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Safety and Effectiveness of Micafungin in Japanese Pediatric Patients: Results of a Postmarketing Surveillance Study

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Summary: Limited data are available about the safety and efficacy of micafungin in children. A postmarketing surveillance study was conducted to assess the safety and effectiveness of micafungin, an echinocandin antifungal, in pediatric patients. A prospective multicenter postmarketing observational study was carried out between October 2006 and September 2008 in Japan. Pediatric patients under 16 years received an intravenous infusion of micafungin at a dose of 1 mg/kg for candidiasis and 1 to 3 mg/kg for aspergillosis, with the option of increasing the dose if required to 6 mg/kg once daily. All adverse events were recorded. A total of 201 pediatric patients were enrolled. There were 55 adverse drug reactions reported among 42 of 190 patients evaluated for safety (22.1%); the most frequently reported adverse drug reaction was hepatobiliary disorders. No adverse drug reactions were reported in 18 neonates (aged below 4 wk). The overall clinical response rate in 91 patients evaluated for efficacy was 86.8%. The response rate in neonates was 90.0%, and there were no differences in the response rate by age. Micafungin was found to have sufficient safety and effectiveness for the treatment of fungal infections in pediatric patients with various backgrounds.

Key Words: effectiveness, micafungin, postmarketing surveillance study, safety

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Invasive fungal infections are an important cause of morbidity and mortality in immunocompromised children.[1,2] *Candida* and *Aspergillus* species are the most common fungal pathogens in pediatric patients, and are associated with mortality rates of 19% to 31% and 68% to 77%, respectively.[2–4]

Micafungin, an echinocandin antifungal agent, specifically inhibits the synthesis of 1,3-β-D-glucan, a major component of the fungal cell wall, and exerts potent antifungal activity against *Candida* and *Aspergillus* species in vitro.[1,5–7] This antifungal agent is effective against candidemia, candidiasis, and aspergillosis, and is generally well tolerated in adult patients,[1,7–11] and is approved for the treatment of patients with invasive fungal infections, such as candidiasis or aspergillosis, in many countries worldwide.

Although micafungin has been licensed for children in Japan since April 2006, in Europe since April 2008, and then in the United States since June 2013, there are limited data available regarding the efficacy and safety of micafungin in children, largely because the primary objectives in some of these studies were pharmacokinetic analyses.[1,12–15] Recently, safety data from the pooled micafungin pediatric clinical trials (phase I, II, and III), conducted before 2006, were summarized.[3] However, prospective studies in larger numbers of patients are needed to clarify the role of micafungin for the management of fungal infections in children. Thus, the first postmarketing surveillance study was conducted in 201 patients to confirm the safety and effectiveness of micafungin in clinical practice.

MATERIALS AND METHODS

This prospective multicenter observational surveillance study was conducted between October 2006 and September 2008. Pediatric patients aged under 16 years who were receiving micafungin (Astellas Pharma Inc., Japan) for deep mycosis caused by *Candida* or *Aspergillus* were registered prospectively at a central office within 6 days of the initiation of micafungin treatment. This was a postmarketing study conducted in compliance with the ministerial ordinance on Good Postmarketing Study Practice, which was authorized by Ministry of Health, Labour and Welfare in Japan, Ordinance No. 171 dated December 20, 2004.

Data on the following were obtained: sex, age, body weight, diagnosis of fungal infection, complications, baseline hepatic and renal function, daily dose and duration of micafungin treatment, concomitant drugs, clinical response, and adverse events. Diagnosis of fungal infection, clinical response, and adverse events were determined by the physician in charge. The severity of hepatic or renal impairment at the start of micafungin treatment was assessed according to the grade classification, which was issued by the Ministry of Health, Labour and Welfare, Ordinance No. 80 dated June 29, 1992, and the Common Terminology Criteria for Adverse Events (CTCAE) version 4. The protocol of this surveillance study was reviewed and approved by the Institutional Review Board of each participating institution in accordance with the rules of each institution.

Study Drug and Dosage Regimen

Micafungin was administered once daily by intravenous infusion over at least 60 minutes at a dose of 1 mg/kg of body weight for candidiasis and 1 to 3 mg/kg for

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aspergillosis, which are the approved dosages in Japan, with the option of increasing the dose, if required, up to 6 mg/kg daily.

Assessment of Safety

All remarks regarding adverse events, including abnormal changes in laboratory test findings, were recorded during micafungin treatment. Adverse drug reactions were classified based on the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA/J, version 13.1). In cases where symptoms and findings defined as adverse drug reactions were ongoing at the end of the administration of micafungin, cases were to be followed up, in principle, until symptoms and findings resolved, and the outcome (eg, recovery, remission) was reported by the primary investigators at each site. The degree of seriousness was classified as serious or nonserious by the principal investigators at each site, in accordance with the classification of adverse events, which is provided in the Pharmaceutical Affairs Law, Enforcement Regulations. The causal relationship of each event with micafungin was assessed on a 4-point scale: probable, possible, not related, or unknown. All adverse events except for those deemed to be "not related" were defined as adverse drug reactions, in accordance with the ICH E2A guideline (International Conference on Harmonisation, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Assessment of Efficacy

Patients who received >5 days' micafungin were evaluated by primary physicians for improvement in clinical symptoms and findings, imaging findings, mycological tests, and serological tests at the end of treatment, scoring results on a 3-point scale: response, no response, or indeterminate.[9]

Statistical Analyses

The χ^2 test was used, and the Cochran-Armitage test was used when category order had to be considered. The level of significance was set at <5% 2-sided. All statistical analyses were performed using JMP 9 software (SAS Institute Inc., Cary, NC).

RESULTS

Study Population

A total of 201 patients were enrolled in the study from 59 medical institutions around Japan (Fig. 1). Of these, 11 patients were excluded from the safety analysis for reasons such as enrollment outside the registration period and insufficient safety data for assessment. Of the remaining 190 patients, 99 were excluded from the efficacy analysis for reasons such as insufficient efficacy data for assessment, giving a total of 91 patients ultimately included in the efficacy analysis.

The patient characteristics of both all 190 and the 91 patients evaluated for safety and efficacy are summarized in Table 1. Of the 190 patients, 103 were males (54.2%) and 87 were females (45.8%), and of the 91 patients evaluated for safety and efficacy there were 51 males (56.0%) and 40 females (44.0%). The median ages were 5.5 and 5.0 years, respectively, and 18 neonates under 4 weeks of age were included. Of the 190 patients, common underlying conditions were hematopoietic stem cell and other

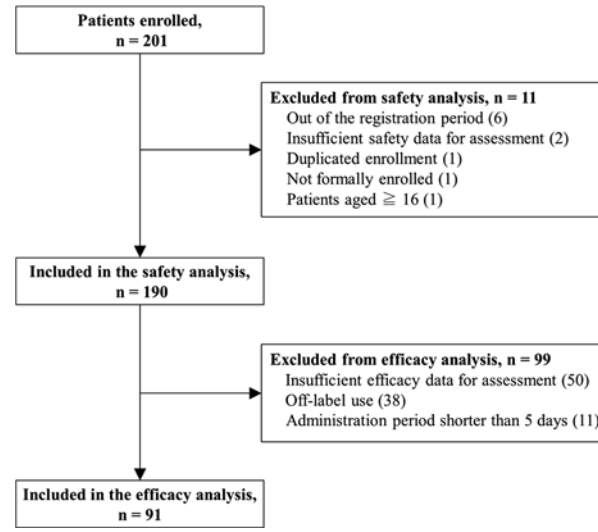

FIGURE 1. Number of patients enrolled and included in the safety and efficacy analysis.

transplantations (61.1%), solid tumor (15.8%), and low birth weight (6.3%). Micafungin was used for candidiasis in 49 patients (25.8%), aspergillosis in 15 (7.9%), empiric therapy in 42 (22.1%), febrile neutropenia in 42 (22.1%), and prophylaxis of fungal infection in 30 patients (15.8%). Eighty-four patients (44.2%) were neutropenic at baseline (absolute neutrophil count <500 cells/μL). Hepatic and renal dysfunctions were reported in 23.2% and 7.4% of patients, respectively.

Micafungin Exposure

The mean maximal daily micafungin dose (ie, the maximal dose used at any point during the entire course of observation) for the assessment of safety was 3.4 and for efficacy was 3.6 mg/kg, and the mean treatment duration was 19.7 days (range, 1 to 168 d) for the safety evaluation and 20.5 days (range, 5 to 91 d) for the efficacy evaluation, and these were similar when analyzed by diagnosis (Table 2). Of the 190 patients, 41 patients (21.6%) received concomitant antifungal therapy.

Safety

Fifty-five adverse drug reactions were reported in 42 of 190 patients evaluated for safety (22.1%, Table 3). The most frequently reported adverse drug reactions were hepatobiliary disorders, with an incidence of 13.7% (27 episodes in 26 patients). Nineteen episodes (10.0%) of laboratory abnormalities, including increases in alanine aminotransferase (2.1%) and aspartate aminotransferase (2.6%), were reported in 19 patients.

Among 42 patients who had adverse drug reactions, recovery or remission was observed in 13 patients after cessation of micafungin treatment, and in 23 patients without discontinuation of micafungin. One patient who had hepatic function abnormal died due to exacerbation of the primary disease (acute lymphocytic leukemia). One patient who had increased blood bilirubin, aspartate aminotransferase, and alanine aminotransferase died due to exacerbation of sepsis that developed during the treatment of the primary disease (acute lymphocytic leukemia). One patient died of aggravated trichosporonosis that developed during micafungin administration. There were 3 cases

TABLE 1. Baseline Characteristics of Pediatric Patients Participating in Postmarketing Surveillance of Micafungin

	n (%)	
	Safety Analysis (n = 190)	**Efficacy Analysis (n = 91)**
Sex		
Male	103 (54.2)	51 (56.0)
Female	87 (45.8)	40 (44.0)
Age (y)		
Median (minimum-maximum)	5.5 (0-15)	5.0 (0-15)
Age group		
< 4 wk	18 (9.5)	10 (11.0)
4 wk- < 1 y	14 (7.4)	9 (9.9)
1 y- < 7 y	68 (35.8)	32 (35.2)
7 y- < 16 y	90 (47.4)	40 (44.0)
Weight (mean ± SD) (kg)	23.4 ± 18.0	22.6 ± 19.7
Weight group (kg)		
< 10	43 (22.6)	24 (26.4)
< 20	61 (32.1)	31 (34.1)
< 30	25 (13.2)	9 (9.9)
< 40	19 (10.0)	9 (9.9)
< 50	26 (13.7)	10 (11.0)
≥ 50	16 (8.4)	8 (8.8)
Underlying disease		
Hematology	116 (61.1)	52 (57.1)
Acute lymphocytic leukemia	58 (30.5)	26 (28.6)
Acute myelogenous leukemia	36 (19.0)	18 (19.8)
Non-Hodgkin lymphoma	11 (5.8)	5 (5.5)
Others	11 (5.8)	3 (3.3)
Solid tumor	30 (15.8)	14 (15.4)
Low birth weight	12 (6.3)	6 (6.6)
Cardiac disease	10 (5.3)	4 (4.4)
Other	22 (11.6)	15 (16.5)
Diagnosis		
Candidiasis	49 (25.8)	34 (37.4)
Candidemia	29 (15.3)	21 (23.1)
Other	20 (10.5)	13 (14.3)
Aspergillosis	15 (7.9)	12 (13.2)
Invasive pulmonary aspergillosis	10 (5.3)	8 (8.8)
Other	5 (2.6)	4 (4.4)
Empiric therapy	42 (22.1)	23 (25.3)
Febrile neutropenia	42 (22.1)	19 (20.9)
Prophylactic treatment	30 (15.8)	0 (0.0)
Other fungal infections	12 (6.3)	3 (3.3)
Neutrophil count before treatment (cells/μL)		
< 500	84 (44.2)	35 (38.5)
500- < 1000	16 (8.4)	4 (4.4)
≥ 1000	70 (36.8)	40 (44.0)
Unknown	20 (10.5)	12 (13.2)
Hepatic dysfunction at the start of micafungin administration		
Mild disorder	28 (14.7)	16 (17.6)
Moderate disorder	15 (7.9)	6 (6.6)
Severe disorder	1 (0.5)	1 (1.1)
Renal dysfunction at the start of micafungin administration		
Mild disorder	10 (5.3)	7 (7.7)
Moderate disorder	3 (1.6)	1 (1.1)
Severe disorder	1 (0.5)	0 (0.0)
Surgery and transplantation		
Surgery	26 (13.7)	15 (16.5)
HSCT	35 (18.4)	11 (12.1)
Concomitant treatment		
Antifungal agents	41 (21.6)	25 (27.5)
Fluconazole	22 (11.6)	9 (9.9)
Voriconazole	12 (6.3)	10 (11.0)
L-amphotericin B	10 (5.3)	7 (7.7)
Itraconazole	7 (3.7)	5 (5.5)
Antimicrobial agents	183 (96.3)	85 (93.4)
Antiviral agents	36 (18.9)	13 (14.3)
G-CSF	90 (47.4)	37 (40.7)
M-CSF	2 (1.1)	0
γ-globulin	52 (27.4)	25 (27.5)
Glucocorticoid	45 (23.7)	18 (19.8)
Antineoplastic agents	30 (15.8)	11 (12.1)
Immunosuppressants	23 (12.1)	8 (8.8)

G-CSF indicates granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplantation.

where follow-up reporting from the primary investigator was not completed.

Seven serious adverse drug reactions (1 event each of *Trichosporon* infection, liver disorder, rash, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, and hepatic enzyme increased) were observed in 5 patients. Except for *Trichosporon* infection, the outcome of these events was recovered or remitted.

The incidence of adverse drug reactions was analyzed by baseline patient characteristics and micafungin exposure (Table 4). No adverse drug reactions were reported in the 18 neonates. When analyzed by diagnosis, the incidence of adverse drug reactions in the 42 patients with febrile neutropenia (35.7%) seemed to be slightly higher than in patients with other diagnoses. No adverse drug reactions were observed in patients with renal dysfunction, and hepatic dysfunction did not affect the incidence of adverse drug reactions. Three of 9 patients treated with micafungin at a dose of > 6 mg/kg experienced adverse drug reactions of nonserious hepatobiliary disorders. There were no relationships between the incidence of adverse drug reaction and micafungin daily dose or treatment duration, or with concomitant antifungal agents.

Effectiveness

The overall clinical response rate in 91 patients analyzed for efficacy was 86.8% (Table 5). The response rate in neonates (below 4 wk of age) was 90.0% (9/10 patients), and there were no differences in the response rate by age. When analyzed by diagnosis, the response rate was 88.2% (30/34) among patients with candidiasis, 75.0% (9/12) among patients with aspergillosis, 91.3% (21/23) among patients receiving empiric therapy, and 89.5% (17/19) among patients receiving treatment for febrile neutropenia. The response rate among patients with neutropenia, < 500/μL throughout the micafungin treatment, was 92.9% (13/14 patients, Table 6). No marked differences in response rates were observed in terms of patient characteristics (sex or body weight), duration of micafungin treatment, daily dose of micafungin, use of previous medication with antifungals, or concomitant antifungals.

TABLE 2. Exposure of Micafungin and Other Antifungals

	Safety Analysis (N = 190)		Efficacy Analysis (N = 91)	
Dose	**Maximum Daily Dose**	**Average Daily Dose**	**Maximum Daily Dose**	**Average Daily Dose**
Overall (mean [SD])	3.4 ± 1.7	3.3 ± 1.6	3.6 ± 1.7	3.5 ± 1.6
Age group (mean [SD]) (kg)				
< 4 wk	2.0 ± 0.8	1.9 ± 0.8	2.1 ± 0.9	2.0 ± 0.8
4 wk- < 1 y	2.8 ± 1.8	2.7 ± 1.7	3.0 ± 1.6	3.0 ± 1.6
1 y- < 7 y	3.9 ± 1.6	3.8 ± 1.6	4.2 ± 1.6	4.1 ± 1.6
7 y- < 16 y	3.4 ± 1.7	3.2 ± 1.5	3.7 ± 1.7	3.5 ± 1.5
Diagnosis (mean [SD]) (mg/kg)				
Candidiasis	3.4 ± 1.7	3.2 ± 1.6	3.4 ± 1.7	3.2 ± 1.6
Aspergillosis	4.5 ± 1.6	4.3 ± 1.5	4.2 ± 1.7	4.0 ± 1.6
Empiric therapy	3.1 ± 1.7	3.1 ± 1.7	3.3 ± 2.0	3.3 ± 1.9
Febrile neutropenia	3.9 ± 1.5	3.7 ± 1.4	4.0 ± 1.4	3.9 ± 1.3
Prophylactic treatment	2.8 ± 1.6	2.5 ± 1.3	—	
Maximum daily dose (n [%]) (mg/kg)				
< 1	10 (5.3)		5 (5.5)	
1-3	80 (42.1)		34 (37.4)	
3-6	91 (47.9)		45 (49.5)	
> 6	9 (4.7)		7 (7.7)	
Duration of micafungin treatment (mean ± SD [range]) (d)				
Overall	19.7 ± 20.7 (1-168)		20.5 ± 18.7 (5-91)	
Candidiasis	17.7 ± 16.5 (3-85)		20.6 ± 18.8 (5-85)	
Aspergillosis	30.9 ± 26.9 (5-91)		34.2 ± 28.9 (5-91)	
Empiric therapy	12.5 ± 11.9 (1-64)		16.7 ± 13.3 (5-64)	
Febrile neutropenia	17.3 ± 16.4 (5-75)		18.3 ± 14.5 (6-65)	
Prophylactic treatment	26.2 ± 18.9 (4-62)		—	
Duration of micafungin treatment (n [%]) (d)				
1-7	50 (26.3)		15 (16.5)	
8-14	57 (30.0)		32 (35.2)	
15-28	47 (24.7)		26 (28.6)	
29-42	14 (7.4)		7 (7.7)	
43-56	10 (5.3)		6 (6.6)	
> 56	12 (6.3)		5 (5.5)	

TABLE 3. Adverse Drug Reactions (n = 190)

	n (%)	
	Episodes	**Serious Episodes**
No. patients with adverse drug reactions	42 (22.1)	5 (2.6)
No. adverse drug reactions	55 [54]*	7
Infections and infestations	2 (1.1)	1 (0.5)
Trichosporon infection	1 (0.5)	1 (0.5)
Pseudomonas infection	1 (0.5)	0
Metabolism and nutrition disorders	1 (0.5)	0
Hypertriglyceridemia	1 (0.5)	0
Gastrointestinal disorders	2 (1.1)	0
Diarrhea	1 (0.5)	0
Vomiting	1 (0.5)	0
Hepatobiliary disorders	27 [26]* (13.7)	1 (0.5)
Hepatic function abnormal	25 [24]* (12.6)	0
Hyperbilirubinemia	1 (0.5)	0
Liver disorder	1 (0.5)	1 (0.5)
Skin and subcutaneous tissue disorders	3 (1.6)	1 (0.5)
Drug eruption	1 (0.5)	0
Rash	2 (1.1)	1 (0.5)
General disorders and administration-site conditions	1 (0.5)	0
Pyrexia	1 (0.5)	0
Investigations	12(6.3)	2 (1.1)
Alanine aminotransferase increased	4 (2.1)	1 (0.5)
Aspartate aminotransferase increased	5 (2.6)	1 (0.5)
Blood bilirubin increased	3 (1.6)	1 (0.5)
γ-glutamyltransferase increased	2 (1.1)	0
Blood alkaline phosphatase increased	3 (1.6)	0
Hepatic enzyme increased	1 (0.5)	1 (0.5)
Urinary sediment abnormal	1 (0.5)	0

*Two events of hepatic function abnormality were observed in the same patient.

TABLE 4. Incidence of Adverse Drug Reactions by Baseline Patient Characteristics and Exposure of Micafungin and Other Antifungal Agents

	No. Patients Analyzed for Safety	No. Patients With Adverse Drug Reactions (n [%])	*P*
Overall	190	42 (22.1)	
Age group			
< 4 wk	18	0 (0.0)	0.0236
4 wk- < 1 y	14	4 (28.6)	
1 y- < 7 y	68	13 (19.1)	
7 y- < 16 y	90	25 (27.8)	
Sex			
Male	103	24 (23.3)	NS
Female	87	18 (20.7)	
Weight (kg)			
< 10	43	6 (14.0)	
< 20	61	12 (19.7)	
< 30	25	7 (28.0)	NS
< 40	19	5 (26.3)	
< 50	26	7 (26.9)	
> 50	16	5 (31.3)	
Diagnosis			
Candidiasis	49	10 (20.4)	
Aspergillosis	15	3 (20.0)	
Empiric therapy	42	4 (9.5)	NS
Febrile neutropenia	42	15 (35.7)	
Prophylactic treatment	30	7 (23.3)	
Others	12	3 (25.0)	
Hepatic dysfunction at the start of micafungin treatment			
Normal	144	28 (19.4)	
Mild disorder	28	10 (35.7)	NS
Moderate disorder	15	3 (20.0)	
Severe disorder	1	1 (100)	
Renal dysfunction at the start of micafungin treatment			
Normal	175	42 (24.0)	
Mild disorder	10	0 (0.0)	NS
Moderate disorder	3	0 (0.0)	
Severe disorder	1	0 (0.0)	
Daily maximum dose (mg/kg)			
< 1	10	0 (0.0)	
1-3	80	19 (23.8)	NS
3-6	91	20 (22.0)	
> 6	9	3 (33.3)	
Duration of micafungin treatment (d)			
1-7	50	11 (22.0)	
8-14	57	10 (17.5)	
15-28	47	10 (21.3)	NS
29-42	14	3 (21.4)	
43-56	10	4 (40.0)	
> 56	12	4 (33.3)	
Concomitant antifungal agents			
Absent	149	34 (22.8)	
Present	41	8 (19.5)	
Fluconazole	22	3 (13.6)	NS
Voriconazole	12	2 (16.7)	
L-amphotericin B	10	4 (40.0)	
Itraconazole	7	0 (0.0)	

NS indicates not significant.

DISCUSSION

In the present postmarketing surveillance study, the incidence of adverse drug reactions was 22.1% (42/190 patients), and hepatobiliary disorders were the most common adverse drug reaction (13.7%). The incidence of adverse drug reactions in this study was similar to that seen

TABLE 5. Efficacy by Clinical Characteristics and Study Treatment

	No. Patients Analyzed for Efficacy	No. Responders (n [%])	*P*
Overall	91	79 (86.8)	
Age group			
< 4 wk	10	9 (90.0)	
4 wk- < 1 y	9	7 (77.8)	NS
1 y- < 7 y	32	28 (87.5)	
7 y- < 16 y	40	35 (87.5)	
Sex			
Male	51	45 (88.2)	NS
Female	40	34 (85.0)	
Weight (kg)			
< 10	24	19 (79.2)	
< 20	31	29 (93.6)	
< 30	9	7 (77.8)	NS
< 40	9	8 (88.9)	
< 50	10	9 (90.0)	
> 50	8	7 (87.5)	
Diagnosis			
Candidiasis	34	30 (88.2)	
Aspergillosis	12	9 (75.0)	
Empiric therapy	23	21 (91.3)	NS
Febrile neutropenia	19	17 (89.5)	
Others	3	2 (66.7)	
Daily maximum dose (mg/kg)			
< 1	5	5 (100)	
1-3	34	31 (91.2)	NS
3-6	45	37 (82.2)	
> 6	7	6 (85.7)	
Duration of micafungin treatment (d)			
1-7	15	14 (93.3)	
8-14	32	26 (81.3)	
15-28	26	24 (92.3)	NS
29-42	7	6 (85.7)	
43-56	6	5 (83.3)	
> 56	5	4 (80.0)	
Concomitant antifungal agents			
Absent	66	60 (90.9)	
Present	25	19 (76.0)	
Fluconazole	9	7 (77.8)	NS
Voriconazole	10	6 (60.0)	
L-amphotericin B	7	5 (71.4)	
Itraconazole	5	4 (80.0)	

NS indicates not significant.

TABLE 6. Efficacy by Change in Neutrophil Count

Before Treatment (cells/μL)	After Treatment (cells/μL)	Efficacy (n/N [%])	*P*
< 500	< 500	13/14 (92.9)	
	≥ 500- < 1000	3/3 (100.0)	NS
	≥ 1000	17/18 (94.4)	
≥ 500- < 1000	< 500	0/0	
	≥ 500- < 1000	1/1 (100.0)	NS
	≥ 1000	2/2 (100.0)	
≥ 1000	< 500	3/5 (60.0)	
	≥ 500- < 1000	2/2 (100.0)	NS
	≥ 1000	23/28 (82.1)	

Data were analyzed in patients whose neutrophil count was available both before and after micafungin treatment.
NS indicates not significant.

in the data from the pooled micafungin pediatric clinical trials (phase I, II, and III) conducted before 2006 in Europe, the Americas, and South or Southeast Asia (26.7%, 79/296 patients).[3] The incidence of adverse drug reactions observed in this postmarketing surveillance study (22.1%, 42/190 patients) was comparable with or lower than the incidence of treatment-related adverse events (ie, adverse drug reactions) in pediatric patients with invasive candidiasis in a randomized double-blind trial (36.5%, 19/52 patients).[14] In addition, in this study, the incidences of adverse drug reactions and hepatobiliary disorders including investigations for such (19.4%, 37/190 patients) in these pediatric patients were similar to those in a Japanese postmarketing surveillance study in adult patients (adverse drug reactions: 28.5%, 306/1074 patients; hepatobiliary disorders: 16.8%).[9] Causality between hepatobiliary disorders and micafungin treatment was assessed as possibly related or not related in most instances, and several other causative factors—such as concomitant medications and underlying diseases—were reported by physicians.

In the present surveillance study, 1 *Trichosporon* infection was observed in a patient treated with 100 mg/d micafungin for 63 days; the patient died of aggravated trichosporonosis, although voriconazole was administered for trichosporonosis after the discontinuation of micafungin treatment. Although it is possible that micafungin treatment may cause breakthrough trichosporonosis in patients with hematological diseases,[16,17] it is unlikely that micafungin directly causes the breakthrough of trichosporonosis because other strong confounders are more plausible explanations for the relationship with trichosporonosis in reported cases.

In this surveillance study, the incidence of adverse drug reactions was slightly higher in patients with febrile neutropenia than in patients with other diagnoses. It might be possible to speculate that several antibiotics and antifungals, which were concomitantly used for the treatment of febrile neutropenia, may affect the incidence of adverse events. The dosage of micafungin can be increased up to 6 mg/kg based on the patient's condition for severe or refractory candidiasis/aspergillosis. Although adverse drug reactions of nonserious hepatobiliary disorders were recorded in 3 of 9 patients treated with micafungin at a dose of >6 mg/kg, their causal relationship with micafungin was not assessed as probable because 2 cases developed after discontinuation of micafungin, and the remaining 1 case recovered during micafungin treatment. Thus, the data suggest that the micafungin dose has little influence on safety. In addition, no adverse drug reactions were reported in 18 neonates. Other factors including age, duration of treatment, and baseline hepatic/renal function were not found to have any impact on the incidence of adverse drug reactions.

It has been demonstrated that micafungin can be effective against candidemia, candidiasis, and aspergillosis in pediatric and adult patients.[1,11–15] For instance, treatment success was observed in 72.9% of pediatric patients with invasive candidiasis treated with micafungin (2 mg/kg) in a randomized double-blind trial.[14] In a Japanese surveillance study, the clinical response rates for adult patients with candidiasis and aspergillosis were 86.3% and 70.8%, respectively, and the overall response rate was 83.0%.[9] Thus, the response rates in candidiasis and aspergillosis in the presented surveillance study in pediatric patients (88.2% and 75.0%, respectively; overall response, 86.8%) are comparable with those in previous reports in both pediatrics and adults.[9,14] In addition, it is notable that the response rate—even in the persistent neutropenic patients, whose neutrophil count was $<500/\mu$L throughout micafungin treatment—was 92.9% (13/14). However, this study is limited by its small sample size, as well as by the fact that more than half of all patients were excluded from efficacy assessment because of lack of data for analysis. Furthermore, about 60% of patients evaluated for efficacy did not have confirmed invasive fungal infections; among these patients, micafungin was administered empirically or prophylactically. Therefore, verification of the findings in this study will require further studies with an increased number of patients with confirmed invasive fungal infection.

In conclusion, we evaluated the safety and effectiveness of micafungin in real clinical practice using data obtained from the first postmarketing surveillance study, which enrolled 201 Japanese pediatric patients. It is suggested that micafungin has sufficient safety and effectiveness when used for candidiasis, aspergillosis, empiric therapy, febrile neutropenia, or prophylaxis of fungal infection in pediatric patients with various backgrounds, although this finding needs to be further validated in additional large-scale, prospective studies.

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