Clinical efficacy and safety of Micafungin in Japanese patients with chronic pulmonary aspergillosis: a prospective observational study

Short Title: Efficacy and Safety of Micafungin for CPA

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Summary

Background

Aspergillosis has been the prevailing deep-seated mycosis in Japan since the 1990s. Although micafungin (MCFG) has been approved in Japan for the management of patients with deep-seated mycosis caused by *Candida* species or *Aspergillus* species, there are relatively few reports on its use in patients with chronic pulmonary aspergillosis (CPA).

Objectives

A prospective observational study was conducted to evaluate the efficacy and safety of MCFG in Japanese patients with CPA.

Methods

The efficacy of MCFG in CPA patients was assessed based on improvements in clinical symptoms and radiological findings. In addition, adverse events, including abnormal laboratory findings were assessed.

Results

The overall clinical efficacy rate was 68.4% (26/38 patients), which is comparable to the results of the clinical trial for marketing approval conducted in Japan. Adverse drug reactions were observed in 6 patients (15.8%); none of which were serious. The most common adverse drug reaction being abnormal liver functions. No relation between the incidence of adverse drug reactions and age, MCFG dose, or duration of treatment was observed.

Conclusions

MCFG has favorable efficacy and safety profiles in Japanese CPA patients with various backgrounds.

Introduction

The incidence of deep-seated mycosis, especially aspergillosis, has increased in recent years [1, 2]. Based on pathology autopsy cases including Japanese patients, aspergillosis has been considered the prevailing deep-seated mycosis since the 1990s [3, 4]. An increasing number of immunocompromised patients associated with acquired immunodeficiency syndrome, bone marrow transplantation, or chemotherapy is considered to be the main contributing population to this growing prevalence of aspergillosis [5, 6].

Pulmonary aspergillosis is classified into three major categories, invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA) including chronic necrotizimg pulmonary aspergillosis (CNPA), chronic cavitary pulmonary aspergillosis (CCPA also known as complex aspergilloma), chronic fibrosing pulmonary aspergillosis (CFPA) and simple aspergilloma [7, 8]. IPA often occurs in patients after hematopoietic stem cell transplantation or with severe hematological disorders such as acute leukemia [5, 6, 9-11]. IPA rapidly progresses, and a definite diagnosis is generally deemed difficult [5, 12]. CPA can occur in patients with underlying respiratory diseases such as tuberculosis sequelae, chronic obstructive pulmonary disease, or associated with pulmonary surgery, radiotherapy, pneumococcal infection, diabetes mellitus, collagen disease, corticosteroid-induced immunosuppressive conditions. In most cases, CPA requires long-term treatment [7, 8, 13], however, limited evidence is available for CPA management.

Micafungin (MCFG), an echinocandin antifungal agent, is a selective inhibitor of the synthesis of (1,3)-beta-D-glucan, a primary component of fungal cell walls. MCFG exerts its fungicidal action on *Candida*, and causes rupture of mycelial tips of *Aspergillus* by the potent inhibition of mycelial extension [14-17]. Although various clinical studies that demonstrate the effectiveness of MCFG for invasive fungal infections have been reported [18-29], there are few reports on its use for the treatment of CPA [25, 30]. We recently published the first large scale prospective study comparing the efficacies of intravenous MCFG and intravenous voriconazole in the treatment of CPA [31]. There was a favorable response rate with both MCFG (60.0%) and voriconazole (53.2%); however fewer side effects were reported for MCFG (26.4%) than for voriconazole (61.1%) [31]. We also had conducted another prospective observational study to clarify the efficacy and safety profile of MCFG with 38 CPA patients from 28 Japanese medical institutions between April 2003 and March 2005. This study is relatively small, non-randomized observational study, however, the information obtained from a clinical setting could be also beneficial for clinicians facing CPA.

Materials and Methods

Study Patients

The enrollment criteria for prospective clinical studies of CPA proposed by Denning *et al*. [7] was slightly modified, and utilized in this study. Briefly, patients were enrolled in this study if they had clinical symptoms caused by pulmonary Aspergillosis [any of cough, sputum, hemosputum, haemoptysis, and pyrexia (≥ 37.0°C axillary temperature)], and elevated levels of inflammatory markers (any of C-reactive protein value, white blood cell count, and erythrocyte sedimentation) before the treatment with MCFG, and if they met at least one of the following three criteria:

1) A causative fungus (*Aspergillus* spp.) identified by cultural or histopathological examination.
2) The appearance of new nodules or the expansion of the existing nodules on a chest X-ray or computed tomography (CT) suspected by aspergillosis and with positive result of the serological or mycological tests.
3) Suspected complex aspergilloma with positive feature on a chest X-ray or CT.

Patients with features of invasive pulmonary aspergillosis (i.e. symptoms of less than 1 month) and allergic bronchopulmonary aspergillosis were excluded.

Patients were treated with MCFG for 4-84 days with doses of 50-150 mg once daily by intravenous drip infusion. In severe or refractory cases, a dose increase up to 300 mg daily

was allowed. The dose of MCFG was accepted to be changed by the decision of attending physicians depending on the severity of disease, since no data was available about the dose effect of MCFG.

The following information was reviewed from the patient's medical records, patient characteristics (e.g., sex, age, body weight), treatment conditions (e.g., dose of MCFG, duration of MCFG therapy, all other antifungals or antibiotics used during the 7 days prior to the initiation of MCFG therapy, other concomitant therapies), clinical symptoms or findings, radiological findings of chest X-ray, CT, and adverse events.

This study was approved by the Institutional Review Board at each institution. Since this was an observational study, informed consent was not required.

Efficacy Assessment

The efficacy of MCFG was assessed based on improvements in CPA-related clinical symptoms and radiological findings such as chest X-ray and CT. Improvement in clinical symptoms were rated as "improved," "worsened" or "unchanged." Changes in the radiological findings of chest X-ray and CT were rated as "improved" when the shadows on the images were reduced or diminished, "worsened" when the shadows were increased, and "unchanged" otherwise.

Overall clinical efficacy ("effective" or "not effective") was assessed based on the

improvement in both ratings of clinical symptoms and radiological findings. Overall clinical efficacy was assessed as “effective” when clinical symptoms were rated as “improved” and radiological findings were not rated as “worsened.” Overall clinical efficacy was also assessed as “effective” when radiological findings were rated as “improved” and the clinical symptom was not rated as “worsened.” Overall clinical efficacy was assessed as “not effective” when both the clinical symptoms and the radiological findings were rated as “unchanged” or either of them was rated as “worsened.”

Safety Assessment

All adverse events, including abnormal laboratory findings noted after the initiation of MCFG therapy, were recorded. Adverse events that the investigator suspected to have a causal relationship with MCFG were classified as adverse drug reactions, and the seriousness was classified into three levels of “mild,” “moderate (neither mild nor serious),” and “serious” in accordance with the ICH Harmonised Tripartite Guideline [32].

Statistical Analysis

The data were expressed as mean ± SD. Categoric variables were expressed as a percentage and were analyzed by the Fisher exact test. A P-value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Table 1 summarizes patient characteristics. The patients consisted of 25 males (65.8%) and 13 females (34.2%). Patients aged 65 or older predominated (27 patients [71.1%], maximum; 90 years, mean: 68.8 years). The mean body weight was 45.1 kg.

The duration of MCFG therapy was 14 days or less in 6 patients (15.8%), 15-28 days in 13 patients (34.2%), and 29 days or longer (up to a maximum of 84 days) in the remaining 19 patients (50.0%). The mean duration was 33.7 ± 19.9 days. The mean daily dose was 167.0 ± 54.4 mg/day, with approximately half of the patients (55.3%) receiving 150 mg/day.

Clinical Efficacy

1) Clinical response by clinical symptoms and radiological findings (Table 2)

Overall clinical efficacy was assessed as “effective” in 26 patients (overall clinical efficacy rate: 68.4%). Among them, 10 patients showed improvement in both clinical symptoms and radiological findings, and the remaining 16 patients showed improvements in either clinical symptoms or radiological findings. Of the 12 patients in which overall clinical efficacy was assessed as “not effective”, 2 patients showed worsening in both clinical symptoms and radiological findings, and 10 patients showed worsening in either clinical symptoms or radiological findings.

2) Clinical response by duration of treatment and mean daily dose (Table 3)

The observed clinical efficacy rate when analyzed by duration of treatment was lower in patients treated for 14 days or less (3/6 patients) than in the other groups. The efficacy rate were 92.3% in patients treated for 15-28 days, and 57.9% in patients treated for 29-84 days.

The clinical efficacy rate treated with 100 mg/day, more than 100 mg/day and less than 150 mg/day, 150 mg/day, more than 150 mg/day and less than 300 mg/day, 300 mg/day were 100.0% (3/3 patients), 80.0% (4/5 patients), 66.7% (14/21 patients), 60.0% (3/5 patients), and 50.0% (2/4 patients), respectively.

Safety

1) Incidence of adverse drug reactions (Table 4)

A total of 38 adverse events occurred in 16 of 38 patients. Of them, 10 events in 6 patients (15.8%) were regarded as adverse drug reactions related to MCFG.

Common adverse drug reactions were reported as 7 events of abnormal liver functions including increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (γ-GT), and blood alkaline phosphatase (ALP). Among the 10 adverse drug reactions, the seriousness was classified as moderate for 5 reactions and mild for 5 reactions. No serious adverse drug reactions classified by the ICH guideline [32]

were observed. Treatment with MCFG was discontinued in one patient because of increases of AST from 40 U/L to 199 U/L and ALT from 36 U/L to 175 U/L. The investigator assessed these events as moderate, and suggested the contribution of concomitant drugs such as arbekacin and imipenem/cilastatin.

2) Incidence of adverse drug reactions by age, dose, and duration (Table 5)

The incidence of adverse drug reactions by age was 9.1% (1/11 patients) in patients aged under 65 years and 18.5% (5/27 patients) in those aged 65 years or older. The latter age group of 65 years or older included 6 patients aged 80 years or older, in whom the incidence of adverse drug reactions was 16.7% (1/6 patients).

The incidence of adverse drug reactions in patients treated with 150 mg/day was 19.0% (4/21 patients). The remaining 2 patients, in whom adverse drug reactions were observed, were treated with 117 mg/day and 300 mg/day, respectively. The incidence of adverse drug reactions by duration of treatment was 33.3% (2/6 patients) in patients treated for 14 days or less, 15.4% (2/13 patients) in patients treated for 15-28 days, and 10.5% (2/19 patients) in patients treated for 29-84 days.

Discussion

A multicenter, observational study of 38 CPA patients treated with MCFG showed that the overall clinical efficacy rate was 68.4% (26/38 patients), which is comparable to the results of our previous studies [25,31], though the design of studies are different. CPA in which mycelia do not penetrate the surrounding cavity wall is generally defined as simple aspergilloma, but in practice it is often difficult to clearly distinguish between CNPA, CCPA, and CFPA. Indeed, Hope *et al*. consider these pathological conditions to be a continuous series of the infection process [13]. In consideration of such circumstance, we considered the enrollment criteria proposed by Denning *et al*. [7] the most practical, and utilized it as inclusion criteria in this study.

The clinical trial of MCFG conducted for marketing approval also demonstrated clinical efficacy rates of 67% (6/9 patients) for CNPA, and 55% (12/22 patients) for aspergilloma [25]. The efficacy of MCFG shown in this study with patients of various backgrounds in a post-marketing setting seems comparable with that of the above-mentioned trial, although there are still differences in methodology, baseline patient characteristics, dosage regimen, and timing of assessment.

The Infectious Diseases Society of America guidelines for aspergillosis recommend MCFG as an alternative therapy to voriconazole for CNPA and CCPA. For simple aspergilloma, the guidelines recommend surgical resection as the primary treatment, and oral

itraconazole and voriconazole as alternative therapies in unresectable cases [8]. In our previous studies including this study, MCFG achieved an overall clinical efficacy rate of approximately 60-70%. This result and result from comparing study with MCFG and voriconazole suggests that MCFG has potential as an alternative therapy to itraconazole and/or voriconazole.

There are no significant differences between the efficacy and the dose of MCFG. However, the clinical efficacy rate in the patients who were treated more than 150mg was relatively lower than other patients. Nine of the patients who were treated with more than 150 mg/day included 5 responders and 4 non-responders. No obvious differences were found in clinical symptoms/inflammatory findings at the start of MCFG treatment between these responders and non-responders. On the other hand, a comparison of the radiological findings revealed that only 1 of 5 responders was assessed to have severe disease represented by shadows covering 2/3 or more of either lung field, whereas 3 of 4 non-responders were considered to have severe disease with shadows covering almost the entire lung field unilaterally. In order to clarify the relationship between the severity of the disease and the MCFG dose, an additional clinical study in a larger patient population will be needed in the future.

It is difficult to draw a clear conclusion on the appropriate duration of treatment of MCFG from this observational study, in which each investigator determined whether MCFG

therapy should be continued or discontinued. However, the patients treated with MCFG for 15-28 days and those treated for 29 days or longer showed slightly higher efficacy rates in comparison with those discontinued within 14 days, and most of patients had been treated for more than 14 days. These data may suggest that treatment for more than 14 days is recommended for anticipating the sufficient efficacy of MCFG, although the number of patients treated for up to 14 days was limited in this study. Therefore, the appropriate duration of treatment based on each patient's condition should further be explored in the future.

With regard to the safety of MCFG, the incidence of adverse drug reactions was 15.8% (6/38 patients), and abnormal liver functions were the most reported adverse drug reactions. In the Japanese open-label, non-controlled clinical trial of MCFG in 70 deep-seated mycosis patients for marketing approval, 33 adverse drug reactions occurred in 21 patients (incidence: 30.0%) [25]. Our MCFG and voriconazole comparative study also indicated incidence rate of 26.4%, which is not different from previous study [31]. Common reactions included increases in hepatic enzymes like γ-GT and blood ALP, blood urea nitrogen, and creatinine. None of these reactions were assessed as serious [25, 31]. Even though the present study was conducted in CPA patients with varying backgrounds, no marked differences were found between these three studies concerning the type or seriousness of the adverse drug reactions.

When the incidence of adverse drug reactions was analyzed in terms of factors that may affect their incidence, no relationship was observed between the incidence of adverse

drug reactions and increase in age, dose or duration of treatment. In addition, we were able to assess adverse drug reactions in patients not enrolled in the clinical trial of MCFG for marketing approval, particularly patients aged 80 years or older, in patients treated at a dose of more than 150 mg/day and treated for 57 days and longer. The only adverse drug reaction reported in the patient aged 80 years or older was an abnormal liver function, which did not result in discontinuation of the treatment and was reported to have subsided 24 days after onset. The patient treated at a dose of more than 150 mg/day experienced 3 events of abnormal liver functions, of which 2 were classified as moderate and 1 as mild. Concomitant drugs such as arbekacin and imipenem/cilastatin may also have contributed to the onset of these adverse drug reactions, as well as MCFG, in this patient. The outcomes of these adverse drug reactions were not traceable in this case because of death caused by aggravation of the underlying disease. No adverse drug reaction was observed after treatment with MCFG for 57 and longer.

In conclusion, MCFG achieved satisfactory treatment results in CPA patients with varying backgrounds. The safety profiles of MCFG obtained from this study was similar with other previous studies. Accumulation of clinical data will be beneficial in the management of CPA patients.

Conflict of interest

All authors have received consultation fees from Astellas, Co. Ltd.

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Table 1. Patient characteristics

Characteristic	Number of Patients
Total	38
Sex	
Male	25
Female	13
Age (years)	
23 to 64	11
65 to 90	27
(Mean± SD)	(68.8±10.9)
Body weight (kg)	
(Mean± SD)	(45.1±10.6)
Duration of treatment (days)	
4 to 14	6
15 to 28	13
29 to 84	19
(Mean± SD)	(33.7±19.9)
Mean daily dose (mg/day)	
100	3
> 100 to < 150	5
150	21
> 150 to < 300	5
300	4
(Mean± SD)	(167.0±54.4)

Mean± SD; Mean± Standard Deviation

Table 2. Clinical response by clinical symptoms and radiological findings

Clinical Response (%)	Clinical symptoms	Radiological findings
effective 26/38 (68.4%)	improved (23) *	improved (10) *
		unchanged (13) *
	unchanged (3) *	improved (3) *
not effective 12/38 (31.6%)	unchanged (6) *	unchanged (4) *
		worsened (2) *
	worsened (6) *	unchanged (4) *
		worsened (2) *

*Number of patients

Table 3. Clinical efficacy rates by duration of treatment with micafungin and mean daily dose

Variable	Clinical efficacy rate (%)		Statistical test*
Total	26/38	(68.4)	-
Duration of treatment (days)			
4 to 14	3/6	(50.0)	p=0.050
15 to 28	12/13	(92.3)	
29 to 84	11/19	(57.9)	
Mean daily dose (mg)			
100	3/3	(100.0)	p=0.786
> 100 to < 150	4/5	(80.0)	
150	14/21	(66.7)	
> 150 to < 300	3/5	(60.0)	
300	2/4	(50.0)	

* Fisher exact test

Table 4. Profile of adverse drug reactions (by seriousness)

Type of adverse drug reaction *)	Number of events	Seriousness		
		Serious	Moderate	Mild
Abnormal liver function (including increased AST, ALT, gamma-GT, and ALP)	7	0	3	4
Injection site extravasation	1	0	1	0
Edema peripheral	1	0	1	0
Eosinophil count increased	1	0	0	1
Total	10	0	5	5

*Note) : Determined by investigator to be definitely, probably, or possibly drug related.
AST; aspartate aminotransferase, ALT; alanine aminotransferase,
gamma-GT; gamma-glutamyltransferase, ALP; alkaline phosphatase

Table 5. Incidence of adverse drug reactions by age,

mean daily dose or duration of treatment

Variable	Incidence of adverse drug reactions (%)	Statistical test*
Total	15.8 (6/38)	-
Age(years)		
23 to 64	9.1 (1/11)	p=0.650
65 to 90	18.5 (5/27)	
Mean daily dose(mg/day)		
100	0.0 (0/ 3)	p=0.898
> 100 to < 150	20.0 (1/ 5)	
150	19.0 (4/21)	
> 150 to < 300	0.0 (0/ 5)	
300	25.0 (1/ 4)	
Duration of treatment(day)		
4 to 14	33.3 (2/ 6)	p=0.410
15 to 28	15.4 (2/13)	
29 to 84	10.5 (2/19)	

* Fisher exact test