AEs). One hundred and fifty patients (55 children, 95 adults) were enrolled. Micafungin prophylaxis was initiated at 50 mg in adults and at a median 1.01 mg/kg (range: 0.6–2.2) in children. Fifteen patients (10%) experienced an IFI during prophylaxis. IFI breakthrough occurred in 15% children, 7% adults, 3.1% allogeneic transplant patients, 8.7% acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) patients, 7.0% other patients (never allotransplanted/non-AML/MDS). Nineteen patients (12.7%) experienced an IFI during 3-month follow-up. Micafungin was well tolerated with few treatment-related AEs, supporting its use in this patient population in France.

1. Introduction

Invasive fungal infections (IFIs) can be life-threatening in immunocompromised patients, including those with hematological malignancies and hematopoietic stem cell transplant (HSCT) recipients (Aversa et al., 2008). Prophylactic antifungal treatment may therefore be important in this population.

In Europe, 28–58% of IFIs are caused by *Candida* and 38–80% by *Aspergillus* species (Lass-Florl, 2009; Leroy et al., 2009). Echinocandins are a class of antifungal molecules with effectiveness — at least in vitro — against both *Candida* and *Aspergillus* and include micafungin, the only drug of this class indicated for antifungal prophylaxis. Micafungin does not interact with drugs metabolized through the cytochrome P450 pathway (Niwa et al., 2005); therefore, no dose adjustment is necessary when co-administered with calcineurin inhibitors, which are commonly prescribed for graft-versus-host disease prophylaxis in patients undergoing allogenic SCT. This, together with its action against both *Aspergillus* and *Candida* species, makes micafungin a potential candidate for prophylaxis of some IFIs (Petraitis et al., 2002).

In clinical studies, micafungin has demonstrated comparable efficacy to fluconazole and itraconazole and improved tolerability to itraconazole for IFI prophylaxis in patients with hematological malignancies and in HSCT recipients (Heimann et al., 2014; Hiramatsu et al., 2008; Huang et al., 2012; Park et al., 2016; van Burik et al., 2004). These findings are supported by limited data from observational studies performed in Europe and the United States (El-Cheikh et al., 2013; Nachbaur et al., 2015; Neofytos et al., 2015). In France, micafungin was marketed in 2009 (European Medicines Agency, 2011); however, additional real-world data are needed to help practitioners better determine the place of micafungin for IFI prevention in this setting (El-Cheikh et al., 2015; Haute Autorite de Sante: Commission de la Transparence Mycamine, 2008).

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https://doi.org/10.1016/j.diagmicrobio.2019.01.011

The multicenter, observational OLYMPE (NCT02127788) study aimed to determine the real-world conditions of micafungin use for antifungal prophylaxis of hematology patients hospitalized in France.

2. Materials and methods

2.1. Study design

OLYMPE was a longitudinal, prospective, observational, multicenter study conducted in 18 hematological, oncohematological, or transplant units in France.

2.2. Ethics

The study protocol and 1 amendment were approved by the appropriate French authorities (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche Dans le Domaine de Santé; Commission Nationale Informatique et Libertés; Conseil National de l'Ordre des Médécins). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with Good Clinical Practices. Informed consent was obtained from each adult patient or parent/guardian of children before enrollment in the study.

2.3. Patients

2.3.1. Inclusion/exclusion criteria

We included in this study adults (aged ≥18 years) with hematological malignancies and children (<18 years) with hematological malignancies or solid tumors who received antifungal prophylaxis with micafungin. Patients with ongoing documented fungal infection at study initiation, those participating in other clinical studies that could affect the management of an IFI, and those unavailable for a 3-month follow-up visit were excluded. Enrollment closed when the enrollment target of 150 patients was reached.

2.3.2. Treatment and follow-up

Micafungin was prescribed according to usual clinical practice. The prescribing physician selected the best treatment management strategy for each patient, and no treatment duration was imposed. All patients had a baseline visit and a follow-up visit 3 months after prophylaxis initiation even if micafungin was discontinued; other visits were based on usual clinical practice.

2.4. Study assessments and endpoints

The primary objective was to assess the incidence of IFI for 3 months after the initiation of micafungin prophylaxis in routine clinical practice. The primary endpoint was breakthrough incidence of IFI, defined according to physician judgment, during micafungin prophylaxis. Additionally, a centralized review of the data was performed to assess IFI classification according to the revised European Organisation for Research and Treatment of Cancer (EORTC)/Mycose Study Group (MSG) criteria (De Pauw et al., 2008). Secondary endpoints included incidence of IFI in the 3 months following micafungin initiation, description of the conditions of micafungin use, and characterization of participating units and physicians. Safety and tolerability were also assessed via the number of patients with at least 1 adverse event (AE)/serious AE (SAE), and the number and description of AEs.

Baseline demographic and clinical patient characteristics were collected. All AEs reported during the follow-up period were recorded and coded using the Medical Dictionary for Regulatory Activities by system organ class and preferred term. An AE was defined as any untoward and unintended symptom during treatment, regardless of relatedness to micafungin. When a causal relationship with micafungin was expected, an AE was considered an adverse drug reaction (ADR). An SAE was defined as an AE that was lethal; was likely to be life-threatening; resulted in disability, significant/permanent incapacity, or prolonged hospitalization; or resulted in an abnormality or birth defect. Prescribing physicians notified the sponsor of any AE, ADR, or any special situation.

Data for clinical laboratory parameters were collected at the initiation and end of prophylaxis.

2.5. Statistical analyses

The sample size was based on a maximum of 30 sites each recruiting 5 patients over 12 months ($N = 150$). With 150 patients, the semi-width of the 95% confidence interval (CI) to describe IFI incidence was 3.0–4.5%.

The analysis population comprised all eligible patients included in the study. Subgroup analyses were performed for the primary and secondary endpoints and were defined by age (children and adults) and by transplant and pathology profile (allogeneic transplantation, autologous transplantation, or no transplantation with acute myeloid leukemia or myelodysplastic syndrome [AML/MDS] or autologous or no transplant with other pathology [other]).

The type of IFI (proven, probable or possible, based on physician judgment) was recorded, and episodes were described by age, time to first occurrence, and diagnostic criteria. The cumulative incidence of IFI was calculated by dividing the number of patients with an IFI (between baseline and up to 7 days after treatment discontinuation) by the total number of eligible patients. The 95% CI was calculated according to the Wilson method. The incidence adjusted on the duration of exposure (i.e., the density of incidence [DI]) was calculated dividing the total number of IFI during the period of interest by the duration of exposure expressed in person-years, i.e., the sum of duration of periods of interest for each patient expressed in years, and censored at the date of occurrence of IFI, at the date of last day of prophylaxis if no IFI occurs, at the date of last visit if no IF occurs and the prophylaxis is still ongoing at the end of the study, at the date of death, or at the date of last contact. The DI is presented with the associated 95% CI calculated according to the Poisson distribution.

Factors associated with IFI occurrence were identified using logistic regression based on conventional univariate statistical tests: distributions of quantitative variables were compared using the χ^2 test or Fisher's exact test if the expected frequency in any of the cells of the contingency table was less than 5 and using a Student's t test if normally distributed (verified by a Shapiro–Wilk test); otherwise, a Wilcoxon Mann–Whitney test was used. The results are presented as odds ratios with 95% CI.

Statistical analyses were performed using SAS® software, Version 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Patient demographics and baseline characteristics

A total of 150 patients (children, $N = 55$ [36.7%]; adults, $N = 95$ [63.3%]) were enrolled in the study by 30 physicians representing 18 units between 3 July 2014 and 26 October 2015. Mean (range) age was 8.0 (0.3–17.1) and 48.5 (18.7–78.1) years for children and adults, respectively (Table 1). At the time of study inclusion, most patients had been hospitalized for 1–15 days (Table 1), and in most cases, no clinically abnormal laboratory workup was recorded (Supplementary Table 1).

The most common underlying disease was acute lymphoblastic leukemia in children ($N = 26$ [47.3%]) and AML in adults ($N = 67$ [70.5%]; Table 1). Most patients ($N = 141$ [94.0%]) had ongoing chemotherapy at inclusion, and most were in the induction phase of treatment for the current disease episode (Table 1). Forty-eight (92.3%) children and 62 (69.7%) adults had received 1 or 2 lines of chemotherapy. At baseline, 26 children were receiving intensive induction chemotherapy, and 46

Table 1
Patient baseline characteristics, and disease and treatment status.

	Children ($N = 55$)	Adults ($N = 95$)	Total ($N = 150$)
Patient characteristics			
Age (years)			
Mean ± SD	8.04 ± 5.45	48.51 ± 16.38	33.67 ± 23.73
Median (range)	8.42 (0.25–17.10)	50.38 (18.71–78.10)	33.26 (0.25–78.10)
Male	34 (61.8%)	53 (55.8%)	87 (58.0%)
Weight (kg)			
Mean ± SD	28.89 (20.77)	73.20 (14.45)	56.84 (27.37)
Median (range)	20.00 (4.70–82.70)	74.50 (45.00–108.00)	63.75 (4.70–108.00)
Time since hospitalization			
≥30 days	3 (5.5%)	1 (1.1%)	4 (2.7%)
15–30 days	12 (21.8%)	15 (15.8%)	27 (18.0%)
1–15 days	39 (70.9%)	78 (82.1%)	117 (78.0%)
Underlying disease			
AML	18 (32.7%)	67 (70.5%)	85 (56.7%)
MDS	0 (0.0%)	6 (6.3%)	6 (4.0%)
ALL	26 (47.3%)	7 (7.4%)	33 (22.0%)
HL	1 (1.8%)	6 (6.3%)	7 (4.7%)
NHL	0	7 (7.4%)	7 (4.7%)
Myeloma	0	7 (7.4%)	7 (4.7%)
Severe aplastic anemia	4 (7.3%)	1 (1.1%)	5 (3.3%)
Other	6 (10.9%)	4 (4.4%)	10 (6.8%)
Disease status			
Time since diagnosis			
<6 months	44 (80.0%)	51 (58.0%)	95 (66.4%)
6–24 months	6 (10.9%)	20 (22.7%)	26 (18.2%)
≥24 months	5 (9.1%)	17 (19.3%)	22 (15.4%)
Relapse/refractory patients	12 (21.8%)	26 (27.4%)	38 (25.3%)
Chemotherapy status			
Ongoing chemotherapy	52 (94.5%)	89 (93.7%)	141 (94.0%)
Treatment phase	$N = 36$[a]	$N = 36$[b]	$N = 72$[c]
Induction	27 (75.0%)	30 (83.3%)	57 (79.2%)
Consolidation	6 (16.7%)	2 (5.6%)	8 (11.1%)
Salvage therapy	3 (8.3%)	4 (11.1%)	7 (9.7%)
Number of treatment lines	$N = 52$	$N = 89$	$N = 141$
1	35 (67.3%)	41 (46.1%)	76 (53.9%)
2	13 (25.0%)	21 (23.6%)	34 (24.1%)
≥3	4 (7.7%)	27 (30.5%)	31 (22.0%)
Type of chemotherapy			
Intensive induction	26 (50.0%)	24 (27.0%)	50 (35.5%)
Intensive consolidation	5 (9.6%)	1 (1.1%)	6 (4.3%)
Intensive salvage therapy	3 (5.8%)	4 (4.5%)	7 (4.7%)
Autologous conditioning regimen	4 (7.7%)	7 (7.9%)	11 (7.8%)
Allogeneic conditioning regimen	12 (23.1%)	46 (51.7%)	58 (41.1%)
Other	2 (3.8%)	7 (7.9%)	9 (6.4%)
Transplant status[d]			
No transplant	37 (67.3%)	41 (43.2%)	78 (52.0%)
Allogeneic transplant	14 (25.5%)	47 (49.5%)	61 (40.7%)
Autologous transplant	4 (7.3%)	16 (16.8%)	20 (13.3%)
Time since allogeneic transplant	$N = 14$	$N = 47$	$N = 61$
<2 months	12 (85.7%)	46 (97.9%)	58 (95.1%)
2–6 months	1 (7.1%)	1 (2.1%)	2 (3.2%)
≥6 months	1 (7.1%)	0	1 (1.6%)
Time since autologous transplant	$N = 4$	$N = 16$	$N = 20$
<2 months	4 (100.0%)	7 (46.7%)	11 (57.9%)
≥2 months	0	8 (53.3%)	8 (42.1%)

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; HL = Hodgkin's lymphoma; MDS = myelodysplastic syndrome; NHL = non-Hodgkin's lymphoma; SD = standard deviation.
[a] Missing values: $N = 16$.
[b] Missing values: $N = 53$.
[c] Missing values: $N = 69$.
[d] Patients could have received both autologous and allogeneic transplant.

adults were undergoing an allogeneic conditioning regimen (Table 1). At inclusion, 37 (67.3%) children and 41 (43.2%) adults had not received a previous HSCT.

Overall, 131/150 [87.3%] patients had a baseline absolute neutrophil count <0.5 g/L; the median time since onset of neutropenia was 7.0 days (children, 5.0 days; adults, 9.0 days). Digestive colonization by *Candida* was present in 18 (32.7%) children and 5 (5.3%) adults (only 64.2% of adults were assessed for digestive colonization compared with 100% of children). Fever was ongoing in 24 (43.6%) children and 38 (40.0%) adults.

Most patients ($N = 121$ [80.7%]) had no comorbidities at inclusion; of those with at least 1 comorbidity, respiratory disease was most common ($N = 16$ [10.7%]). Most patients were receiving antibiotics ($N = 125$ [83.3%]) and/or immunosuppressive treatment ($N = 79$ [52.7%]). Overall, 5/55 (9.1%) children and 2/95 (2.1%) adults had a history of IFI.

3.2. Patient disposition

Overall, 147/150 patients discontinued micafungin treatment over the 3-month follow-up period, including 68/147 (46.3%) who completed prophylaxis. Common reasons for treatment discontinuation included an AE ($N = 42$ [28.6%]; in 21 [14.3%] patients, this was not necessarily related to micafungin), lack of efficacy ($N = 34$ [23.1%]), and switch to oral antifungal prophylaxis ($N = 19$ [12.9%]) (Fig. 1). A change of antifungal strategy was reported for 34/147 (23.1%) patients who discontinued, including 19/34 (55.9%) who switched to an empirical antifungal strategy for persistent febrile neutropenia, 6/34 (17.6%) to a preemptive antifungal strategy, and 9/34 (26.5%) to a curative strategy. A patient could have more than 1 reason for treatment discontinuation.

3.3. Effectiveness assessment

3.3.1. Incidence of IFI during micafungin prophylaxis

Fifteen patients (10%) experienced an IFI during micafungin prophylaxis (from the inclusion visit to 7 days after treatment discontinuation); 11 IFIs were rated as proven or probable. The incidence of IFI was proportionally greater in children (14.5%) versus adults (7.4%) (Table 2). The median (range) time to infection was 16.5 (1.0–68.0) days for children and 25 (4.0–68.0) days for adults. The DI (95% CI) was 1.72 (0.74–3.38) and 0.97 (0.39–1.99) person-years for children and adults, respectively. The most common clinical sign associated with IFI was fever ($N = 6/8$ children; $N = 2/7$ adults), and when identified, the fungus was commonly *Candida* ($N = 4/9$) or *Aspergillus* ($N = 4/9$) (Supplementary Table 2).

The incidence of IFI during micafungin prophylaxis was 13.1% for allogeneic transplant patients, 8.7% for AML/MDS patients, and 7.0% for other patients.

3.3.2. Incidence of IFI within 3 months of micafungin initiation

Overall, 19 (12.7%) patients (children, $N = 8$ [14.5%; 3 proven; 2 probable; 3 possible]; adults, $N = 11$ [11.6%; 7 proven; 2 probable; 2 possible]), including those who discontinued prophylaxis early, experienced an IFI within 3 months of micafungin initiation (Table 2). Between the end of prophylaxis and the 3-month follow-up visit, 1 [1.8%] child (second episode of IFI) and 4 [4.2%] adults experienced an IFI. DI (95% CI) was 0.64 (0.28–1.27) and 0.52 (0.26–0.93) person-years in children and adults, respectively, and the median (range) time to IFI occurrence was 16.5 (1.0–68.0) and 27 (4.0–68.0) days. IFI occurred in 10/61 (16.4%) allogeneic transplant recipients versus 5/46 (10.9%) patients with AML/MDS, and 4/43 (9.3%) patients never allotransplanted or with a disease other than AML/MDS.

3.4. Conditions of micafungin use

Micafungin prophylaxis was initiated at 50 mg in adult patients and at a median dose of 1.01 mg/kg (range: 0.6–2.2) in children (Table 3). At the month 1 visit, 26 (17.3%) patients were still receiving micafungin;

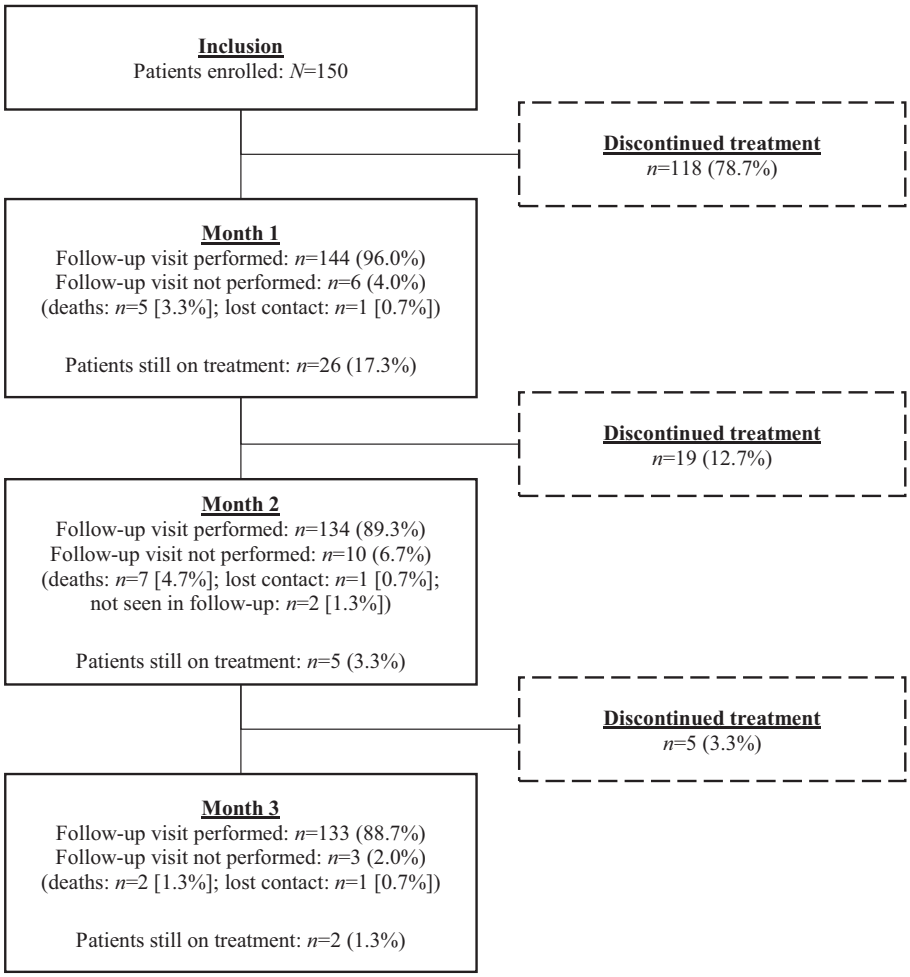

Fig. 1. Patient disposition.

this decreased to 5 (3.3%) and 2 (1.3%) at month 2 and 3, respectively (Fig. 1). The median total exposure was 22.0 (range: 1.0–93.0) days. Six (4.0%) patients received concomitant administration of another antifungal treatment upon micafungin initiation.

3.5. Overall survival

Fourteen (9.3%) patients died during the observational period; the minimum and maximum time to death following micafungin initiation was 0.3 and 0.6 month, respectively. The estimated survival probability after 1, 2, and 3 months was 97%, 93%, and 90%, respectively. These deaths were all considered unrelated to micafungin treatment (Supplementary Table 3).

3.6. Hospitalization and rehospitalization during follow-up

Most patients ($N = 92$ [61.3%]) were initially hospitalized for 30–60 days, with 28 and 30 patients hospitalized for <30 and >60 days, respectively. Fifty-eight (38.7%) patients were rehospitalized at least once (total rehospitalizations, 116); none were due to an AE related to micafungin administration. Five patients were rehospitalized within 7 days of initial discharge because of an infection not related to an IFI (Supplementary Table 4).

3.7. Safety and tolerability

Overall, 119/150 (79.3%) patients experienced a total of 840 AEs, and 73 (48.7%) experienced 173 SAEs (Table 4). Most were related to concomitant disease, concomitant drugs, or other conditions not related to micafungin. Ten (6.7%) patients reported 15 AEs considered related to micafungin, and 5 (3.3%) patients reported 6 SAEs considered related to micafungin (general disorders and administration site disorders [$N = 3$] , infections and infestations [$N = 2$], and blood and lymphatic system disorders [$N = 1$]). Overall, 2.7–12.17% of patients had clinically significant changes from baseline in aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, creatinine clearance, alkaline phosphatase, or total bilirubin at the end of the observation period (Supplementary Table 5).

4. Conclusion

Data from this prospective observational study, conducted in hematological and oncohematological units in France, support the effectiveness and safety of micafungin prophylaxis in hospitalized patients at high risk for IFI, with only a small number of breakthrough infections observed. These findings are consistent with previous data on the real-world use of micafungin in this setting, including a small observational study conducted in France, in which micafungin prophylaxis decreased the incidence of IFI in high-risk patients undergoing allogeneic SCT, both during the neutropenic phase and 3–6 months posttransplant (El-Cheikh et al., 2013).

In our study, the incidence of proven or probable breakthrough IFI during micafungin prophylaxis was 7.3%; this was in a similar range to that reported in previous postmarketing or retrospective studies (range: 4.4–9.0%) (Kobayashi et al., 2015; Nachbaur et al., 2015; Neofytos et al., 2015). However, IFIs were classified according to

Table 2
Incidence of IFI.

Outcome	Children ($N = 55$)	Adults ($N = 95$)	Total ($N = 150$)
Patients with an IFI during micafungin prophylaxis[a]	8 (14.5%)	7 (7.4%)	15 (10.0%)
Type of IFI[b]	$N = 8$	$N = 7$	$N = 15$
Proven	3 (37.5%)	4 (57.1%)	7 (46.7%)
Probable	2 (25.0%)	2 (28.6%)	4 (26.7%)
Possible	3 (37.5%)	1 (14.3%)	4 (26.7%)
DI[c] (person-years [95% CI])	1.72 [0.74–3.38]	0.97 [0.39–1.99]	1.26 [0.71–2.08]
Time to occurrence (days, median [range])	16.5 [1.0–68.0]	25.0 [4.0–68.0]	24.0 [1.0–68.0]
Patients with an IFI during 3-month follow-up[d]	8 (14.5%)	11 (11.6%)	19 (12.7%)
Type of IFI[b]	$N = 9$[e]	$N = 11$	$N = 20$
Proven	4 (44.4%)	7 (63.6%)	10 (52.6%)
Probable	2 (22.2%)	2 (18.2%)	4 (21.1%)
Possible	3 (33.3%)	2 (18.2%)	5 (26.3%)
DI[c] (person-years [95% CI])	0.64 [0.28–1.27]	0.52 [0.26–0.93]	0.57 [0.34–0.89]
Time to occurrence (days, median [range])	16.5 [1.0–68.0]	27.0 [4.0–68.0]	25.0 [1.0–68.0]

CI = confidence interval; IFI = invasive fungal infection.
[a] Defined as the number of patients in the analysis population with an IFI (N = probable, possible, or proven) during the time between the inclusion visit and the end of micafungin prophylaxis) divided by the total number of patients in the analysis population (%).
[b] According to physician judgment.
[c] Defined as the quotient of the total number of IFIs during the period of interest by the duration of exposure expressed in person-years. The 95% CI is based on the Poisson distribution.
[d] Defined as the number of patients in the analysis population with an IFI (N = probable, possible, or proven) during the time between the inclusion visit and the 3-month follow-up visit) divided by the total number of patients in the analysis population (%).
[e] One child had 2 IFIs.

Table 4
Summary of adverse events.

	Patients with AE N (%)	Total AEs [N]
Any AE	119 (79.3%)	[840]
Infections and infestations[a]	81 (54.0%)	
General disorders and administration site conditions	70 (46.7%)	
Blood and lymphatic system disorders	45 (30.0%)	
Gastrointestinal disorders	43 (28.7%)	
Skin and subcutaneous disorders	33 (22.0%)	
Thoracic and mediastinal disorders	25 (16.7%)	
Renal and urinary disorders	24 (16.0%)	
Metabolism and nutrition disorders	21 (14.0%)	
Immune system disorders	20 (13.3%)	
Nervous system disorders	20 (13.3%)	
Vascular disorders	18 (12.0%)	
Any SAE	73 (48.7%)	[173]
Infections and infestations	36 (24.0%)	
Blood and lymphatic system disorders	24 (16.0%)	
General disorders and administration site conditions	19 (12.7%)	
Any AE related to micafungin	10 (6.7%)	[15]
Infections and infestations	4 (2.6%)	
Drug ineffective	2 (1.3%)	
AST increased	2 (1.3%)	
Any SAE related to micafungin	5 (3.3%)	[6]
Any AE related to a concomitant disease	86 (57.3%)	[332]
Any AE related to a concomitant drug	64 (42.7%)	[231]
Any AE related to other condition	78 (52.0%)	[266]

AE = adverse event; AST = aspartate aminotransferase; SAE = serious adverse event.
[a] Mainly bronchopulmonary aspergillosis or candida infection, staphylococcal infection, and sepsis.

physician judgment, and the centralized review highlighted some discrepancies between physician judgment and the revised EORTC/MSG criteria (De Pauw et al., 2008). Inconsistencies have been noted for classification of both the IFI and the antifungal strategy (Supplementary Table 2). The centralized review of the data indicated that some physicians have based IFI classifications on subjective criteria rather than on the EORTC/MSG criteria; thus, the incidence of IFI may have been overestimated. This also accounts for the mismatch between the number of patients who switched to a preemptive or curative strategy due to probable or proven IFI, and the assessment of IFI incidence. Mycotic infections could be documented in 70% of cases. This rate is close to that reported in a recent publication on the categorization of invasive aspergillosis episodes (Herbrecht et al., 2015). The cases that were not documented mycologically in our study were possible aspergillosis, febrile neutropenia, or uncertain cases according to the definitions used by Herbrecht et al. (2015).

A recent network meta-analysis of 54 comparative trials showed that posaconazole, liposomal amphotericin, micafungin, itraconazole, voriconazole, aerosolized amphotericin B, and fluconazole were all associated with effective prophylaxis of IFI (Lee et al., 2018). When the network meta-analysis was restricted to proven IFI, only posaconazole, micafungin, itraconazole, and fluconazole significantly reduced the rate of IFI. Posaconazole had the highest protective effect and micafungin ranked second. A safety analysis was conducted on the 28 studies, providing appropriate data. Furthermore, based on ranking probability scores, micafungin was associated with the lowest rate of overall adverse events, without significance, compared to other agents or to placebo.

Generally, micafungin was well tolerated, with no unexpected AEs observed. Although a large number of AEs and SAEs were reported, as expected in this population, few were considered related to micafungin; this was anticipated as AEs were collected throughout the study even if micafungin had been discontinued. Although micafungin-induced hepatotoxicity has been previously observed in some studies (Park et al., 2014), our study did not highlight such complication as was observed in a small French observational study (El-Cheikh et al., 2013). Overall, AEs reported were mainly related to concomitant disease and concomitant medication.

The large cohort from multiple centers, in addition to the prospective nature, strengthens our study. However, inherent to the observational design are some limitations, including the lack of a control group, limited control imposed over patient management, and lack of consistency in the use of EORTC/MSG criteria for IFI classification. Additionally, pathogen identification was only achieved for <4% of patients.

Table 3
Conditions of micafungin use.

Outcome	Children ($N = 55$)	Adults ($N = 95$)	Total ($N = 150$)
Dose initiated (median [range])	1.01 mg/kg (0.6–2.2)	50 mg	–
Micafungin exposure (days, median [range])	23.0 (2.0–93.0)	22.0 (1.0–91.0)	22.0 (1.0–93.0)
Receiving micafungin at each follow-up visit			
Month 1	9 (16.4%)	17 (17.9%)	26 (17.3%)
Month 2	3 (5.5%)	2 (2.1%)	5 (3.3%)
Month 3	1 (1.8%)	1 (1.1%)	2 (1.3%)

The low incidence of IFIs and the number of patients in the subgroups make it difficult to confirm between-group differences.

In conclusion, the OLYMPE study demonstrated the clinical effectiveness and tolerability of micafungin in high-risk patients under real-world conditions of clinical practice in France. These findings should help practitioners to better determine the place of micafungin in the prevention of IFI in hematology patients.

Conflict of interest statement

No conflicts of interest to declare.

Acknowledgments

The authors acknowledge the study site personnel for the conduct of the study and all enrolled patients for their participation.

This study was supported by Atsellas Pharma, France 92309 Levallois-Perret, France. This manuscript was prepared with the assistance of Lise Bosquet and Andrew Lane (on behalf of ICTA PM) and Lisa Jolly of Bioscript Science in accordance with the European Medical Writers Association guidelines and Good Publication Practice, with funding from Astellas Pharma Inc.

SD-L reports grants from Astellas for advisory board participation. RH reports personal fees from Astellas, Basilea, Gilead, MSD, and Pfizer and grants from Pfizer outside the submitted work. JHD reports personal fees from Astellas during the conduct of the study and outside of the submitted work. PC and JEC report no relevant conflicts of interest. ED is an employee of Astellas Pharma, France. All authors were provided full access to the data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2019.01.011.

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