ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2010, p. 1864–1871 Vol. 54, No. 5
0066-4804/10/$12.00 doi:10.1128/AAC.00911-09

Caspofungin Use in Patients with Invasive Candidiasis Caused by Common Non-*albicans Candida* Species: Review of the Caspofungin Database▽

Arnaldo L. Colombo,[1] Angela L. Ngai,[2] Michael Bourque,[2] Susan K. Bradshaw,[2] Kim M. Strohmaier,[2] Arlene F. Taylor,[2] Robert J. Lupinacci,[2] and Nicholas A. Kartsonis[2]*

Division of Infectious Diseases, Universidade Federal de Sao Paulo, Sao Paulo, Brazil,[1] and Merck Research Laboratories, West Point, Pennsylvania[2]

Received 2 July 2009/Returned for modification 10 October 2009/Accepted 4 March 2010

Increasing rates of invasive candidiasis caused by non-*albicans Candida* species have been reported worldwide. Particular concerns have been raised for *C. parapsilosis* because of reduced *in vitro* susceptibility to echinocandins. We identified 212 patients with invasive candidiasis due to non-*albicans Candida* species (≥5 cases per species) in 5 clinical trials of caspofungin monotherapy from the pharmaceutical sponsor's (Merck and Co., Inc.) database: 71 cases were caused by *C. parapsilosis*, 65 by *C. tropicalis*, 54 by *C. glabrata*, 10 by *C. krusei*, 9 by *C. guilliermondii*, and 5 by *C. lusitaniae*. One hundred sixty-seven cases caused by *C. albicans* were also identified. Efficacy was assessed at the end of caspofungin therapy. Success (favorable overall response) required favorable clinical and microbiological responses. The mean APACHE II scores were 16.5 in the non-*albicans* group and 15.7 in the *C. albicans* group. Neutropenia at study entry was more common in the non-*albicans* group (12%) than in the *C. albicans* group (5%). The median duration of caspofungin therapy was 14 days in both groups. The success rates were 77% in both groups and at least 70% for each non-*albicans* species: 74% for *C. parapsilosis*, 71% for *C. tropicalis*, 85% for *C. glabrata*, 70% for *C. krusei*, 89% for *C. guilliermondii*, and 100% for *C. lusitaniae*. The times to negative blood culture were similar for the various species. The overall mortality rates were 26% in the non-*albicans* group and 29% in the *C. albicans* group. Drug-related serious adverse events and discontinuations due to caspofungin toxicity were uncommon. Although the sample sizes were limited, caspofungin demonstrated favorable efficacy and safety profiles in the treatment of invasive candidiasis caused by the following non-*albicans Candida* species: *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. guilliermondii*, and *C. lusitaniae*.

Candida albicans remains the most common pathogen isolated in invasive candidiasis; however, increasing rates of candidemia caused by non-*albicans Candida* species, including *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and *C. krusei*, have been reported worldwide (16). Non-*albicans Candida* species accounted for over half the documented cases of candidemia in several studies from Latin America, Europe, and the United States (5, 8, 16), and the prevalence of different species varies substantially from region to region (15, 16). Some of these species are relatively less susceptible than *C. albicans* to fluconazole. Specifically, *C. krusei* is inherently resistant and *C. glabrata* is routinely less susceptible to fluconazole (7, 17). The current treatment guidelines for invasive candidiasis issued by the Infectious Diseases Society of America (IDSA) recommend the use of an echinocandin for infections caused by these 2 species (13). Conversely, *in vitro* studies have shown that *C. parapsilosis* and *C. guilliermondii* are less susceptible to the echinocandins than are other *Candida* species (10, 11, 18), but the clinical implications of these findings are not clear.

Caspofungin, a member of the echinocandin class, is fungicidal against most *Candida* species, having demonstrated activity against *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. glabrata*, and *C. lusitaniae* (1, 3). Caspofungin targets the fungal cell wall, thereby retaining activity against clinical isolates with documented resistance to either the azoles or the polyenes (1, 3). Efficacy results from comparative trials have shown caspofungin to be an effective first-line agent for invasive candidiasis (4, 12). Although the activity for caspofungin against non-*albicans Candida* species in these studies was encouraging, the extent of efficacy data for each species was often limited (≤10 patients per treatment arm). To gain a better understanding of the efficacy of caspofungin in patients with non-*albicans Candida* infection, we performed a retrospective *post hoc* review of the current Merck database to identify all caspofungin-treated patients with invasive candidiasis caused by non-*albicans Candida* species. The results are described in this report relative to results for patients with invasive candidiasis caused by *C. albicans.*

MATERIALS AND METHODS

Patient population. Data from patients receiving caspofungin for the treatment of invasive candidiasis are available from 5 phase II/III clinical studies in the Merck database (Table 1), 2 of which are comparator-controlled trials (protocols 014 and 801) (4, 12) and 3 of which are noncomparative studies (protocols 024, 045, and 043) (6, 9, 19). All 5 studies required that patients had proven invasive candidiasis, as defined by the consensus definitions from the European Organization for the Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) (2). The one notable exception was the allowance for patients with probable cases of chronic disseminated candidiasis in protocol

* Corresponding author. Mailing address: Merck & Co., Inc., UG 3D-56, 351 N. Sumneytown Pike, P.O. Box 1000, North Wales, PA 19454. Phone: (267) 305-7269. Fax: (267) 305-6530. E-mail: nicholas_kartsonis@merck.com.

▽ Published ahead of print on 15 March 2010.

TABLE 1. Description of caspofungin studies for treatment of invasive candidiasis

Protocol	Study title	Treatment group	Caspofungin treatment sample size[a]	Reference
014	A multicenter, randomized, double-blind, comparative study to evaluate the safety, tolerability, and efficacy of caspofungin vs amphotericin B in the treatment of invasive candidiasis in adults	Caspofungin 50 mg daily (after 70 mg on day 1) vs amphotericin B deoxycholate 0.6–1.0 mg/kg of body wt daily	109	12
801	A multicenter, randomized, double-blind, comparative study to evaluate the safety, tolerability, and efficacy of 2 dosing regimens of caspofungin in the treatment of invasive candidiasis in adults	Caspofungin 50 mg daily (after 70 mg on day 1) vs caspofungin 150 mg daily	197 (102 received the 50-mg dose; 95 received the 150-mg dose)	4
024	A multicenter, open-label, noncomparative, compassionate-use study to evaluate the safety and tolerability of caspofungin for the treatment of invasive candidiasis in adults refractory to or intolerant of amphotericin B or amphotericin B lipid formulations	Caspofungin 50 mg daily (after 70 mg on day 1)	15	9
045	A multicenter, open-label, noncomparative study to estimate the safety, tolerability, and efficacy of caspofungin in the treatment of adults with invasive *Candida* infections (excluding patients with candidemia as the sole site of infection)	Caspofungin 100 mg daily in patients with *Candida* endocarditis, osteomyelitis, or septic arthritis; caspofungin 50 mg daily (after 70 mg on day 1) in all other patients	48 (42 received the 50-mg dose; 6 received the 100-mg dose)	6
043	A multicenter, open-label, noncomparative study to evaluate the safety, tolerability, and efficacy of caspofungin in children (3 months to 17 years of age) with documented *Candida* or *Aspergillus* infections	Caspofungin 50 mg/m^2 daily (after 70 mg/m^2 on day 1 [maximum daily dose not to exceed 70 mg])	37	19

[a] Sample size is based on modified-intention-to-treat (or full analysis set) population. A total of 27 patients were not included in this *post hoc* analysis either because they had an infection caused by a less common non-*albicans Candida* species or because they did not have available identification of *Candida* to the species level.

045 (6). Patients received caspofungin as monotherapy in all of these studies; details of the specific treatment regimens for each study are provided in Table 1. In general, patients were treated with caspofungin for at least 10 days, and all antifungal therapy (including subsequent oral fluconazole) was administered for at least 14 days after the last positive culture of a *Candida* sp. from blood or another normally sterile body site. In all studies, careful management of preexisting catheters in patients with candidemia was required. Prior to the initiation of study therapy, all peripheral intravenous or intra-arterial catheters were to be removed and all central venous catheters were to be removed or changed over a guide wire. Patients in whom these catheters were not removed are discussed in the original reports (4, 6, 9, 12, 19).

Efficacy assessment. In all studies, efficacy in all patients who had a confirmed diagnosis of invasive candidiasis and received at least 1 dose of caspofungin therapy (referred to as the modified-intention-to-treat population [6, 9, 12, 19] or the full-analysis-set population [4]) was assessed. In all trials, the primary efficacy measure was a favorable overall response at the end of caspofungin therapy; this required a favorable clinical response and a favorable microbiological response. A favorable clinical response was defined as resolution (complete response) (4, 6, 12) or improvement (partial response) (9, 19) of all signs, symptoms, and radiographic abnormalities attributed to *Candida* infection. A favorable microbiological response required clearance of *Candida* from follow-up cultures, including negative results for *Candida* in blood cultures at the end of caspofungin therapy in patients with candidemia. For patients with nonblood candidiasis for whom a follow-up culture could not be obtained, presumptive eradication (i.e., both clinical and radiographic resolution of infection) was considered a favorable microbiological response. Relapse assessments varied by trial; therefore, for this analysis, relapse was assessed at 2 weeks and 4 to 8 weeks after the end of therapy in all patients for whom the proper follow-up information was available.

Safety assessment. In all studies, adverse events were collected from all patients for the evaluation of safety. Investigators identified the seriousness, causality, and action taken on study therapy for all clinical and laboratory adverse events during the treatment period and for ≥14 days posttreatment. Adverse events that were considered by the site investigator to be definitely, probably, or possibly related to study therapy were classified as drug related.

Statistical considerations. For this *post hoc* analysis, all patients with a confirmed case of invasive candidiasis due to non-*albicans Candida* species were identified, provided there were at least 5 cases of infection for that particular species. The data for patients in each non-*albicans* group are shown as a separate column in the tables, followed by a column for the total non-*albicans* group. Data for patients with mixed infections caused by 2 or more non-*albicans* species are shown separately in each non-*albicans* group but are only listed once in the total non-*albicans* column. All patients with invasive candidiasis due to *C. albicans* were also identified and included. Data for patients with mixed infections caused by *C. albicans* and a non-*albicans Candida* species are presented separately under each species. Efficacy was assessed irrespective of caspofungin dose because prior studies failed to demonstrate a benefit of higher doses relative to results obtained with the standard 50-mg daily maintenance dose (4, 6).

The design and sample size of this analysis were not intended to test specific hypotheses with regard to efficacy or safety. This retrospective *post hoc* analysis was predominantly designed as a descriptive comparison of the results across the different *Candida* groups. All different analyses and subgroup assessments, including tabular displays, were predefined by the authors prior to the compilation of the data. For the primary efficacy outcome (overall response at the end of caspofungin therapy), a 95% confidence interval (CI) was calculated as an exact CI based on the binomial distribution. Assuming a sample size of 50 patients for each *Candida* species, the study could rule out observed differences (based on nonoverlapping 95% CI) between groups of 30 percentage points. For those groups with at least 10 patients with candidemia, a Kaplan-Meier analysis was used to assess any differences in the time to negative blood cultures; the log-rank chi-square statistic was also calculated.

This *post hoc* analysis focused predominantly on the results from the Merck database for caspofungin. Of note, the results from a large, prospective study of caspofungin versus micafungin in invasive candidiasis were not included (14) due

TABLE 2. Patient demographics and baseline characteristics

Characteristic	Value [no. (%) of patients or as indicated] for group							
	C. glabrata	*C. guilliermondii*	*C. krusei*	*C. lusitaniae*	*C. parapsilosis*	*C. tropicalis*	Total non-*albicans* species[a]	*C. albicans*
Total no. of patients	54	9	10	5	71	65	212	167
Gender								
Male	21 (39)	4 (44)	5 (50)	3 (60)	50 (70)	33 (51)	115 (54)	88 (53)
Female	33 (61)	5 (56)	5 (50)	2 (40)	21 (30)	32 (49)	97 (46)	79 (47)
Race								
Caucasian	41 (76)	7 (78)	7 (70)	2 (40)	45 (63)	40 (62)	141 (67)	116 (69)
Black	4 (7)	2 (22)	1 (10)	1 (20)	7 (10)	10 (15)	24 (11)	15 (9)
Asian	2 (4)				10 (14)	11 (17)	23 (11)	9 (5)
Hispanic	6 (11)		2 (20)	1 (20)	9 (13)	3 (5)	21 (10)	20 (12)
Other	1 (2)			1 (20)		1 (1)	3 (1)	7 (4)
Age (yr)								
Mean	57.8	42.1	45.4	34.7	47.7	51.8	50.8	52.7
Median	61.0	35.0	46.0	3.0	49.0	54.0	54.5	57.0
Range	3–90	7–67	6–73	2–90	1–87	2–90	1–90	1–88
APACHE II score[b]								
≤20	36 (67)	5 (56)	8 (80)		46 (65)	42 (65)	135 (64)	117 (70)
>20	9 (17)	2 (22)	1 (10)	2 (40)	16 (23)	17 (26)	47 (22)	31 (19)
Mean	16.2	16.9	12.2	30.5	15.8	17.4	16.5	15.7
Median	15.0	17.0	12.0	30.5	15.0	17.0	16.0	15.0
Range	8–34	12–21	0–21	29–32	2–37	2–39	0–39	2–38
Neutropenia status at study entry[c]								
ANC, >500 cells/μl	51 (94)	7 (78)	7 (70)	5 (100)	68 (96)	51 (78)	187 (88)	159 (95)
ANC, ≤500 cells/μl	3 (6)	2 (22)	3 (30)		3 (4)	14 (22)	25 (12)	8 (5)
Reason for study entry								
Primary therapy	47 (87)	9 (100)	8 (80)	5 (100)	69 (97)	62 (95)	199 (94)	151 (90)
Salvage therapy	7 (13)		2 (20)		2 (3)	3 (5)	13 (6)	16 (10)
Most common risk factor[d]								
Active malignancy	12 (22)	6 (67)	5 (50)	2 (40)	18 (25)	23 (35)	65 (30)	39 (23)
Broad spectrum antibiotics	37 (69)	7 (78)	9 (90)	5 (100)	63 (89)	50 (77)	169 (79)	125 (75)
Major surgery	28 (52)	1 (11)	2 (20)	2 (40)	35 (49)	22 (34)	88 (41)	85 (51)
Total parenteral nutrition	29 (54)	1 (11)	1 (10)	2 (40)	31 (44)	17 (26)	81 (38)	66 (40)
Site of *Candida* infection								
Blood	37 (69)	9 (100)	7 (70)	5 (100)	69 (97)	59 (91)	185 (87)	118 (71)
Intra-abdominal abscess	11 (20)		2 (20)			1 (2)	13 (6)	16 (10)
Bone/joint space	1 (2)		1 (10)		1 (1)		3 (1)	5 (3)
Peritoneal fluid	2 (4)					2 (3)	4 (2)	14 (8)
Pleural fluid	1 (2)				1 (1)	1 (2)	3 (1)	1 (1)
Other[e]	2 (4)					2 (3)	4 (2)	13 (8)

[a] Data for patients with mixed infections are displayed under each applicable pathogen but only once in the total non-*albicans* group.
[b] APACHE II scores were not collected in protocols 024 and 043.
[c] ANC, absolute neutrophil count.
[d] Patients with more than 1 risk factor are counted in each of the different categories.
[e] Other sites of infection among the non-*albicans* group included 2 patients with pyelonephritis (both with *C. glabrata*) and 2 patients with nonabdominal abscesses (both with *C. tropicalis*). Other sites of infection among the *C. albicans* group included 8 patients with other abscesses, 2 patients with *Candida* pneumonia, and 3 patients with pancreatic involvement.

to the unavailability of the full data set at the *Candida* species level. A sensitivity analysis which includes the primary efficacy results from this additional study combined with the results of the 5 studies from the Merck database (4, 6, 9, 12, 19) has been included in Results.

RESULTS

Patients. In these 5 studies, a total of 212 patients with invasive candidiasis caused by 6 different non-*albicans Candida*

TABLE 3. Caspofungin dosage and duration of therapy

Pathogen (total no. of patients in group)	No. (%) of patients receiving caspofungin daily dosage of:		Duration of therapy (days)		
	50 mg[a]	≥100 mg	Mean	Median	Range
C. glabrata (54)	44 (81)	10 (19)	16.8	14	6–37
C. guilliermondii (9)	8 (89)	1 (11)	12.9	14	3–28
C. krusei (10)	8 (80)	2 (20)	13.7	12	4–35
C. lusitaniae (5)	4 (80)	1 (20)	14.4	16	3–21
C. parapsilosis (71)	49 (69)	22 (31)	14.8	14	2–48
C. tropicalis (65)	46 (71)	19 (29)	13.4	12	1–57
Non-*albicans* species (212)[b]	157 (74)	55 (26)	14.6	14	1–57
C. albicans (167)	121 (72)	46 (28)	15.3	14	1–85

[a] Pediatric patients received 50 mg/m^2 daily following a 70-mg/m^2 loading dose on day 1 (maximum not to exceed 70 mg/day).

[b] Data for patients with mixed infections are displayed for each applicable pathogen but only once in the total non-*albicans* group.

species (Table 2), including *C. glabrata* ($n = 54$), *C. guilliermondii* ($n = 9$), *C. krusei* ($n = 10$), *C. lusitaniae* ($n = 5$), *C. parapsilosis* ($n = 71$), and *C. tropicalis* ($n = 65$), were identified. Two patients had mixed infections caused by 2 non-*albicans Candida* species, including one patient with *C. guilliermondii* and *C. parapsilosis* infection and another patient with *C. glabrata* and *C. krusei* infection. Data are also available for 167 patients with invasive candidiasis caused by *C. albicans* who were in these 5 studies. The distribution of patient demographics was generally similar in the combined non-*albicans* group and the *C. albicans* group. The median APACHE II score was between 15 and 17 for all species except for *C. krusei* and *C. lusitaniae.* APACHE II scores at study entry were higher in patients with *C. lusitaniae* infection than in any other group, but the number of patients with this species was limited. Patients with *C. guilliermondii*, *C. krusei*, or *C. tropicalis* infection had higher rates (each >20%) of neutropenia than the other groups at study entry. Across the combined non-*albicans* group and the *C. albicans* group, the most common risk factors were broad spectrum antibiotics, followed by major surgery, total parenteral nutrition, and active malignancy. Candidemia was the most common site of infection in all groups, ranging from 69 to 100% of patients. Approximately 20% of patients with *C. glabrata* or *C. krusei* infection had intra-abdominal abscess.

Caspofungin was predominantly dosed at 50 mg daily (following a 70-mg loading dose on day 1) in adults or 50 mg/m^2 daily (following a 70-mg/m^2 loading dose on day 1), with the maximum not to exceed 70 mg, in pediatric patients; these regimens were used in 74% of patients with non-*albicans Candida* infection and in 72% of those with *C. albicans* infection. The remaining patients (all adults) received caspofungin at 100 or 150 mg daily (Table 3). The duration of caspofungin therapy ranged from 1 to 57 days (median, 14 days) and was generally similar across the different groups (Table 3).

Efficacy. At the end of caspofungin therapy, a favorable overall response was achieved in 70% to 100% of patients with non-*albicans* infections. Notably, a response rate of 74% (46/65) was seen in patients with infections caused by *C. parapsilosis* (Table 4). For comparison, the success rate was 77% in the 167 patients with *C. albicans* infection from these same 5 studies. Response rates by site of *Candida* infection or by reason for study entry (primary or salvage treatment) were generally similar across the different species. Among neutropenic patients, the response rate was somewhat lower in patients with *C. tropicalis* (6/14, 43%) or *C. albicans* (2/8, 25%) infection than in patients with the other non-*albicans Candida* species.

Reasons for unfavorable responses were generally similar across the *Candida* species. One notable finding was that a slightly higher proportion of patients with *C. parapsilosis* (12/70, 17%) had persistently positive cultures listed as the primary reason for failure at the end of study therapy than was the case for groups with other *Candida* spp., among which the proportions of patients with persistently positive cultures were 10% (1/10) with *C. krusei*, 8% (14/166) with *C. albicans*, 5% (3/65) with *C. tropicalis*, and 2% (1/54) with *C. glabrata*. However, this finding was not confirmed when an analysis evaluating the time to a negative blood culture was performed in patients with candidemia. In those groups with at least 10 patients with candidemia, the median times to achieving a negative blood culture for *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. albicans* were 2.0, 2.5, 3.0, 3.5, and 5.0 days, respectively (Fig. 1). The log-rank chi-square statistic was not significant ($P = 0.522$), suggesting that there was no difference among the *Candida* species with respect to time to achieve a negative blood culture. Among these same groups, an assessment was also made to determine the proportion of patients with persistent candidemia at 72 h after the beginning of caspofungin therapy. The proportions were similar across the 4 non-*albicans* groups and the *C. albicans* group.

At 2 weeks after the end of caspofungin therapy, relapse of invasive candidiasis occurred in 3% of patients in the combined non-*albicans* group and 4% of patients in the *C. albicans* group. The relapse rates at 4 to 8 weeks after the end of therapy were 6% and 8%, respectively (Table 4).

Mortality from all causes was 26% across the combined non-*albicans* group and 29% in the *C. albicans* group (Table 4). Mortality was slightly higher among patients with *C. tropicalis* (38%) or *C. krusei* (40%) infection. The mortality rate in patients with *C. parapsilosis* (20%) was lower than the mean overall mortality but was comparable to the rate in patients with *C. glabrata* infection (20%) and higher than that in patients with *C. guilliermondii* infection (11%).

A sensitivity analysis was performed which included the primary efficacy results from the caspofungin treatment group in the caspofungin *versus* micafungin study of invasive candidiasis (14). With the inclusion of this data, the observed overall response rates for caspofungin against each of the 5 most common *Candida* species remain above 70% (Table 5).

Safety. Serious drug-related adverse events occurred in 2 patients (1%) with non-*albicans Candida* infection (one with *C. glabrata* and one with *C. tropicalis* infection) and 2 patients (1%) with *C. albicans* infection. Caspofungin therapy was discontinued due to a drug-related adverse event in 4 patients (2%) with non-*albicans Candida* infection (2 with *C. tropicalis*, one with *C. glabrata*, and one with *C. parapsilosis*) and 3 patients (2%) with *C. albicans* infection. All serious drug-related adverse events and drug-related adverse events leading to discontinuation of caspofungin were distinct terms; no specific adverse event occurred in more than 1 patient.

TABLE 4. Patient outcomes after caspofungin therapy

Type of response and parameter	No. of patients with favorable response, relapse, or mortality/no. of patients in subgroup (%)							
	C. glabrata	*C. guilliermondii*	*C. krusei*	*C. lusitaniae*	*C. parapsilosis*	*C. tropicalis*	Total non-*albicans* species[a]	*C. albicans*
Favorable response at end of therapy								
Overall[b]	46/54 (85); 73, 93	8/9 (89); 52, 100	7/10 (70); 35, 93	5/5 (100); 48, 100	52/70 (74); 62, 84	46/65 (71); 58, 81	162/211 (77); 70, 82	127/166 (77); 69, 83
Neutropenic status at study entry								
ANC of >500 cells/μl	43/51 (84)	6/7 (86)	5/7 (71)	5/5 (100)	50/67 (75)	40/51 (78)	147/186 (79)	125/158 (79)
ANC of ≤500 cells/μl	3/3 (100)	2/2 (100)	2/3 (67)		2/3 (67)	6/14 (43)	15/25 (60)	2/8 (25)
Reason for study entry								
Primary therapy	39/47 (83)	8/9 (89)	6/8 (75)	5/5 (100)	51/69 (74)	43/62 (69)	151/199 (76)	114/151 (75)
Salvage therapy	7/7 (100)		1/2 (50)		1/1 (100)	3/3 (100)	11/12 (92)	13/15 (87)
Site of infection								
Abscess (intra-abdominal)	10/11 (91)		2/2 (100)			1/1 (100)	12/13 (92)	13/16 (81)
Blood	31/37 (84)	8/9 (89)	5/7 (71)	5/5 (100)	50/68 (74)	40/59 (68)	138/184 (75)	87/118 (74)
Bone/joint space	1/1 (100)		0/1 (0)		1/1 (100)		2/3 (67)	4/4 (100)
Peritoneal fluid	1/2 (50)					2/2 (100)	3/4 (75)	12/14 (86)
Pleural fluid	1/1 (100)				1/1 (100)	1/1 (100)	3/3 (100)	1/1 (100)
Other	2/2 (100)					2/2 (100)	4/4 (100)	10/13 (77)
Relapse following successful completion of therapy[c]								
2-wk follow-up	1/38 (3)	0/7 (0)	0/7 (0)	0/5 (0)	2/48 (4)	1/37 (3)	4/140 (3)	4/107 (4)
4- to 8-wk follow-up	3/38 (8)	1/7 (14)	0/7 (0)	0/5 (0)	2/48 (4)	2/37 (5)	8/140 (6)	9/107 (8)
All-cause mortality	11/54 (20)	1/9 (11)	4/10 (40)	1/5 (20)	14/71 (20)	25/65 (38)	56/212 (26)	48/167 (29)

[a] Data for patients with mixed infection are displayed under each applicable pathogen but only once in the total non-*albicans* group.
[b] The proportion, percentage, and 95% CI values are shown.
[c] Forty-one patients (21 with non-*albicans Candida*, 19 with *C. albicans*, and 1 with mixed non-*albicans* and *C. albicans*) with a favorable response at the end of caspofungin therapy were excluded from this analysis because there was no follow-up information on them.

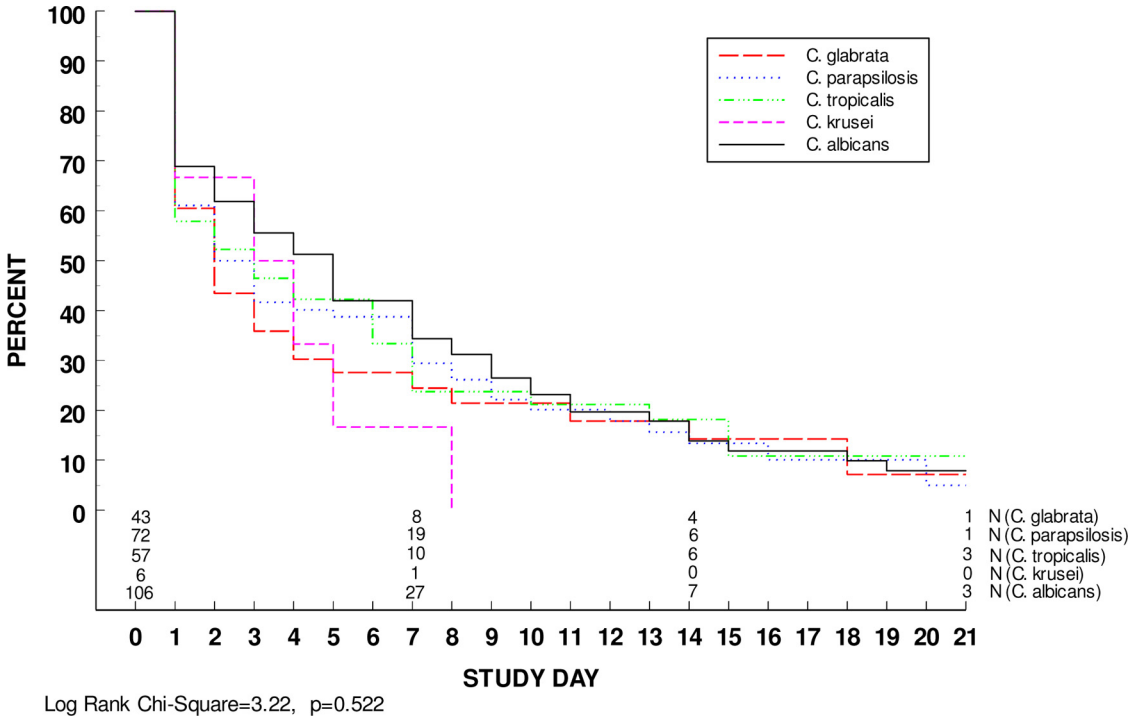

FIG. 1. Kaplan-Meier curves of the proportions of patients with positive blood cultures by day of study therapy and by *Candida* species (N, number of patients included at the specified time point). For those species infecting at least 10 patients, all patients with candidemia who had a positive blood culture at baseline were included. One patient had positive blood cultures for *C. glabrata* and *C. tropicalis* at baseline; time to *C. glabrata* eradication and time to *C. tropicalis* eradication are displayed separately for this patient.

DISCUSSION

Candida species other than *C. albicans* account for 40 to 55% of yeast bloodstream infections worldwide (16). Notably, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* are the most commonly recovered non-*albicans* species overall, accounting for 15%, 15%, and 9%, respectively, of all candidemia cases in the SENTRY antimicrobial surveillance program (17). Although it is encountered less frequently, *C. krusei* is also an important non-*albicans* species due to its inherent resistance to fluconazole (7, 17). To better understand the efficacy of caspofungin against non-*albicans Candida* species, we utilized data from 5 clinical studies to examine patient outcomes in 212 cases of invasive candidiasis caused by these 4 species (*C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*) and 2 other less common species (*C. guilliermondii* and *C. lusitaniae*).

In these 212 patients, success rates were generally high across the various non-*albicans* species, with a minimum success rate of 70% for each of these species. For comparison, a success rate of 77% was seen in the 167 patients with *C. albicans* infection from these same 5 studies. Even in specific patient subgroups, success was seen for the various non-*albicans* groups. Among patients with a non-*albicans Candida* infection, favorable responses were seen in patients with underlying neutropenia, patients with less common forms of invasive candidiasis, and patients receiving caspofungin as a second-line (salvage) treatment option.

TABLE 5. Patient efficacy outcomes, including results from the caspofungin treatment group in the caspofungin versus micafungin study, for invasive candidiasis

Pathogen	No. of patients with a favorable response/no. of patients in subgroup (%)	95% CI
C. glabrata	68/87 (78)	68, 86
C. krusei	10/14 (71)	42, 92
C. parapsilosis	79/112 (71)	61, 79
C. tropicalis	70/97 (72)	62, 81
C. albicans	188/249 (76)	70, 81

Particular attention has been focused on those non-*albicans* species which have been reported to be less susceptible to the echinocandins, namely, *C. parapsilosis* and *C. guilliermondii* (10, 11, 18). Recent IDSA guidelines recommend that patients with an infection caused by *C. parapsilosis* should be treated with fluconazole, although the continuation of an echinocandin is reasonable for those patients showing clinical and microbiological improvement following initial treatment with an echinocandin (13). In this analysis, the success rate among patients with a *C. parapsilosis* infection was 74%, and the time to clearance of infection from the bloodstream and the rate of relapse in this group were comparable to those seen with other *Candida* species. Additionally, the success rate was 89% in patients with a *C. guilliermondii* infection. Even though the baseline APACHE II scores in patients with *C. parapsilosis* or *C. guilliermondii* were comparable to those seen with other species, the overall mortality with these 2 species was only 19%. This finding may attest to the less virulent nature of these 2 pathogens.

The observed safety profile of caspofungin in patients with non-*albicans Candida* infection was generally similar to that in patients with *C. albicans* infection. In both groups, serious drug-related adverse events and discontinuations due to drug-related adverse events were uncommon. About 25% of the patients in this analysis received caspofungin at higher than approved doses. Previous studies have shown that the safety profile of caspofungin at these higher doses is similar to that observed for the standard regimen (50 mg daily after 70 mg on day 1) (4, 6).

This analysis has several notable limitations. First, efficacy was assessed irrespective of different doses of caspofungin. Although this approach was justified by the knowledge that the overall efficacy of caspofungin across different doses in adults (50 to 150 mg daily) (4, 6) and pediatric patients (50 mg/m^2 daily) (19) was comparable, differences within patient subgroups may have been influenced by the chosen dose. Second, these 5 studies were conducted at different centers and over different time periods. The efficacy against different species may have been influenced by site-specific differences at these different centers over time. Third, this analysis was conducted as a *post hoc* analysis. The combination of the data across these 5 studies was not predefined in any of the protocols or statistical analysis plans for these different studies. A final limitation of the current analysis is that it does not include all clinical studies of caspofungin in the treatment of invasive candidiasis conducted to date. Particularly, the results from a large, prospective study of caspofungin versus micafungin in invasive candidiasis were excluded from all analyses because the results of the baseline characteristics, demographics, duration of therapy, and safety were summarized at the treatment group level and not the species level. A major strength of our analysis is that all the detailed data across these different indices have been included at the *Candida* species level, thereby allowing for a more accurate assessment of the efficacy of caspofungin for each of the different *Candida* species without bias to potential underlying factors. Nevertheless, a sensitivity analysis was also performed with the inclusion of the caspofungin primary efficacy data from the caspofungin versus micafungin study (14). The inclusion of this additional study does not significantly change the findings seen in our analysis.

Although the present study is still underpowered to definitely solve concerns that have arisen from *in vitro* data, the results of this study suggest that caspofungin provides therapeutic efficacy in patients with invasive candidiasis caused by *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. guilliermondii*, and *C. lusitaniae*. Although the number of cases was limited, the observed efficacy of caspofungin in patients with *C. parapsilosis* infection remained over 70%. Caspofungin also manifested a favorable safety profile in patients with non-*albicans Candida* infection, with very few serious drug-related adverse events or discontinuations because of toxicity. It is important to remember that no single randomized clinical trial with sufficient power to evaluate possible differences in the efficacy of antifungal drugs to treat non-*albicans Candida s*pecies has been conducted, and we expect that such a study is not likely to be performed in the near future. In this scenario, our study adds relevant data to the field and provides information suggesting that caspofungin may be used as first-line therapy for invasive candidiasis caused by non-*albicans Candida* species, even in regions where *C. parapsilosis* is highly prevalent.

ACKNOWLEDGMENTS

Funding for this study was provided by Merck & Co., Inc.

Potential conflicts of interest include grants for research and consulting and speaker's bureau fees received by A.L.C. from Merck, Pfizer, and Gilead-United Medical. A.L.N., M.B., S.K.B., K.M.S., A.F.T., R.J.L., and N.A.K. are employees of Merck Research Laboratories and may own stock and/or stock options in the company.

REFERENCES

1. **Abruzzo, G. K., A. M. Flattery, C. J. Gill, L. Kong, J. G. Smith, V. B. Pikounis, J. M. Balkovec, A. F. Bouffard, J. F. Dropinski, H. Rosen, H. Kropp, and K. Bartizal.** 1997. Evaluation of the echinocandin antifungal MK-0991 (L-743,872): efficacies in mouse models of disseminated aspergillosis, candidiasis, and cryptococcosis. Antimicrob. Agents Chemother. **41:** 2333–2338.
2. **Ascioglu, S., J. H. Rex, B. de Pauw, J. E. Bennett, J. Bille, F. Crokaert, et al.** 2002. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin. Infect. Dis. **34:**7–14.
3. **Bartizal, K., C. J. Gill, G. K. Abruzzo, A. M. Flattery, L. Kong, P. M. Scott, J. G. Smith, C. E. Leighton, A. Bouffard, J. F. Dropinski, and J. Balkovec.** 1997. In vitro preclinical evaluation studies with the echinocandin antifungal MK-0991 (L-743,872). Antimicrob. Agents Chemother. **41:**2326–2332.
4. **Betts, R. F., M. Nucci, D. Talwar, M. Gareca, F. Queiroz-Telles, R. J. Bedimo, R. Herbrecht, G. Ruiz-Palacios, J. H. Young, J. W. Baddley, K. M. Strohmaier, K. A. Tucker, A. F. Taylor, and N. A. Kartsonis.** 2009. A multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. Clin. Infect. Dis. **48:**1676–1684.
5. **Colombo, A. L., M. Nucci, B. J. Park, S. A. Nouer, B. Arthington-Skaggs, D. A. da Matta, D. Warnock, and J. Morgan.** 2006. Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. J. Clin. Microbiol. **44:**2816–2823.
6. **Cornely, O. A., M. Lasso, R. Betts, N. Klimko, J. Vazquez, G. Dobb, J. Velez, A. Williams-Diaz, J. Lipka, A. Taylor, C. Sable, and N. Kartsonis.** 2007. Caspofungin for the treatment of less common forms of invasive candidiasis. J. Antimicrob. Chemother. **60:**363–369.
7. **Hope, W., A. Morton, and D. P. Eisen.** 2002. Increase in prevalence of nosocomial non-*Candida albicans* candidaemia and the association of *Candida krusei* with fluconazole use. J. Hosp. Infect. **50:**56–65.
8. **Horn, D. L., D. Neofytos, E. J. Anaissie, J. A. Fishman, W. J. Steinbach, A. J. Olyaei, K. A. Marr, M. A. Pfaller, C.-H. Chang, and K. M. Webster.** 2009. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin. Infect. Dis. **48:**1695–1703.
9. **Kartsonis, N. A., A. Saah, C. J. Lipka, A. Taylor, and C. A. Sable.** 2004. Second-line therapy with caspofungin for mucosal or invasive candidiasis: results from the caspofungin compassionate-use study. J. Antimicrob. Chemother. **53:**878–881.
10. **Laverdiere, M., C. Restieri, and F. Habel.** 2002. Evaluation of the in vitro activity of caspofungin against bloodstream isolates of *Candida* species from cancer patients: comparison of Etest and NCCLS reference methods. Int. J. Antimicrob. Agents **20:**468–471.
11. **Moore, C. B., K. L. Oakley, and D. W. Denning.** 2001. In vitro activity of a new echinocandin, LY303366, and comparison with fluconazole, flucytosine and amphotericin B against *Candida* species. Clin. Microbiol. Infect. **7:** 11–16.
12. **Mora-Duarte, J., R. Betts, C. Rotstein, A. L. Colombo, L. Thompson-Moya, J. Smietana, R. Lupinacci, C. Sable, N. Kartsonis, and J. Perfect.** 2002. Comparison of caspofungin and amphotericin B for invasive candidiasis. N. Engl. J. Med. **347:**2020–2029.
13. **Pappas, P. G., C. A. Kauffman, D. Andes, D. K. Benjamin, Jr., T. F. Calandra, J. E. Edwards, Jr., S. G. Filler, J. F. Fisher, B.-J. Kullberg, L. Ostrosky-Zeichner, A. C. Reboli, J. H. Rex, T. J. Walsh, and J. D. Sobel.** 2009. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin. Infect. Dis. **48:**503–535.
14. **Pappas, P. G., C. M. Rotstein, R. F. Betts, M. Nucci, D. Talwar, J. J. De Waele, J. A. Vazquez, B. F. Dupont, D. L. Horn, L. Ostrosky-Zeichner, A. C. Reboli, B. Suh, R. Digumarti, C. Wu, L. L. Kovanda, L. J. Arnold, and D. N. Buell.** 2007. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin. Infect. Dis. **45:**883–893.
15. **Pfaller, M. A., L. Boyken, R. J. Hollis, S. A. Messer, S. Tendolkar, and D. J.**

Diekema. 2006. In vitro susceptibilities of Candida spp. to caspofungin: four years of global surveillance. J. Clin. Microbiol. **44:**760–763.
16. **Pfaller, M. A., and D. J. Diekema.** 2007. Epidemiology of invasive candidiasis: a persistent public health problem. Clin. Microbiol. Rev. **20:**133–163.
17. **Pfaller, M. A., D. J. Diekema, R. N. Jones, H. S. Sader, A. C. Fluit, R. J. Hollis, S. A. Messer, and the SENTRY Participant Group.** 2001. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program. J. Clin. Microbiol. **39:**3254–3259.
18. **Tawara, S., F. Ikeda, K. Maki, Y. Morishita, K. Otomo, N. Teratani, T. Goto, M. Tomishima, H. Ohki, A. Yamada, K. Kawabata, H. Takasugi, K. Sakane, H. Tanaka, F. Matsumoto, and S. Kuwahara.** 2000. In vitro activities of a new lipopeptide antifungal agent, FK463, against a variety of clinically important fungi. Antimicrob. Agents Chemother. **44:**57–62.
19. **Zaoutis, T. E., H. S. Jafri, L.-M. Huang, F. Locatelli, A. Barzilai, W. Ebell, W. J. Steinbach, J. Bradley, J. M. Lieberman, C.-C. Hsiao, N. Siebel, H.-J. Laws, M. Gamba, M. Petrecz, A. F. Taylor, K. M. Strohmaier, J. W. Chow, N. A. Kartsonis, and A. L. Ngai.** 2009. A prospective, multicenter study of caspofungin for the treatment of documented *Candida* or *Aspergillus* infections in pediatric patients. Pediatrics **123:**877–884.