MAJOR ARTICLE

A Randomized Double-Blind Study of Caspofungin versus Amphotericin for the Treatment of Candidal Esophagitis

Alvaro Villanueva,[1] Eduardo G. Arathoon,[2] Eduardo Gotuzzo,[3] Rayanne S. Berman,[4] Mark J. DiNubile,[4] and Carole A. Sable[4]

[1]Universidad de Antioquia, Medellin, Colombia; [2]Hospital General San Juan de Dios, San Juan de Dios, Guatemala; [3]Universidad Peruana Cayetano Heredia, Lima, Peru; and [4]Merck Research Laboratories, West Point, Pennsylvania

Caspofungin is a new broad-spectrum antifungal drug. A multicenter, double-blind, randomized trial was conducted to assess the efficacy, safety, and tolerability of caspofungin relative to amphotericin B in adults with endoscopically documented symptomatic *Candida* esophagitis. By use of a modified intent-to-treat analysis, endoscopically verified clinical success was achieved in 74% (95% confidence interval [CI], 59%–86%) and 89% (95% CI, 72%–98%) of patients receiving caspofungin at 50 and 70 mg/day, respectively, and in 63% (95% CI, 49%–76%) of patients given amphotericin B at 0.5 mg/kg/day. Therapy was stopped because of drug-related adverse events in 24% of patients in the amphotericin B group and 4% and 7%, respectively, for the caspofungin groups. This report provides the first demonstration of clinical utility for an echinocandin compound. Caspofungin appeared in this study to be as effective as and better tolerated than amphotericin B for the treatment of esophageal candidiasis.

Esophageal candidiasis is among the most common opportunistic infections in patients with advanced HIV infection [1, 2] and is often responsible for incapacitating morbidity in otherwise highly functional persons. Although initially responsive to treatment, these infections tend to recur [3]. Amphotericin B, despite its myriad toxicities, is generally regarded as the treatment of choice for symptomatic patients failing azole therapy [4]. Although some side effects of conventional amphotericin B can be ameliorated with the use of the newer lipid formulations, significant residual toxicities have limited their widespread use [5, 6].

Caspofungin (Cancidas; formerly MK-0991 and L-743,872) is a new semisynthetic lipopeptide drug of the echinocandin family exhibiting fungicidal activity in vitro against most *Candida* species [7–10]. Because of echinocandins' novel mechanism of action as inhibitors of fungal cell wall glucan synthesis [11, 12], cross-resistance would not be anticipated between these drugs and presently marketed antifungal drugs that affect cell membrane ergosterol [7, 8]. If found to be safe and effective, caspofungin could assume an important role in the treatment of azole-refractory *Candida* esophagitis as a generally well-tolerated alternative option to amphotericin B. Here we report the results of a double-blind randomized phase II study of caspofungin designed to estimate the efficacy, safety, and tolerability of 2 different doses of caspofungin relative to a standard dose of amphotericin B in the treatment of esophageal candidiasis.

METHODS

Patient selection. Symptomatic patients were eligible for inclusion into this study if they had endoscopically

Received 2 March 2001; revised 14 May 2001; electronically published 4 October 2001.

Presented in part: 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, 1 October 1997 (abstract LB-33).

The protocol was approved by the institutional review boards at each participating center. Informed consent was obtained from all enrolled patients.

Reprints or correspondence: Dr. Mark DiNubile, Merck Research Laboratories, PO Box 4, BL3-4, West Point, PA 19486 (mark_dinubile@merck.com).

Clinical Infectious Diseases 2001;33:1529–35
© 2001 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2001/3309-0013$03.00

and microbiologically documented *Candida* esophagitis. Patients were excluded if they had a history of allergy or serious reaction to echinocandins or amphotericin B or had another suspected cause of esophagitis in addition to *Candida* infection. Because this was a pilot study of a new class of antifungal agents, patients with possible fluconazole resistance (defined clinically as patients who had experienced a relapse of *Candida* esophagitis, had used fluconazole or ketoconazole for any reason in the prior 2 weeks, or had failure of therapy with fluconazole for a previous episode of *Candida* esophagitis any time in the past) were excluded. Women of childbearing potential or nursing mothers were entered in the study only if they were infected with HIV and the anticipated benefits were thought to outweigh any potential risks. Patients with >4 previous episodes of oropharyngeal or esophageal candidiasis, any elevation of serum creatinine level uncorrected by fluid repletion, increased liver enzyme levels >1.5–2 times the upper limit of the normal range, a significant blood dyscrasia, or frank esophageal ulcerations were ineligible.

Study design. The study was conducted at 7 sites located throughout Latin America. Patients were randomized to receive caspofungin at 50 or 70 mg or amphotericin B at 0.5 mg/kg daily for 14 days. Patients were prospectively stratified on entry on the basis of the endoscopic appearance of their esophageal lesions: Stratum I included patients with less severe disease defined by grade 0.5–2 lesions and stratum II contained patients with more extensive involvement characterized by grade 3–4 lesions (figure 1).

Caspofungin acetate was administered as a single daily dose of either 50 or 70 mg in 200 mL of 0.9% saline solution by iv infusion over a 1-h period followed by an infusion of saline solution at a negligible rate for the next hour. Amphotericin B deoxycholate at a dosage of 0.5 mg/kg/day diluted in 5% dextrose solution to yield a final concentration of 0.1 mg/mL was infused over at least 2 h. Before the initial treatment, a 1-mg dose of study drug was administered to all patients. Any recipient who experienced an adverse reaction during infusion of the test dose (such as chills, fever, and/or tachypnea) received premedication with acetaminophen and/or diphenhydramine before administration of study drug. Other allowable premedications included 25 mg of iv hydrocortisone and up to 500 mL of 0.9% saline solution. An unblinded nurse could extend the duration of the infusion to 4 h.

Outcome measures. Therapeutic responses were evaluated near the time of discontinuation of the study drug and at a follow-up visit 14 days after therapy. The primary outcome measure was prespecified as the combined clinical and endoscopic response assessed 14 days after completion of treatment. Patient responses were classified as "favorable" if and only if they had both complete resolution of all referable symptoms and either total clearing of esophageal lesions (grade 0) or a reduction in endoscopy score by ⩾2 grade levels. A favorable microbiological response required eradication of the pathogen(s) as evidenced by negative results of posttreatment stains and/or cultures for yeast.

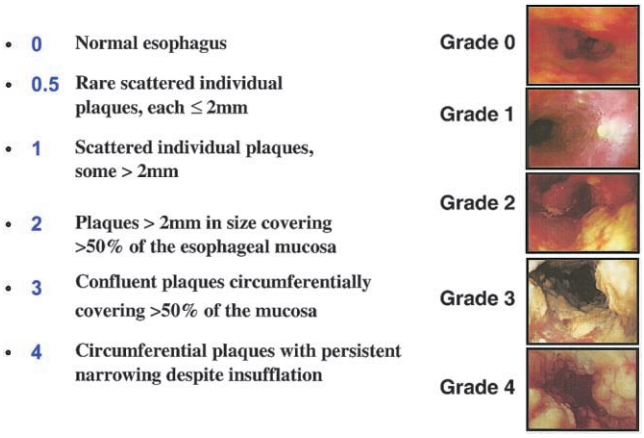

Figure 1. Representative photographs of increasingly extensive lesions of *Candida* esophagitis to illustrate grading system for esophageal candidiasis based on endoscopic appearance as used in this study.

All unintended clinical or laboratory changes temporally associated with the study drug were considered "adverse experiences." The on-site investigators determined the severity of an adverse event and its possible relation to the study drug. For the safety analysis, any adverse event judged to be even possibly caused by the study drug was tabulated as "drug-related."

Statistical analysis. This trial was intended as a dose-ranging estimation study. The modified intention-to-treat included all patients who had received at least 1 dose of study drug. The observed proportion of patients achieving a favorable outcome with 95% CIs based on a binomial distribution was calculated for clinical, endoscopic, combined, and microbiological responses. In the modified intention-to-treat analysis, when data were missing or indeterminate at a given time point, that outcome was regarded as unfavorable. Kaplan-Meier plots were generated for the time taking study drug from initiation of therapy to the resolution of all relevant symptoms. Fisher's exact test was used to compare the incidence of adverse events between any 2 of the treatment arms. For all comparisons, statistical significance was defined by $\alpha = .05$.

RESULTS

Characteristics of the study population. Baseline characteristics of the 128 patients are presented in table 1. For the 103 HIV-seropositive patients, the mean CD4 cell count was 84 cells/mm^3 (median, 60 cells/mm^3; range, 2–430 cells/mm^3). The frequency of HIV infection and the distribution of CD4 cell counts were not significantly different among the 3 treatment

Table 1. Selected baseline patient characteristics by treatment regimen in study of caspofungin versus amphotericin B treatment of *Candida* esophagitis.

Characteristic	Caspofungin, 50 mg	Caspofungin, 70 mg	Amphotericin B, 0.5 mg/kg	Total patients
No. of patients (age range, years)	46	28	54	128
Men	38 (21–59)	22 (22–65)	41 (22–66)	101 (21–66)
Women	8 (35–54)	6 (25–60)	13 (24–60)	27 (24–60)
Race/ethnicity				
Asian	0	1 (3.6)	0	1 (0.8)
Black	1 (2.2)	0	2 (3.7)	3 (2.3)
Caucasian	7 (15.2)	4 (14.3)	7 (13.0)	18 (14.1)
Hispanic	30 (65.2)	16 (57.1)	35 (64.8)	81 (63.3)
Mestizo	8 (17.4)	7 (25.0)	10 (18.5)	25 (19.5)
HIV-seropositive	39 (84.8)	20 (71.4)	44 (81.5)	103 (80.5)
CD4 cell count (mean, median)	83, 54	98, 59	79, 69[a]	84, 60[a]
Endoscopic stratum				
I	29 (63.0)	13 (46.4)	29 (53.7)	71 (55.5)
II	17 (37.0)	15 (53.6)	25 (46.3)	57 (44.5)
Endoscopy grade				
0.5	6 (13.0)	5 (17.9)	5 (9.3)	16 (12.5)
1	12 (26.1)	6 (21.4)	15 (27.8)	33 (25.8)
2	10 (21.7)	2 (7.1)	9 (16.7)	21 (16.4)
3	14 (30.4)	10 (35.7)	18 (33.3)	42 (32.8)
4	3 (6.5)	5 (17.9)	7 (13.0)	15 (11.7)
Missing	1 (2.2)[b]	0	0	1 (0.8)

NOTE. Data are no. (%) unless otherwise indicated.

[a] Because of missing CD4 cell counts for 1 patient in amphotericin group, mean and median were determined on basis of 43 patients in amphotericin group and 102 patients overall.

[b] Not assigned specific endoscopy grade but was placed in stratum I by investigator.

groups. The treatment groups were also comparable with respect to sex, age, racial origin, and clinical status. *Candida* species were recovered from 120 patients; 101 specimens (84%) yielded pure cultures of *Candida albicans,* with caspofungin MICs ranging from 0.06 to 2 μg/L as determined by the standard National Committee for Clinical Laboratory Standards protocol (M27-A). The remainder were mixed infections with *C. albicans* and *Candida* species other than *C. albicans* species (16 cases), mixed infections with multiple *Candida* species other than *C. albicans* (2 cases), and 1 infection with *Candida krusei* alone.

Approximately 50% and 75% of patients denied prior oropharyngeal and esophageal candidiasis, respectively. Fewer than 40% had previously been treated with azoles. The most common prior or ongoing antimicrobial therapies were trimethoprim-sulfamethoxazole and zidovudine, but fewer than half of the patients had ever received antiretroviral treatment. The frequency of antiretroviral treatment did not differ among the 3 treatment arms. Two patients received antifungal medications in the 14 days before enrollment, but exceptions to the protocol were made because the type and duration of treatment in these cases were deemed unlikely to affect the outcome of therapy with the study drug. One of these patients had received a single dose of ketoconazole 3 days before initiation of study drug (amphotericin B), and the other patient had taken nystatin by "swish and swallow" for 12 days, stopping 2 days before beginning study drug (caspofungin at 50 mg).

A total of 122 patients (95%) completed the study (defined as receiving any amount of study drug and completing all follow-up visits), and 108 (84%) completed therapy (receiving the full 14 days of study drug). Within each group, >80% of the patients completed 13–14 days of therapy. Most patients in each treatment group required other medications, but none received nonstudy antifungal therapy while taking the study drug. Nine patients (5 receiving caspofungin at 50 mg and 4 receiving amphotericin B) did take either ketoconazole or fluconazole during the 2-week follow-up period after discontinuation of the study drug because of a relapse of esophagitis or the diagnosis of another fungal infection. These patients were counted as having treatment failure in the modified intention-to-treat analysis.

Clinical, endoscopic, and microbiological results. All 3

Table 2. Proportion of patients with favorable combined clinical and endoscopic responses by baseline endoscopic stratum in modified intention-to-treat analysis of caspofungin versus amphotericin B for treatment of *Candida* esophagitis.

	Caspofungin, 50 mg/d		Caspofungin, 70 mg/d		Amphotericin B, 0.5 mg/kg/d	
Time of evaluation, endoscopic stratum	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
Conclusion of therapy, both strata	39 (85)	71–94	27 (96)	82–100	39 (72)	58–84
Stratum I	25 (86)	68–96	12 (92)	64–100	20 (69)	49–85
Stratum II	14 (82)	57–96	15 (100)	78–100	19 (76)	55–91
14-day posttherapy follow-up, both strata	34 (74)	59–86	25 (89)	72–98	34 (63)	49–76
Stratum I	22 (76)	57–90	11 (85)	55–98	19 (66)	46–82
Stratum II	12 (71)	44–90	14 (93)	68–100	15 (60)	39–79

NOTE. Data are no. of patients with a favorable combined response, followed by (%) responders. The 95% CIs are reported in terms of the (%) responders.

treatment regimens were highly effective in achieving favorable combined responses (table 2), although the response rate was highest for those receiving caspofungin at 70 mg and lowest for the amphotericin B group at both time points. The mean differences in response rates for caspofungin versus amphotericin B were 11% (95% CI, −9% to 32%) and 26% (95% CI, 4%–50%) for those receiving 50 and 70 mg, respectively, at the primary end point 2 weeks after discontinuation of therapy. Time to resolution of symptoms was not appreciably different for any of the treatment groups (figure 2). More than half the patients in each treatment arm had resolution of all symptoms by day 4 of therapy. Symptoms persisted in 3 (7%) of 46, 0 of 28, and 7 (13%) of 54 patients at the end of therapy in the groups receiving caspofungin at 50 mg, caspofungin at 70 mg, and amphotericin B, respectively. Analysis of all evaluable patients (per protocol) essentially mirrored the modified intention-to-treat analysis for combined response rates: 88%, 96%, and 78% at the end of therapy and 77%, 89%, and 68% 2 weeks later for patients receiving caspofungin at 50 mg, caspofungin at 70 mg, and amphotericin B, respectively.

The proportion of patients with endoscopic improvement was slightly higher in the caspofungin than amphotericin B groups. At the 14-day follow-up time point, 34 (74%) of 46 patients receiving caspofungin at 50 mg, 25 (89%) of 28 patients receiving caspofungin at 70 mg, and 34 (63%) of 54 patients receiving amphotericin B had a marked reduction in endoscopic grade. There was no discernible impact of pretreatment strata on posttherapy endoscopic results, even within treatment groups, because the response rates were similar regardless of baseline endoscopic grade.

Caspofungin recipients had a modestly higher rate of fungal eradication than did amphotericin B recipients (table 3). Two weeks after therapy was stopped, *C. albicans* was not recovered from 29 (71%) of 41 patients, 22 (85%) of 26 patients, and 30 (60%) of 50 patients in the groups receiving caspofungin at 50 mg, caspofungin at 70 mg, and amphotericin B, respectively, from whom it was originally isolated. The corresponding eradication rates for *Candida* species other than *C. albicans* were 64%, 71%, and 40%, but this group contained only 19 patients (of which 16 had concomitant infection with *C. albicans*).

Drug safety and tolerability. Patients receiving amphotericin B had a significantly higher incidence of drug-related clinical adverse events than did patients receiving caspofungin: 61% among those receiving caspofungin at 50 mg, 68% among those receiving caspofungin at 70 mg, and 93% among those receiving amphotericin B ($P < .01$ for each caspofungin study arm vs. the amphotericin B group). There was only 1 serious drug-related clinical adverse experience, which occurred in the amphotericin B group. The most frequently reported drug-related clinical adverse events in the caspofungin groups were fever, phlebitis, headache, and rash (figure 3*A*). Significantly fewer patients in the study arm receiving caspofungin at 50 mg than in the amphotericin B group experienced drug-related fever ($P < .01$), chills ($P < .01$), or nausea ($P < .05$); significantly

Table 3. Proportion of patients with microbiological eradication of *Candida* in modified intention-to-treat analysis of caspofungin versus amphotericin B for treatment of *Candida* esophagitis.

	Caspofungin, 50 mg		Caspofungin, 70 mg		Amphotericin B, 0.5 mg/kg	
Time of evaluation	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
Conclusion of therapy	37 (80)	66–91	27 (96)	82–100	39 (72)	58–84
14-day posttherapy follow-up	35 (76)	61–87	25 (89)	72–98	33 (61)	47–74

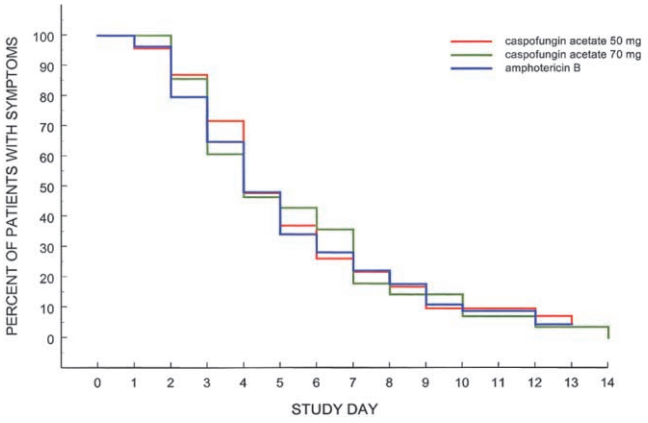

Figure 2. Proportion of patients with persisting symptoms of *Candida* esophagitis as function of time undergoing treatment with caspofungin or amphotericin B. Survival analysis was used to calculate Kaplan-Meier estimates for time from initiation of therapy to full resolution of esophageal symptoms. Kaplan-Meier estimates reflect probability of having symptoms persist beyond given day of treatment. Probability is conditional on number of patients who remain at risk (not yet symptom-free) on each day of study therapy.

fewer patients in the study arm receiving caspofungin at 70 mg than in the amphotericin B group developed fever ($P < .05$) or chills ($P < .01$). Five clinical adverse events resulted in discontinuation of therapy: 2 occurred in the caspofungin groups (1 deemed drug-related) and 3 were in the amphotericin B group (2 deemed drug-related, 1 being considered serious). The sole caspofungin-related clinical adverse event requiring discontinuation of therapy was a generalized rash on day 10 of therapy. There were 6 deaths during the study period, none of which were thought to be drug-related.

Infusion site toxicity was particularly scrutinized for the 65 patients receiving study drug through peripheral iv catheters. Infusions were rated as well-tolerated or moderately well-tolerated in the large majority of this subset of patients, with no important differences among treatment groups. Local tolerability was judged as "poor" in 0 of 22, 1 (7%) of 15, and 2 (7%) of 28 patients receiving caspofungin at 50 mg, caspofungin at 70 mg, and amphotericin B, respectively.

More patients treated with amphotericin B (91%) than with caspofungin (61% and 32% for the groups receiving 50 and 70 mg, respectively) developed drug-related laboratory abnormalities ($P < .01$ for individual comparisons vs. amphotericin B). The most common drug-related laboratory abnormalities in the caspofungin groups were hypoalbuminemia and increased serum levels of alkaline phosphatase and aminotransferase enzymes (figure 3*B*). Drug-related decreases in hemoglobin concentrations were less common in the caspofungin groups than in the amphotericin B group ($P < .01$ for both comparisons vs. amphotericin B). Drug-related hypokalemia occurred in a greater proportion of patients treated with amphotericin B than with either caspofungin dose ($P < .05$ only for caspofungin at 50 mg vs. amphotericin B).

Drug-related increases in blood urea nitrogen levels were observed in 15% of patients receiving amphotericin B but in none of the patients treated with caspofungin at 50 mg ($P < .01$) or 70 mg ($P < .05$). Likewise, serum creatinine concentrations increased in 16 patients (30%) in the amphotericin B group but in only 1 caspofungin patient ($P < .01$ for comparisons vs. amphotericin B). Serum creatinine levels more than doubled in 4 amphotericin B patients (7%), exceeding twice the upper limit of the normal range. The single patient with probable caspofungin-related nephrotoxicity was a 65-year-old man whose baseline serum creatinine concentration of 1.6 mg/dL peaked at 2.2 mg/dL after 4 days of therapy with 70 mg/day. No patient required dialysis. Study drug was discontinued in 3 patients in the caspofungin groups (4%) and 11 in the amphotericin B group (20%) because of drug-related laboratory abnormalities ($P < .05$ only for caspofungin at 50 mg vs. amphotericin B).

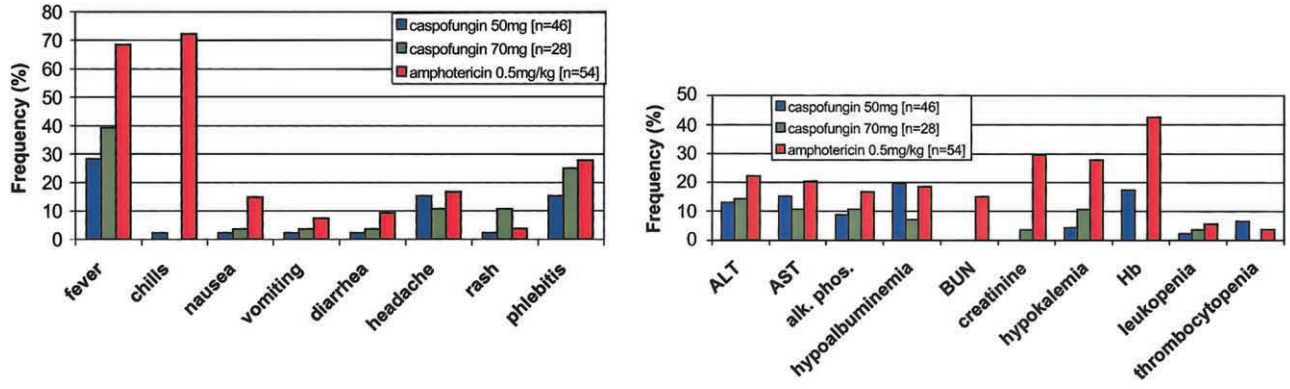

Figure 3. Percentages of patients with drug-related clinical *(left)* and laboratory *(right)* adverse experiences in study of caspofungin versus amphotericin B for treatment of *Candida* esophagitis. alk. phos., elevated alkaline phosphatase level; ALT, elevated alanine aminotransferase level; AST, elevated aspartate aminotransferase level; BUN, elevated blood urea nitrogen level; Hb, decreased hemoglobin concentration.

DISCUSSION

This report describes the first comparative trial of an echinocandin drug in the treatment of human fungal infections [13]. The primary objectives of our study were to estimate the efficacy, safety, and tolerability of 2 doses of caspofungin relative to a standard dose of conventional amphotericin B in patients with documented *Candida* esophagitis. A daily iv infusion of 50 or 70 mg of caspofungin appeared to be at least as effective as amphotericin B at 0.5 mg/kg/day in the treatment of *Candida* esophagitis in this population, as assessed by the response of symptoms and/or esophageal lesions in a modified intention-to-treat analysis. The time to symptom resolution was similar for the 3 treatment groups (median, 4 days). At each time point, a modestly higher proportion of patients in the caspofungin groups than in the amphotericin B group achieved a favorable outcome whether measured clinically, endoscopically, or by culture results. The success rates 2 weeks after discontinuation of therapy were expectedly lower for all regimens, because these included early relapses and reinfections as treatment failures. Further studies are needed to establish the precise efficacy of caspofungin relative to other antifungal agents for the treatment of *Candida* esophagitis.

Caspofungin was generally well tolerated at both doses tested, and no serious drug-related adverse events were identified. The clinical and laboratory side effects characteristically associated with amphotericin B (including fever and chills, decreases in hemoglobin concentration, hypokalemia, and increases in serum creatinine levels) occurred significantly less often with caspofungin. Because there was no apparent increased toxicity but some suggestion of enhanced efficacy with the modest dose escalation of caspofungin examined here, higher doses of caspofungin might enhance the risk-benefit ratio for certain infections; however, optimal dosing will likely depend on the specific indication and require further investigation of the safety and efficacy of doses exceeding 70 mg/day.

This study was designed as a "proof of concept" trial for a novel class of antifungal compounds not previously evaluated in patients. As is commonplace in early phase II protocols, stringent inclusion criteria coupled with prerandomization selection bias may define a subpopulation for study purposes that does not accurately reflect the larger population encountered in clinical practice [14–16]. In this regard, patients with frequently recurring candidal infections heavily treated with azoles in the past were excluded from the present study; thus, patients with azole-resistant infections, a potentially important therapeutic niche for the echinocandins [8–12, 17–24], were underrepresented in this particular comparative trial. Persons with significant preexisting abnormalities of liver and renal function were also excluded from the present study. Given the predictable nephrotoxicity of amphotericin B therapy [25], patients with renal insufficiency might be especially ideal candidates for caspofungin treatment when azole therapy fails. However, this study cannot directly address issues of preexistent renal disease.

Caspofungin appeared to be both effective and generally well-tolerated therapy for *Candida* esophagitis in the largely HIV-infected population enrolled in this study, but the protocol was not designed to show therapeutic noninferiority with amphotericin B. As a result of restrictive inclusion criteria, extrapolation of the findings from this relatively small phase II trial to the population at large must be done judiciously. Uncomplicated cases of oropharyngeal and esophageal candidiasis are routinely treated with oral fluconazole [4]. Not unexpectedly, cross-resistance to all currently available azole compounds is emerging as problem in many parts of the world [17–19, 21, 22, 26–30]. The primary role of caspofungin in clinical practice will likely be limited to subsets of patients who either cannot tolerate medications per orum or whose infection has become refractory to orally administered therapy [23, 31–35]. If further experience confirms our preliminary observations, caspofungin may provide an equally effective but less toxic alternative treatment option to conventional amphotericin B therapy for HIV-infected patients with azole-refractory *Candida* esophagitis. Its ultimate role in clinical practice remains to be determined.

Acknowledgments

We recognize and appreciate the contributions of G. Turcato (São Paulo, Brazil), E. Rojas (Bogota, Columbia), L. Noriega (Santiago, Chile), and C. Rivera (Mexico City) in enrolling patients. We also thank Jeffery Chodakewitz for his insightful suggestions and Joann DiLullo for her expert assistance in manuscript preparation.

References

1. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus–associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. Clin Infect Dis **2000**; 30(Suppl 1):55–14.
2. Centers for Disease Control and Prevention. Guidelines for national human immunodeficiency virus case surveillance, including monitoring for human immunodeficiency virus infection and acquired immunodeficiency syndrome. MMWR Morb Mortal Wkly Rep **1999**: 48(RR-13):1–27, 29–31.
3. Sangeorzan JA, Bradley SF, He X, et al. Epidemiology of oral candidiasis in HIV-infected patients: colonization, infection, treatment, and emergence of fluconazole resistance. Am J Med **1994**; 97:339–46.
4. Rex JH, Walsh, TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Clin Infect Dis **2000**; 30:662–78.
5. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis **1998**; 26:1383–96.
6. Noskin GA, Pietrelli L, Coffey G, Gurwith M, Liang LJ. Amphotericin B colloidal dispersion for the treatment of candidemia in immunocompromised patients. Clin Infect Dis **1998**; 26:461–7.
7. Martinex-Suarez JV, Rodriguez-Tudela JL. In vitro activities of semisynthetic pneumocandin L-733,560 against fluconazole-resistant and -

susceptible *Candida albicans* isolates. Antimicrob Agents Chemother **1996**; 40:1277–9.
8. Vazquez JA, Lynch M, Boikov D, Sobel JD. In vitro activity of a new pneumocandin antifungal, L-743,872, against azole-susceptible and -resistant *Candida* species. Antimicrob Agents Chemother **1997**; 41: 1612–4.
9. Barchiesi F, Schimizzi AM, Fothergill AW, et al. In vitro activity of the new echinocandin antifungal, MK-0991, against common and uncommon clinical isolates of *Candida* species. Eur J Clin Microbiol Infect Dis **1999**; 18:302–4.
10. Pfaller MA, Messer SA, Gee S, et al. In vitro susceptibilities of *Candida dubliniensis* isolates tested against the new triazole and echinocandin antifungal agents. J Clin Microbiol **1999**; 37:870–2.
11. Andriole VT. Current and future antifungal therapy: new targets for antifungal agents. J Antimicrob Chemother **1999**; 44:151–62.
12. Georgopapadakou NH, Walsh TJ. Antifungal agents: chemotherapeutic targets and immunologic strategies. Antimicrob Agents Chemother **1996**; 40:279–91.
13. Sable CA, Villaneuva A, Arathoon E, et al. A randomized, double-blind, multicenter trial of MK-0991 (L-743872) versus amphotericin B (AMB) in the treatment of *Candida* esophagitis in adults [abstract LB-33]. In: Program and abstracts of the 37th Interscience Conference on Antimicrobial Agents Chemotherapy (Toronto). Washington, DC: American Society for Microbiology, **1997**.
14. Horwitz RI, Viscoli CM, Clemens JD, Sadock RT. Developing improved observational methods for evaluating therapeutic effectiveness. Am J Med **1990**; 89:630–8.
15. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? N Engl J Med **2000**; 342:1907–9.
16. Shapiro SH, Weijer C, Freedman B. Reporting the study populations of clinical trials. Clear transmission or static on the line? J Clin Epidemiol **2000**; 53:973–9.
17. Martinez-Suarez JV, Rodriguez-Tudela JL. Patterns of in vitro activity of itraconazole and imidazole antifungal agents against *Candida albicans* with decreased susceptibility to fluconazole from Spain. Antimicrob Agents Chemother **1995**; 39:1512–6.
18. Revankar SG, Kirkpatrick WR, McAtee RK, et al. Detection and significance of fluconazole resistance in oropharyngeal candidiasis in human immunodeficiency virus–infected patients. J Infect Dis **1996**; 174: 821–7.
19. Laguna F, Rodriguez-Tudela JL, Martinez-Suarez JV, et al. Patterns of fluconazole susceptibility in isolates from human immunodeficiency virus–infected patients with oropharyngeal candidiasis due to *Candida albicans.* Clin Infect Dis **1997**; 24:124–30.
20. Walsh TJ, Gonzalez CE, Piscitelli S, et al. Correlation between in vitro and in vivo antifungal activities in experimental fluconazole-resistant oropharyngeal and esophageal candidiasis. J Clin Microbiol **2000**; 38: 2369–73.
21. Rex JH, Pfaller MA, Galgiani JN. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro–in vivo correlation data for fluconazole, itraconazole, and *Candida* infections. Clin Infect Dis **1997**; 24:235–47.
22. Landman D, Saurina G, Quale JM. Failure of all antifungal therapy for infection due to *Candida albicans:* a new AIDS-related problem? Clin Infect Dis **1998**; 26:183–4.
23. Bachman SP, Pera S, Kirkpatrick WR, Patterson TF, Lopez-Ribot JL. In vitro activity of Cancidas (MK-0991) against *Candida albicans* clinical isolates displaying different mechanisms of azole resistance [abstract 196]. In: Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **2000**:352.
24. Hicks PS, Dorso KL, Gerckens LS, et al. Comparative in vitro susceptibility of clinical trial isolates to the echinocandin antifungal caspofungin (Cancidas, MK-0991) [abstract 193]. In: Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **2000**: 351.
25. Patel R. Antifungal agents. Part I: amphotericin B preparations and flucytosine. Mayo Clin Proc **1998**; 73:1205–25.
26. Masia CM, Guiterrez RF, Ortiz de la Tabla DV, et al. Determinants for the development of oropharyngeal colonization or infection by fluconazole-resistant *Candida* strains in HIV-infected patients. Eur J Clin Microbiol Infect Dis **2000**; 19:593–601.
27. Ruhnke M, Eigler A, Tennagen I, Geiseler B, Engelmann E, Tratumann M. Emergence of fluconazole-resistant strains of *Candida albicans* in patients with recurrent oropharyngeal candidosis and human immunodeficiency virus infection. J Clin Microbiol **1994**; 32:2092–8.
28. Newman SL, Flanigan TP, Fisher A, Rinaldi MG, Stein M, Vigilante K. Clinically significant mucosal candidiasis resistant to fluconazole treatment in patients with AIDS. Clin Infect Dis **1994**; 19:684–6.
29. Revankar SG, Dib OP, Kirkpatrick WR, et al. Clinical evaluation and microbiology of oropharyngeal infection due to fluconazole-resistant *Candida* in human immunodeficiency virus–infected patients. Clin Infect Dis **1998**; 26:960–3.
30. Martins MD, Lozano-Chiu M, Rex JH. Point prevalence of oropharyngeal carriage of fluconazole-resistant *Candida* in human immunodeficiency virus–infected patients. Clin Infect Dis **1997**; 25:843–6.
31. Krishnarao TV, Galgiani JN. Comparison of the in vitro activities of the echinocandin LY303366, the pneumocandin MK-0991, and fluconazole against *Candida* species and *Cryptococcus neoformans.* Antimicrob Agents Chemother **1997**; 41:1957–60.
32. Moran GP, Sullivan DJ, Henman MC, et al. Antifungal drug susceptibilities of oral *Candida dubliniensis* isolates from human immunodeficiency virus (HIV)-infected and non–HIV-infected subjects and generation of stable fluconazole-resistant derivatives in vitro. Antimicrob Agents Chemother **1997**; 41:617–23.
33. Schorling SR, Kortinga HC, Froschb M, Muhlschlegel FA. The role of *Candida dubliniensis* in oral candidiasis in human immunodeficiency virus–infected individuals. Crit Rev Microbiol **2000**; 26:59–68.
34. Rex J, Nelson PW, Nelson PW, Paetznick VL, et al. Optimizing the correlation between results of testing in vitro and therapeutic outcome in vivo for fluconazole by testing critical isolates in a murine model of invasive candidiasis. Antimicrob Agents Chemother **1998**; 42:129–34.
35. Graybill JR, Bocanegra R, Luther M, Fothergill A, Rinaldi MJ. Treatment of murine *Candida krusei* or *Candida glabrata* infection with L-743,872. Antimicrob Agents Chemother **1997**; 41:1937–9.