Clinical effects of micafungin, a novel echinocandin antifungal agent, on systemic fungal infections in surgery, emergency, and intensive-care medicine: evaluation using the AKOTT algorithm

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Abstract The clinical efficacy of micafungin (MCFG) in surgery, emergency, and intensive-care medicine has been studied in only a limited number of cases. We conducted a multicenter postmarketing study to evaluate MCFG efficacy and safety in Japan. MCFG was given to patients with a temperature exceeding 37.5°C, either with a proven fungal infection based on mycological or histopathological examination, or those who were regarded as having probable or possible fungal infections (patients who had at least one high-risk factor for the development of a systemic fungal infection and for whom fungi had been detected at multiple sites by surveillance culture or a positive β-D-glucan test). Efficacy was evaluated using the AKOTT algorithm created by our group (AKOTT is an acronym created from the first letter of the surname of each of the five members of the evaluation committee). Of the 180 patients enrolled, 68 were excluded by exclusion criteria or for other reasons, and 112 (58 with proven candidiasis, 1 with proven aspergillosis, and 53 with suspected fungal infection) were evaluated for efficacy. MCFG was administered at a mean daily dose of 104 mg for a mean duration of 14.2 days. It was effective in 72 patients, ineffective in 28, and the effect was undeterminable in 12, for an overall clinical efficacy of 72.0%. MCFG was effective in 78.6% of those with proven candidiasis and in 65.1% with suspected fungal infection, but it was ineffective in the 1 patient with aspergillosis. MCFG eradicated 77.6% (52/67) of fungi isolated. There were 69 drug-related adverse reactions, mainly abnormal hepatic function tests, in 37 of 178 patients evaluated for safety. One adverse reaction, skin eruption, had a probable causal relationship with drug treatment. In conclusion, MCFG had high clinical efficacy and safety in the treatment of deep-seated fungal infections in surgery, emergency, and intensive-care medicine, indicating good potential as a first-line drug for both targeted and empirical therapies.

Key words Fungal infection · Micafungin · Algorithm · Surgery · Intensive-care medicine

Introduction

In recent years, fungi have been increasingly found to be the cause of nosocomial infections worldwide. Candida species are the most common cause of fungal infection in patients in the fields of surgery and emergency and intensive-care medicine (EICM), accounting for 85% of all documented mycoses. However, opportunistic infections due to non-albicans Candida species, including Candida glabrata and Candida krusei, have been reported with increasing frequency. To date, fluconazole has been widely used as a first-line drug for the treatment of fungal infections in these fields. Although C. albicans is sensitive to fluconazole, C. glabrata is less susceptible, and C. krusei is intrinsically resistant to this drug. As C. glabrata is present in the gastrointestinal tract and vagina as well as on the skin, it
often causes infection associated with the use of urinary catheters in patients in these fields. Thus, agents that have antifungal activity not only against *C. albicans* but also against other non-*albicans* *Candida* species will be highly advantageous to the fields of surgery and EICM.

Micafungin (MCFG) is the first echinocandin antifungal agent approved for clinical use in Japan. Recent evidence has demonstrated that MCFG exhibits more potent in vitro and in vivo antifungal activity against a broad spectrum of clinically important *Candida* and *Aspergillus* species than other antifungal agents. In addition, susceptibility survey testing using collected clinical isolates of fungi has indicated that MCFG does not show cross-resistance to azole antifungal agents, and it exhibits potent antifungal activity against a number of *Candida* species, including *C. glabrata* and *C. krusei*. To date, there has been no large-scale report of the clinical effects of MCFG in the fields of surgery or EICM, with this agent having been studied in only a limited number of patients. The aim of this study was to evaluate the efficacy and safety of MCFG in patients with fungal infections in the fields of surgery and EICM in a multicenter, postmarketing study. Moreover, a novel algorithm, AKOTT (an acronym created from the first letter of the surname of each of the five members of the evaluation committee), was formulated for the study as an evaluation method that takes into account the possible influence of bacterial infection alongside fungal infection and antibacterial therapy.

**Patients and methods**

**Study design**

This was an open-label, noncomparative, multicenter postmarketing study conducted at 63 medical institutions with expertise in the fields of surgery and EICM in Japan (Table 1).

**Inclusion and exclusion criteria**

Patients with an axillary temperature of 37.5°C or greater who met the criteria of proven, probable, or possible fungal infection were enrolled. Patients for whom the causative fungi had been identified by fungal culture or histopathological examination were documented as having a proven fungal infection. Patients with at least one high-risk factor for the development of a systemic fungal infection and for whom fungi had been detected at multiple sites by surveillance culture or a positive β-D-glucan test were regarded as having probable or possible fungal infections. The high-risk factors for the development of a systemic fungal infection have been documented in the Japanese *Guidelines for the diagnosis and the treatment of deep-seated mycosis* established in 2003.

The following patients were excluded from the study: those for whom a fungal species other than the indicated strains (*Candida* and *Aspergillus* spp.) was detected at the time of enrollment; those who needed the concomitant use of an antifungal agent along with MCFG at the initiation of MCFG treatment; those who were neutropenic (absolute neutrophil count, <500 cells/μl); and those who were expected to live for less than 3 days.

**Study procedures and dosing**

The initial dose of MCFG was 50 mg per day once daily as an infusion for infections caused by *Candida* species, and 50–150 mg per day for infections caused by *Aspergillus* species. The dose could be increased to up to 300 mg per day, at the individual investigator’s discretion. Duration of treatment was defined as a maximum of 4 weeks.

Clinical symptoms/findings, imaging findings (including chest X-ray, computed tomography [CT], and endoscopic findings), fungal and bacterial cultures, and histopathological findings were recorded at the time of enrollment, and 1, 2, and 4 weeks after initiation of MCFG treatment.

**Formulation of AKOTT algorithm**

In the fields of surgery and EICM, most patients receiving antifungal treatments have associated bacterial infections. Therefore, in order to appropriately evaluate clinical antifungal efficacy, it is important to consider the possibility of coexisting bacterial infection and antibacterial therapy. In addition, clinical antifungal efficacy is generally evaluated based on improvement in clinical symptoms/findings, fungal culture testing, imaging, and serological test findings. However, as these most important data from before and after drug treatment are often lacking in postmarketing surveillance studies, the clinical response to antifungal therapy in these patients is sometimes evaluated as “undeterminable.” Therefore, it is necessary to propose a good method that will make antifungal evaluation easy and reproducible. To address this, the AKOTT algorithm was developed and applied in this study.

The antifungal efficacy of MCFG was independently evaluated by individual investigators and the evaluation committee using the AKOTT algorithm. When the results of efficacy evaluation obtained from individual investigators and the evaluation committee did not agree, the primary investigator’s evaluation was referred back to the individual investigator for confirmation, and the confirmed investigator’s evaluation was used as the final efficacy evaluation of MCFG.

**Evaluation of antifungal activity of MCFG using the AKOTT algorithm**

At the end of MCFG therapy, improvement in clinical symptoms/findings (“marked improvement,” “improvement,” “no change,” “aggravation,” or “undeterminable”) was first evaluated based on clinical symptoms/findings under the conditions of concomitant fungal and bacterial infections (hereafter referred to as “clinical symptoms/findings for fungi + bacteria”). Improvement in imaging findings