Pharmacoeconomic Analysis of Micafungin (Mycamine) 100 mg and 150 mg Daily In the Treatment of Candidemia

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Abstract

We conducted a retrospective study to assess pharmacoeconomic outcomes of patients who received a daily dose of micafungin 100 mg or 150 mg to treat candidemia. The once-daily 100-mg dose resulted in clinical and mycological outcomes similar to those achieved with 150 mg daily and succeeded in reducing drug-acquisition costs for treating hospitalized patients with candidemia.

INTRODUCTION

Candida species represent the fourth leading cause of nosocomial bloodstream infections in the U.S.[1] In recent years, *Candida* non-*albicans*–associated infections have increased specifically in intensive-care units (ICUs).[2] Clinical data indicate that inadequate and delayed antifungal treatment of candidemia is associated with an increased hospital mortality rate of 33% to 47%.[3] Therefore, early and effective therapy that targets the correct species is important.

Although fluconazole (Diflucan, Pfizer) has been shown to be safe and effective in *C. albicans*–associated infections, therapy with fluconazole might not be adequate in light of the emergence of non-*albicans* species. Amphotericin B is effective in most patients with candidemia, but substantial adverse drug events (ADEs) such as nephrotoxicity and infusion-related reactions limit its use.[4] A new class of antifungal agents, the echinocandins, exhibits fungicidal activity against *Candida* species, including triazole-resistant isolates such as *Candida glabrata*.[5] The primary mechanism of action of the echinocandins is the inhibition of beta$_{1-3}$ D-glucan synthase, an essential constituent of the fungal cell wall.

Three echinocandins are currently available in the U.S.: caspofungin (Cancidas, Merck), micafungin (Mycamine, Astellas Pharma US), and anidulafungin (Eraxis, Pfizer). Their limited toxicity profile, non-renal elimination, and minimal drug–drug interactions make them favorable for managing candidemia and invasive candidiasis.

Caspofungin has been approved by the FDA for treating candidemia, refractory aspergillosis, disseminated candidiasis, esophageal candidiasis, and febrile neutropenia.[6,7] Micafungin, on the other hand, has demonstrated efficacy as antifungal prophylaxis in hematopoietic stem cell transplant (HSCT) recipients and in treating esophageal candidiasis in clinical trials. In addition, comparative clinical trials of amphotericin B and micafungin have shown success in candidemia therapy.[4,8]

Pfaller et al. demonstrated that micafungin had excellent activity *in vitro* against invasive candidiasis from medical centers worldwide.[5] In a multicenter, randomized, double-blind noninferiority trial, by Pappas et al., micafungin was noninferior to caspofugin in treating candidema.[9] Another important attribute of this study is the authors' conclusion that micafungin 100 mg/day was as efficacious as 150-mg/day for treating candidemia.[9]

We conducted a study to assess the economic outcomes of patients who were treated for candidemia with micafungin 100 and 150 mg/day.

METHODS

Study Population

We reviewed the charts of hospitalized adults who were 18 years of age and older and who had a diagnosis of candidemia, as defined by at least one blood culture positive for *Candida* organisms. These patients had received micafungin from January 2006 to December 2007; those receiving 100 mg/day were compared with a cohort of patients receiving 150 mg/day. Patients were matched for age (± 5 years), sex, APACHE II scores (Acute Physiology and Chronic Health Evaluation), distribution of *Candida* species, and the presence of a catheter. Patients with proven or suspected *Candida* osteomyelitis, pericarditis, endocarditis, endophthalmitis, or meningitis were excluded from the study.

Study Design

Our retrospective review was conducted at a 1,000-bed acute teaching hospital (Montefiore Medical Center) in Bronx, New York. The institution's Quality Improvement Council approved data collection methods. All links to patient identifiers and chart information were destroyed after data collection and analysis.

Outcome Measures

Treatment outcomes, such as clinical and mycological endpoints, were evaluated for all patients. We classified clinical outcomes as success (defined by a complete or a partial clinical response) or failure. A complete clinical response included resolution of signs and symptoms, normalization of the white

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blood cell (WBC) count, absence of fever, and completion of 14 days of all antifungal therapy. A partial clinical response was defined as a reduction in signs and symptoms, improved WBC counts, an absence of fever, and less than 14 days of all antifungal therapy upon discharge from the hospital.

The mycological outcome was classified as successful if repeated blood cultures were negative after micafungin therapy was initiated.

Pharmacoeconomics

A cost-minimization analysis was performed for three levels of cost from the hospital's perspective.

Level 1 included the drug-acquisition cost of micafungin times the number of days of therapy. Based on contracting cost information from our hospital, the drug-acquisition costs used for all antifungal therapy were as follows: micafungin 100 mg/day ($82.13); micafungin 150 mg/day ($123.21); intravenous (IV) fluconazole 400 mg/dose ($14.84); IV fluconazole 200 mg/dose ($18.31); oral fluconazole 100-mg/tablet ($2.29); voriconazole 200-mg/tablet ($31.72); and amphotericin B lipid complex, 20-mL vial ($73.20).

Level 2 included level 1 costs plus costs associated with other antifungal therapy, treatment of ADEs, and ventilator treatment per day in patients with ventilator-associated pneumonia. The daily cost of treatment for ventilator-associated pneumonia was approximately $621. The cost of treatment of ADEs was not assigned because there was no incidence of adverse effects associated with antifungal therapy in this cohort of patients.

Level 3 included level 2 costs plus the costs associated with length of stay (LOS): $LOS_{ICU–MICA}$ (LOS in the ICU between the start and the end of all candidemia-related antifungal therapy) or $LOS_{NON–ICU–MICA}$ (LOS in the non-ICU between the start and the end of all candidemia-related antifungal therapy). The estimated charges of $1,200 per hospitalization day in the ICU and of $444 in the non-ICU were used to determine level 3 cost analyses.

Statistical Analysis

As for baseline demographic and clinical characteristics, Student's *t* test was used to assess differences between groups. The differences were reported as percentages for discrete variables, means, and standard deviations for continuous variables. Pearson's *chi*-squared test was used to compare response rates between groups. A two-sided *P* value of 0.05 or less was considered statistically significant.

RESULTS

In total, 53 patient charts were reviewed; we assigned 24 patients to the micafungin 150-mg arm and 29 patients to the micafungin 100-mg arm. The two groups were comparable in baseline demographics and in underlying condition or risk factors (Table 1). The most common underlying conditions or risk factors were a catheter in place, a prolonged ICU stay of more than 72 hours, hemodialysis, the need for broad-spectrum antibiotics, and diabetes mellitus. Most patients had at least two of these risk factors. There were no significant differences in APACHE II scores between the two groups; however, these were critically ill patients, and half of them received micafungin in the ICU.

Mycological Outcomes

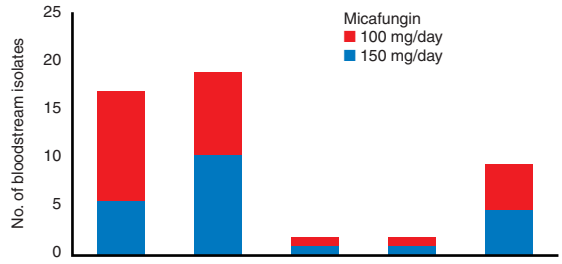
Of 24 evaluable patients in the micafungin 150-mg group, 21 demonstrated a mycological success rate of 87.5%; of 29 evaluable patients in the 100-mg group, 27 demonstrated a mycological success rate of 93.10% (Table 2). We assessed susceptibility to antifungal agents according to the current Clinical and Laboratory Standards and Institute (CLSI) guidelines for performance standards for antimicrobial susceptibility. The most commonly isolated non-*albicans* species of *Candida* were *C. glabrata* and *C. tropicalis*, which were comparable between the two groups. The least common non-*albicans* species were *C. parapsilosis* and *C. tropicalis* (Figure 1).

Information about fluconazole susceptibility was available for all *C. glabrata* isolates and two-thirds of *C. albicans* isolates. For

Table 1 Baseline Demographic and Clinical Characteristics of Patients with Candidemia

	Micafungin 100 mg/day (n = 24)	Micafungin 150 mg/day (n = 29)	*P* Value
Characteristics			
Age in years (mean ± SD)	67.29 ±15.95	71.17 ± 14.30	0.109
Sex			
Male (%)	15 (62.50)	14 (48.28)	0.854
Female (%)	9 (37.50)	15 (51.72)	0.221
APACHE II score (%) (<20)	15 (62.50)	16 (55.17)	0.858
(>20)	9 (37.50)	13 (44.83)	0.394
Underlying condition or risk factor			
Catheter in place	23 (95.83)	28 (96.55)	0.484
Prolonged ICU stay	10 (41.67)	7 (24.14)	0.467
Hemodialysis	10 (41.67)	5 (17.24)	0.197
Broad-spectrum antibiotics	15 (62.50)	23 (79.31)	0.194
Diabetes mellitus	9 (37.50)	13 (44.83)	0.394

APACHE II = Acute Physiology and Chronic Health Evaluation II; ICU = intensive-care unit; SD = standard deviation.



	C. albicans	*C. glabrata*	*C. lusitanae*	*C. parapsilosis*	*C. tropicalis*
Micafungin 100 mg/day	12	9	1	1	5
Micafungin 150 mg/day	6	11	1	1	5

Figure 1 Various *Candida* species isolated from evaluable patients with candidemia.

all *C. glabrata* isolates, 16% were sensitive to fluconazole (minimum inhibitory concentration [MIC], less than 8), 79% were dose-dependent-sensitive to fluconazole (MIC, 8–32), and 5% were resistant to fluconazole (MIC 32–64) (Figure 2*A*). For the C. *albicans* isolates, 94% were sensitive to fluconazole and 5% were resistant to fluconazole (Figure 2*B*). Based on these results, antifungal therapy was de-escalated from micafungin to fluconazole (Table 3), and daily doses ranged from 200 to 800 mg for an average of seven days.

Clinical Outcomes and Adverse Events

Clinical success and failure rates did not differ significantly between the two groups. The overall clinical response rate was 79.31% (23 of 29 patients) with micafungin 100 mg/day and 54.17% (13 of 24 patients) with micafungin 150 mg/day (see Table 2). Overall, micafungin was well tolerated in both groups.

No micafungin-related ADEs were documented in the 52 patient charts reviewed.

Pharmacoeconomics

The mean duration of micafungin therapy was comparable for micafungin 100 mg/day and 150 mg/day (7.21 vs. 7.17 days), but there was a difference between the two groups for the duration of fluconazole therapy (5.81 vs. 10.56 days); this difference was not statistically significant (see Table 3). The mean level 1 cost of micafungin 100 mg/day was lower than that for micafungin 150 mg/day. For an average duration of 7.2 days, the use of micafungin 100 mg/day reduced drug-acquisition costs by $300 per patient (Table 4). Furthermore, mean level 2 and 3 costs were lower with micafungin 100 mg/day with no statistically significant differences.

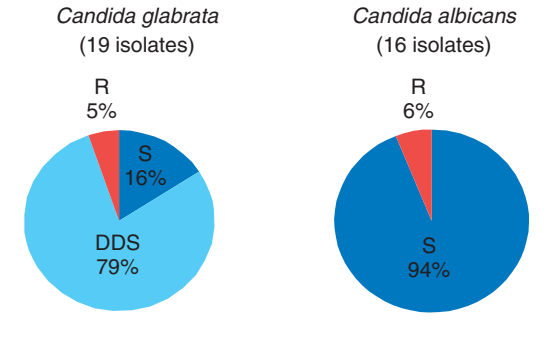


Figure 2*A*,*B* Fluconazole susceptibility patterns.
S = sensitive to fluconazole; DDS = dose-dependent-sensitive to fluconazole; R = resistant to fluconazole.

Table 2 Clinical and Mycological Outcomes of Evaluable Patients with Candidemia

Outcome	No. (%) Patients: *Micafungin 150 mg/day (n = 24)*	*Micafungin 100 mg/day (n = 29)*
Mycological success rate	21 (87.5)	27 (93.10)
Clinical success rate		
Complete clinical response	6 (25)	10 (34.48)
Partial clinical response	7 (29.17)	13 (44.83)
Failure	11 (45.83)	6 (20.69)

DISCUSSION

When the FDA first approved micafungin, clinicians were frequently challenged to select the optimal dose of micafungin that would be appropriate for patients with candidemia. Before the study by Pappas et al.,[9] micafungin 100 mg daily or 150 mg daily had been prescribed interchangeably at Montefiore for treating candidemia. We were intrigued by the possibility of learning whether a 100-mg daily dose would attain similar clinical success and economic benefits as micafungin 150 mg daily. Although efficacy was not measured directly, we did not observe any trends suggesting that 150 mg daily was more efficacious than 100 mg daily in patients with candidemia.

Micafungin therapy was administered for an average of 7 ± 2.1 days in both groups, and the resulting response rates were comparable. The duration of therapy did not differ significantly between these two groups. The remaining course of treatment for candidemia was exhausted with other antifungal therapy based on drug susceptibilities.

Table 3 Comparison of Hospital Length of Stay and Duration of Antifungal Therapy in Patients with Candidemia

Outcome	Average: *Micafungin 150 mg/day (n = 24)*	*Micafungin 100 mg/day (n = 29)*
Duration of micafungin	7.21 ± 6.3	7.17 ± 3.6
Duration of fluconazole	10.56 ± 9.3	5.81 ± 4.2
Length of hospital stay	27.15 ± 19.7	40.89 ± 22.3

Table 4 **Average Costs for Patients Receiving Micafungin**

	Micafungin 150 mg/day (*n* = 24)	Micafungin 100 mg/day (*n* = 29)	*P* Value
Level 1	$888	$589	0.062
Level 2	$1,911*	$1,494†	0.538
Level 3	$9,342*	$8,011†	0.342

* 46% of patients in the intensive-care unit stay and four patients with ventilator-associated pneumonia.

† 31% of patients in the intensive-care unit stay and four patients with ventilator-associated pneumonia.

The most commonly used alternative therapy was fluconazole, which was given for an average of six days in the micafungin 100-mg daily patients and for 11 days in the 150-mg daily group.

In this study, we realized a reduction in drug-acquisition costs, which were decreased by $300 per patient with micafungin 100 mg daily versus 150 mg daily. For a 14-day course of candidemia treatment, there was a potential savings of $600 per patient in drug-acquisition costs when 100 mg daily was ordered instead of 150 mg daily, irrespective of contractual agreements. Furthermore, antifungal susceptibilities and de-escalation of antifungal therapy allowed for only 50% of the total recommended days of treatment for candidemia (i.e., an average duration of micafungin therapy of approximately seven days) (see Table 3).

Rentz et al.[10] had previously reported an overall cost of treating each episode of candidemia at $35,000 to $45,000. Our level 3 costs were significantly lower, because the costs of associated medications, ventilator-associated pneumonia, and length of stay in the ICU were the only direct medical expenditures that we examined.

LIMITATIONS OF THE STUDY

Because of inherent limitations in our study—a small sample size, a retrospective design (lack of a control group), and a lack of sensitivity analysis—we could not draw conclusions about level 2 and level 3 costs. It is possible that our small sample size contributed to the lack of statistical significance differences in all three levels of costs between the two groups. However, identifying large groups of patients with blood cultures positive for *Candida* infection is a challenge.

Furthermore, because of our study's retrospective design, information obtained from charts reviewed for this analysis was as accurate as the data that were reported in the patient's chart, which made it difficult to assess micafungin-related ADEs. Although our analysis was conducted over a two-year period, we did not consider the inflation factor in our cost-minimization analysis, because contracting for micafungin over the two-year period did not change at our institution.

CONCLUSION

In our study, the most common bloodstream isolates were *C. glabrata* and *C. albicans*, which were dose-dependent-sensitive or sensitive to fluconazole. Antifungal therapy was streamlined and de-escalated from micafungin to fluconazole according to susceptibility results.

From our institution's perspective, micafungin 100 mg daily reduced drug-acquisition costs of treating candidemia by $300 per patient. The savings might be only modest with micafungin 100 mg daily versus 150 mg daily; however, with available clinical information, 50% of the duration of antifungal therapy for candidemia can be used with fluconazole. This yields significant cost savings in our institution's drug budget for antimicrobial medications when compared with a full course of treatment for candidemia with an echinocandin.

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