

A Randomized, Double-Blind Trial of Anidulafungin versus Fluconazole for the Treatment of Esophageal Candidiasis

David S. Krause,¹ A. E. Simjee,³ Christo van Rensburg,⁴ Johann Viljoen,⁵ Thomas J. Walsh,² Beth P. Goldstein,¹ Michele Wible,¹ and Timothy Henkel¹

¹Vicuron Pharmaceuticals, King of Prussia, Pennsylvania; ²Infectious Diseases Section, National Cancer Institute, Bethesda, Maryland; and ³Nelson R. Mandela School of Medicine and King Edward VIII Hospital, Durban, ⁴Tigerberg Hospital, Cape Town, and ⁵Bloemfontein, Republic of South Africa

(See the editorial commentary by Darouiche on pages 850–2 and the article by de Wet et al. on pages 842–9)

Anidulafungin is a novel antifungal agent of the echinocandin class. This randomized, double-blind, double-dummy study compared the efficacy and safety of intravenous anidulafungin to that of oral fluconazole in 601 patients with endoscopically and microbiologically documented esophageal candidiasis. Patients received intravenous anidulafungin (100 mg on day 1, followed by 50 mg per day) or oral fluconazole (200 mg on day 1, followed by 100 mg per day) for 7 days beyond resolution of symptoms (range, 14–21 days). At the end of therapy, the rate of endoscopic success for anidulafungin (242 [97.2%] of 249 treated patients) was found to be statistically noninferior to that for fluconazole (252 [98.8%] of 255 treated patients; treatment difference, –1.6%; 95% confidence interval, –4.1 to 0.8). The safety profile of anidulafungin was similar to that of fluconazole; treatment-related adverse events occurred in 9.3% and 12.0% of patients, respectively. Laboratory parameters were similar between treatment arms. Anidulafungin is as safe and effective as oral fluconazole for the treatment of esophageal candidiasis, when assessed at the completion of therapy.

The rate of fungal infections has increased in recent decades for a number of reasons: acquired immunosuppression associated with HIV infection, iatrogenic immunosuppression caused by treatment of cancer and the prevention of transplanted-organ rejection, widespread use of broad-spectrum antibiotics and corticosteroids, and use of increasingly invasive surgical techniques and technologies in compromised hosts. Mucocutaneous candidiasis may be the first sign of HIV infection. In individuals with advanced HIV disease, esophageal candidiasis, which is characterized by odynophagia, dysphagia, and retrosternal chest pain, is as common as oropharyngeal candidiasis [1] and may be

responsible for incapacitating illness [2]. Esophageal candidiasis may be asymptomatic or may cause substantial morbidity and discomfort and serve as a focus of invasive disease. It may arise as a contiguous extension of oropharyngeal infection, or it may arise de novo, without concomitant thrush [3]. *Candida albicans* is the most often implicated species in esophageal candidiasis; it consistently accounts for $\geq 90\%$ of baseline isolates [3–7]. Because patients may have inability to swallow, parenteral therapy may be required [4].

Prompt therapy with a systemic agent is indicated [4]. Unfortunately, almost all patients with AIDS and successfully treated esophageal candidiasis will develop a recurrence in the absence of immune reconstitution, usually within 2–3 months [8]. Therefore, chronic suppressive prophylaxis or intermittent therapy is the current standard of care after an initial course of treatment of esophageal candidiasis [9].

Anidulafungin, an echinocandin, is a novel drug in development for the treatment of fungal infections.

Received 9 December 2003; accepted 11 March 2004; electronically published 27 August 2004.

Reprints or correspondence: David S. Krause, Vicuron Pharmaceuticals, 455 S. Gulph Rd., Ste. 310, King of Prussia, PA 19406 (dkrause@vicuron.com).

Clinical Infectious Diseases 2004;39:770–5

© 2004 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2004/3906-0003\$15.00

Members of this class are noncompetitive inhibitors of (1,3)-beta-D-glucan synthase, an enzyme required for the synthesis of glucan (the polysaccharide that constitutes the major portion of the cell wall of many pathogenic fungi). Glucan synthase is not found in mammalian cells and thus represents an ideal target for antifungal agents. Consistent with its mechanism of action (interference with cell wall synthesis), anidulafungin is fungicidal for *Candida* species [10, 11]. The spectrum of activity of anidulafungin includes *Candida* (all species tested, including those strains that are resistant to fluconazole and amphotericin) and *Aspergillus* species [11–19]. When administered parenterally, anidulafungin is highly efficacious in animal models of esophageal and disseminated candidiasis, including immunosuppressed and immunocompetent mice and rabbits [20–23].

Clinical studies have shown that the half-life of anidulafungin is ~1 day and reflects slow chemical degradation [24]. The same slow chemical degradation occurs in vitro at physiologic pH and temperatures. Anidulafungin is not metabolized by the liver, is not eliminated in the urine, and is not a substrate, inhibitor, or inducer of the enzymes in the cytochrome P450 system. No dosage adjustments appear to be required based on sex, weight, age, ethnicity, or disease status or for patients with any degree of hepatic or renal insufficiency or who are receiving concomitant medications [25]. In a phase 2 dose-ranging study, anidulafungin was well tolerated and efficacious in patients with invasive candidiasis [26]. The present study was conducted to compare the efficacy and safety of intravenous anidulafungin (50 mg q.d.) with that of oral fluconazole (100 mg q.d.) for the treatment of patients with esophageal candidiasis.

METHODS

Patients. This study was conducted in accordance with the Declaration of Helsinki (1996), the International Conference on Harmonization Guideline for Good Clinical Practice (2000), and applicable local regulations. An independent ethics committee or institutional review board for each site approved the study, and written informed consent was obtained from each patient before study participation.

Male or female patients (age, 18–65 years) who had esophageal candidiasis diagnosed and who had a predisposing risk factor for fungal infection (including antibiotic, corticosteroid, or radiation therapy; myelosuppression; malnutrition; or AIDS) were eligible for the study. The diagnosis of esophageal candidiasis was based on endoscopic findings, clinical symptoms (odynophagia, dysphagia, and/or retrosternal pain), biopsy exclusion of herpes simplex virus and cytomegalovirus infection, and mycological findings (isolation of *Candida* species and/or evidence of yeast on microscopy).

Patients with evidence of systemic fungal infection, ulcerative esophageal lesions, or known hypersensitivity to anidulafungin, its excipients, or other echinocandins were excluded from the

study. Other major exclusion criteria were receipt of systemic antifungals in the week before study enrollment, a life expectancy of <2 months, serum aminotransferase or total serum bilirubin levels of >3 times the upper limit of the normal range, a serum creatinine level of >2.5 times the upper limit of the normal range, an absolute neutrophil count of <500 neutrophils/mm³, or a platelet count of <60,000 platelets/mm³.

Study design and treatment. The trial was a multicenter, randomized, double-blind, double-dummy, noninferiority study. Patients were randomized either to receive intravenous anidulafungin (a 100-mg loading dose on day 1, followed by 50 mg q.d.) and oral placebo (given daily) or to receive intravenous placebo (given daily; i.e., anidulafungin vehicle without active drug) and oral fluconazole (a 200-mg loading dose on day 1, followed by 100 mg q.d.). Intravenous loading and daily maintenance doses were administered over 90- and 45-min periods, respectively. Therapy was to be continued for 7 days after resolution of symptoms but not for <14 or >21 days in total.

Endoscopic, clinical and mycological assessments (including culture and speciation of *Candida* isolates) were performed at baseline, at end of therapy, and at a follow-up visit that occurred 2 weeks after the end of treatment. In the event of clinical recurrence, the follow-up assessment was conducted earlier. Endoscopic appearance of the esophageal mucosa was graded as follows: 0, normal esophageal mucosa; 1, individual plaques, each ≤2 mm in diameter; 2, individual plaques >2 mm in diameter; or 3, confluent plaques and/or increased friability of mucosa [27]. The severity of odynophagia and/or dysphagia and retrosternal pain was assessed daily and classified as absent, mild, moderate, or severe. Investigator sites were provided with standard definitions of symptoms. For example, mild dysphagia was defined as “discomfort on swallowing solids but little discomfort on swallowing liquids.” At screening, presumptive microscopic diagnosis of *Candida* infection was made by demonstration of yeast and/or hyphal forms in brushings or biopsies of plaque smears or exudates using Gram, periodic acid-Schiff, or silver staining. In addition, endoscopic material was obtained for culture for identification and susceptibility testing. *Candida* isolates were sent to a central laboratory for speciation and determination of antifungal MICs (M. Pfaller; University of Iowa) [28].

Efficacy analyses. The prospectively defined primary analysis of efficacy was a comparison of endoscopic response in evaluable (per-protocol) patients at the end of therapy. Endoscopic response was scored as a success if patients had complete resolution of esophageal lesions (i.e., cure; grade 0) or a decrease of ≥1 grade from the baseline level (i.e., improvement).

Secondary efficacy analyses included clinical response (a successful response was defined as the absence or improvement of symptoms, compared with baseline) and mycological re-

Table 1. Selected demographic and baseline characteristics of study participants.

Characteristic	Intravenous anidulafungin group (n = 300)	Oral fluconazole group (n = 301)
Age, years		
Mean ± SD	37.5 ± 10.4	37.0 ± 9.6
Range	18–69	18–65
Sex		
Male	127 (42.3)	145 (48.2)
Female	173 (57.7)	156 (51.8)
Ethnicity ^a		
White	44 (14.7)	41 (13.6)
Black	146 (48.7)	144 (47.8)
Hispanic	1 (0.3)	2 (0.7)
Asian	46 (15.3)	46 (15.3)
Other	62 (20.7)	68 (15.3)
AIDS	223 (74.3)	233 (77.4)
Endoscopy grade		
1	61 (20.3)	53 (17.6)
2	112 (37.3)	101 (33.6)
3	127 (42.3)	147 (48.8)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

^a Ethnic information for 1 patient in the anidulafungin group is missing.

sponse (a successful response was defined as proven or presumed eradication of *Candida* species present at baseline). All responses, including endoscopic response, were evaluated for the intent-to-treat and evaluable populations at the end of therapy and at the follow-up visit. In addition, the time to resolution of symptoms and the duration of therapy were determined.

The evaluable population consisted of patients who completed ≥10 days of therapy, had an end-of-therapy assessment with a clinical outcome other than indeterminate, had an endoscopic result recorded at the end of therapy, and did not have any protocol violations up to the end of therapy visit that impacted the assessment of efficacy. All safety analyses were performed with the intent-to-treat population, which consisted of all randomized patients who received ≥1 dose of study drug.

Safety. Safety assessments (hematological analysis, chemistry, urinalysis, determination of vital signs, physical examination, and 12-lead electrocardiography) were performed throughout the study. Adverse events were assessed daily, at the end of therapy, and at the follow-up visit. Treatment-related adverse events were those considered by the investigator to be possibly or probably related to use of study medication or those with an unknown relationship to use of study medication.

Statistical analysis. For the primary and secondary analyses, Pearson's χ^2 test was used to compare the proportion of patients with success in the anidulafungin and fluconazole

treatment arms. For testing the hypothesis, the 2-sided 95% CI for the difference in endoscopic success rates (rate for the anidulafungin minus rate for the fluconazole arm) at the end of therapy was calculated. Noninferiority was concluded if the lower bound of the 95% CI was greater than -10%. Time to resolution of symptoms was summarized using Kaplan-Meier estimates. Duration of therapy was compared between the 2 treatment arms using Student's *t* test.

RESULTS

Patients. The trial was conducted during the period of April 2001 through October 2002. Patients were enrolled from sites in the Republic of South Africa (453 patients), Thailand (91 patients), Argentina (51 patients), and the United States (6 patients). Of 601 randomized patients, 300 received anidulafungin and 301 received fluconazole. Demographic and baseline characteristics were comparable between treatment groups, with no statistically significant differences (table 1). Most patients had AIDS, although few patients were receiving antiretroviral drugs at baseline (7 patients in the fluconazole arm and 3 patients in the anidulafungin arm). However, more patients in the fluconazole arm than in the anidulafungin arm started receiving antiretroviral therapy during the course of antifungal treatment (58 vs. 26 patients). All patients received a diagnosis of esophageal candidiasis. The groups were well matched with regard to prior antifungal use (mostly nystatin); however, prior use of fluconazole was rare: only 9 patients (4 in the anidulafungin arm and 5 in the fluconazole arm) reported such prior use. The disease characteristics of esophageal candidiasis assessed at baseline were similar between the treatment groups. Overall, 97.7% of patients in the anidulafungin group and 97.0% of patients in the fluconazole group experienced odynophagia/dysphagia, and 79.7% and 76.7% of the anidulafungin- and fluconazole-treated patients experienced retrosternal pain, respectively. The highest proportion of patients had severe (grade 3) endoscopy grades (table 1).

Mycological diagnosis was confirmed by microscopy for

Table 2. Endoscopic responses at the completion of intravenous anidulafungin or oral fluconazole therapy.

Endoscopic response	No. (%) of patients		Treatment difference, % (95% CI)
	Intravenous anidulafungin group (n = 249)	Oral fluconazole group (n = 255)	
Success			
All	242 (97.2)	252 (98.8)	-1.6 (-4.1 to 0.8)
Cure	219 (88.0)	238 (93.3)	...
Improvement	23 (9.2)	14 (5.5)	...
Failure	7 (2.8)	3 (1.2)	...

Table 3. Clinical and mycological success at the completion of intravenous anidulafungin or oral fluconazole therapy.

Response	No. of patients with response/no. of patients with data (%)	
	Intravenous anidulafungin recipients	Oral fluconazole recipients
Clinical success	246/249 (98.8)	254/255 (99.6)
Mycological success	156/180 (86.7)	169/186 (90.9)

98.7% of patients in the anidulafungin group and for 97.7% of patients in the fluconazole group. Of the 442 patients with culture-confirmed esophageal candidiasis, 401 had *C. albicans* as the sole baseline pathogen, 7 had *Candida glabrata*, 1 had *Candida tropicalis*, and 9 had an unspiciated *Candida* isolate. The remainder had coinfection with 2 *Candida* isolates.

Efficacy analyses. A total of 504 patients (83.8%) complied with the protocol and were evaluable for efficacy analyses at the end of therapy. Of these, 242 (97.2%) of 249 patients in the anidulafungin group had endoscopic success (i.e., cure or improvement), compared with 252 (98.8%) of 255 patients in the fluconazole group (table 2). The treatment difference of -1.6% had an associated 95% CI of -4.1 to 0.8, thus meeting the predefined criteria for noninferiority. In both groups, most endoscopic successes were cures (i.e., an endoscopic grade of 0; 88.0% in the anidulafungin and 93.3% in the fluconazole group). An intent-to-treat analysis of endoscopic response at the end of therapy showed similar success rates for anidulafungin (86.7%) and fluconazole (88.0%) (95% CI, -6.7 to 3.9).

For both treatment arms, the clinical (i.e., symptomatic) success rate was high (table 3). Almost all clinical successes were cures (97.2% and 98.0% for the anidulafungin and fluconazole arms, respectively). Time to resolution of symptoms was also similar, as was the mean duration of therapy (table 4). Results of the intent-to-treat analysis were similar to the findings of the analysis of evaluable patients. Mycological success was achieved in the majority of evaluable patients at the end of therapy in both arms (table 3).

At the 2-week follow-up visit, 462 patients underwent endoscopy and were otherwise evaluable for a follow-up evaluation. Of these, 150 (64.4%) of 233 patients who received anidulafungin and 205 (89.5%) of 229 patients who received fluconazole had sustained endoscopic success (95% CI, -32.5% to -17.8%; $P < .001$).

Safety evaluation. Overall, 237 (79.0%) of 300 anidulafungin-treated patients and 226 (75.1%) of 301 fluconazole-treated patients reported ≥ 1 adverse event. Treatment-related (per investigator attribution) adverse events were reported by 28 (9.3%) and 36 (12.0%) patients in the anidulafungin and fluconazole groups, respectively. No drug-related adverse events

occurred in $\geq 2\%$ of patients treated with anidulafungin. The most common drug-related adverse events are shown in table 5. One patient in the anidulafungin group experienced a subjective sensation of "flushing" associated with the infusion. No patient experienced hypotension, wheezing, or anaphylaxis.

The number of serious adverse events related to or possibly related to use of a study drug was low in both treatment arms (2 serious events in each). In the anidulafungin arm, the events were a maculopapular rash in one patient and multisystem organ failure in the other. The latter patient had multiple comorbid conditions, including cor pulmonale with right-side congestive heart failure, bronchiectasis, and recently treated tuberculosis. The patient died on study day 3 of a presumed cardiorespiratory arrest attributed to his underlying illness. The serious drug-related adverse events in the fluconazole arm were pancytopenia and renal failure. Study medication was discontinued for 5 patients because of a drug-related adverse event (the 4 aforementioned patients plus 1 fluconazole recipient with rash). During the course of the study, there were 43 deaths (23 in the anidulafungin group and 20 in the fluconazole group).

Patients in both study arms manifested minor effects on hematological and hepatic parameters with a similar frequency. The most common treatment-related laboratory adverse events were increased γ -glutamyl transferase level (4 patients in each group), elevated aspartate aminotransferase (AST) level (1 patient in the anidulafungin group and 7 patients in the fluconazole group), and increased alanine aminotransferase level (3 patients in the fluconazole group). There were no important discernible differences between groups with regard to changes in the AST, alanine aminotransferase, alkaline phosphatase, bilirubin, or γ -glutamyl transferase level over the course of treatment.

DISCUSSION

To our knowledge, this study represents the largest controlled efficacy trial involving patients with esophageal candidiasis, having enrolled 601 patients with documented disease. The

Table 4. Time to resolution of symptoms and duration of intravenous anidulafungin or oral fluconazole therapy.

Variable	Intravenous anidulafungin recipients (n = 249)	Oral fluconazole recipients (n = 255)
No. (%) of patients with resolution of symptoms ^a	248 (99.5)	251 (98.4)
Time to resolution of symptoms, ^a median days	5	5
Duration of therapy, median days	14	14

^a Odynophagia/dysphagia and retrosternal pain.

Table 5. Patients with treatment-related adverse events, by body system.

Body system, adverse event	Intravenous anidulafungin group (n = 300)	Oral fluconazole group (n = 301)
Blood and lymphatic disorders		
Neutropenia	1.0	...
Leukopenia	0.7	1.3
Digestive system		
Nausea	1.0	1.0
Vomiting	0.7	1.0
Dyspepsia aggravation	0.3	1.0
General disorders: pyrexia	0.7	1.0
CNS: headache	1.3	1.0
Vascular disorders:		
phlebitis/thrombophlebitis	1.3	1.3

NOTE. Adverse events occurred in $\geq 1.0\%$ of patients; relationship to use of study drug was determined by the investigator to be possibly or probably related or unknown.

treatment groups were well matched with respect to demographic variables and disease severity. The majority of patients in each group had AIDS. As is typical of esophageal candidiasis, $>95\%$ of patients with available culture results had *C. albicans* identified at baseline. Compliance with the protocol was excellent: 84% of patients remained in the evaluable population at the end of therapy.

Because of the high recurrence rate associated with esophageal candidiasis [8], the end of therapy was prospectively defined as the primary time point of interest. In this immunocompromised population, anidulafungin was as efficacious as fluconazole, the current standard of care. Both drugs demonstrated high rates of endoscopic response, clinical cure, and mycological response in both the evaluable population and the intent-to-treat population.

The results of this study underscore the high recurrence rate for this illness [8]. A lower sustained response rate was noted in the anidulafungin-treated patients at the 2-week follow-up. More patients in the fluconazole arm than in the anidulafungin arm received antiretrovirals during study treatment, potentially confounding the findings at follow-up. An earlier randomized study of caspofungin (another echinocandin) in esophageal candidiasis also revealed a trend toward a greater frequency of late relapse in the echinocandin arm than in the fluconazole arm [29]. In the absence of immune reconstitution, most patients will require long-term suppression or intermittent therapy. Therefore, the follow-up data are less clinically relevant than the data obtained at the end of therapy.

Anidulafungin was well tolerated in this patient population. The most common treatment-related adverse events occurred with a similar frequency in both treatment groups. Potentially clinically significant changes in hematology and hepatic param-

eters were infrequent in both study arms, although more patients in the fluconazole group had treatment-related (per investigator attribution) increases in the AST level. In addition, the frequency of infusion-associated systemic reactions appeared to be very low or nonexistent in this study.

The rate of successful outcomes in this study is as high, or higher, than historical rates with systemic antifungals for treatment of esophageal candidiasis [5, 29, 30]. The distribution of baseline isolates was consistent with the epidemiology of esophageal candidiasis [4, 6] in the United States and elsewhere and thus should be generalizable. The data from this study indicate that anidulafungin is as safe and effective as oral fluconazole for the treatment of esophageal candidiasis, when assessed at the completion of therapy. Anidulafungin is well tolerated and may be a valuable treatment alternative for patients with esophageal candidiasis, particularly for those who are intolerant of oral therapy or other parenteral agents. Clinical trials with anidulafungin in patients with fluconazole-refractory oropharyngeal and esophageal candidiasis and with invasive candidiasis are currently in progress.

Acknowledgments

We would like to acknowledge the contribution of Prudence Ive, Lucy Connell, Glenda Gray, J. H. Mynhardt, Mariette Botes, Trevor Winter, Louis van Zyl, Johannes Roos, and D. M. Kelbe (South Africa); Somit Tansuphaswadikul, Comson Lertkupinet, and Piroon Mootsikapun (Thailand); Alvaro Reymunde (Puerto Rico); Jose Vazquez (United States); and Jorge Olmos, Pedro Cahn, Jorge Corral, Ricardo Negroni, Javier Altclas, Hector Laptume, Lucila Massera, Sergio Lupo, Daniel David, and Ricardo Lambergini (Argentina), for enrolling patients. We also thank Taylor Kilfoil (Inclin; San Carlos, CA) for project management, Deborah Matour (DL Matour & Co.; Harleysville, PA) for preparation of the manuscript, Michael Pfaller (University of Iowa; Iowa City) for the mycology central laboratory, and John Rex (University of Texas, Houston; currently at AstraZeneca, Macclesfield, UK) for assistance with trial design.

Financial support. Vicuron Pharmaceuticals.

Conflict of interest. D.S.K., T.H., M.W., and B.P.G. are employees of Vicuron Pharmaceuticals, the manufacturer of anidulafungin. T.J.W. has received research funding from Vicuron Pharmaceuticals and has a Cooperative Research and Development agreement with Fujisawa. All other authors: No conflict.

References

1. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. *Ann Intern Med* 1996;124:633–42.
2. Kaplan J, 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:S5–14.
3. Vazquez JA, Sobel JD. Mucosal candidiasis. *Infect Dis Clin North Am* 2002;16:793–820.
4. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 2000;30:662–78.
5. Ally R, Schuermann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in

- the treatment of esophageal candidiasis in immunocompromised patients. *Clin Infect Dis* **2001**; 33:1447–54.
6. Wilcox CM, Darouiche RO, Laine L, Moskovitz BL, Mallegol I, Wu J. A randomized, double-blind comparison of itraconazole oral solution and fluconazole tablets in the treatment of esophageal candidiasis. *J Infect Dis* **1997**; 176:227–32.
 7. Barbaro G, Barbarini G, Calderon W, et al. Fluconazole versus itraconazole for *Candida* esophagitis in acquired immunodeficiency syndrome. *Gastroenterology* **1996**; 111:1169–77.
 8. Laine L. The natural history of esophageal candidiasis after successful treatment in patients with AIDS. *Gastroenterology* **1994**; 107:744–6.
 9. Vazquez JA. Therapeutic options for the management of oropharyngeal and esophageal candidiasis in HIV/AIDS patients. *HIV Clin Trials* **2000**; 1:47–59.
 10. Klepser ME, Ernst EJ, Ernst ME, Messer SA, Pfaller MA. Evaluation of endpoints for antifungal susceptibility determinations with LY303366. *Antimicrob Agents Chemother* **1998**; 42:1387–91.
 11. Moore CB, Oakley KL, Denning DW. In vitro activity of a new echinocandin, LY303366, and comparison with fluconazole, flucytosine and amphotericin B against *Candida* species. *Clin Microbiol Infect* **2001**; 7:11–6.
 12. Ostrosky-Zeichner L, Rex JH, Pappas PG, et al. Comparative antifungal susceptibility survey of 2,000 bloodstream isolates of *Candida* spp. from the United States. *Antimicrob Agents Chemother* **2003**; 47:3149–54.
 13. Chavez M, Bernal S, Valverde A, Gutierrez MJ, Quindos G, Martin Mazuelos E. In-vitro activity of voriconazole (UK-109,496), LY303366 and other antifungal agents against oral *Candida* spp. isolates from HIV-infected patients. *J Antimicrob Chemother* **1999**; 44:697–700.
 14. Cuenca-Estrella M, Mellado E, Diaz-Guerra TM, Monzon A, Rodriguez JL. Susceptibility of fluconazole-resistant clinical isolates of *Candida* spp. to echinocandin LY303366, itraconazole and amphotericin B. *J Antimicrob Chemother* **2000**; 46:475–7.
 15. Espinel-Ingroff A. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. *J Clin Microbiol* **1998**; 36:2950–6.
 16. Pfaller MA, Messer SA, Coffman S. In vitro susceptibilities of clinical yeast isolates to a new echinocandin derivative, LY303366, and other antifungal agents. *Antimicrob Agents Chemother* **1997**; 41:763–6.
 17. Uzun O, Kocagoz S, Cetinkaya Y, Arikan S, Unal S. In vitro activity of a new echinocandin, LY303366, compared with those of amphotericin B and fluconazole against clinical yeast isolates. *Antimicrob Agents Chemother* **1997**; 41:1156–7.
 18. Quindos G, Carrillo-Munoz AJ, Arevalo MP, et al. In vitro susceptibility of *Candida dubliniensis* to current and new antifungal agents. *Chemotherapy* **2000**; 46:395–401.
 19. Zhanel GG, Karlowsky JA, Harding GA, et al. In vitro activity of a new semisynthetic echinocandin, LY303366, against systemic isolates of *Candida* species, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Aspergillus* species. *Antimicrob Agents Chemother* **1997**; 41:863–5.
 20. Turner WW, Current WL. Echinocandin antifungal agents. In: Strohl WR, ed. *Biotechnology of industrial antibiotics*. 2nd ed. New York: Marcel Dekker, **1997**:315–34.
 21. Zeckner D, Butler T, Boylan C, et al. LY303366, activity in a murine systemic candidiasis model [abstract 365]. In: Program and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy (New Orleans). Washington, DC: American Society for Microbiology, **1993**.
 22. Petraitis V, Petraitiene R, Groll AH, et al. Dosage-dependent antifungal efficacy of V-echinocandin (LY303366) against experimental fluconazole-resistant oropharyngeal and esophageal candidiasis. *Antimicrob Agents Chemother* **2001**; 45:471–9.
 23. Petraitiene R, Petraitis V, Groll AH, et al. Antifungal activity of LY303366, a novel echinocandin B, in experimental disseminated candidiasis in rabbits. *Antimicrob Agents Chemother* **1999**; 43:2148–55.
 24. Dowell J, Knebel W, Ludden T, Stogniew M, Krause D, Henkel T. A population pharmacokinetic analysis of anidulafungin. In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society of Microbiology, **2003**.
 25. Dowell J, Stogniew M, Krause D. Anidulafungin dosage adjustments are not required for patients with hepatic and/or renal impairment [abstract P1222]. *Clin Microbiol Infect* **2003**; 9:290.
 26. Krause D, Goldstein B, Wible M, Kilfoil G, Henkel T. A phase 2 dose-ranging study of the safety and efficacy of anidulafungin in invasive candidiasis [abstract O403]. *Clin Microbiol Infect* **2003**; 9:73.
 27. Kods BE, Wickremesinghe C, Kozinn PJ, Iswara K, Goldberg PK. *Candida* esophagitis: a prospective study of 27 cases. *Gastroenterology* **1976**; 71:715–9.
 28. NCCLS. Reference method for broth dilution antifungal susceptibility testing of yeasts; approved standard. NCCLS document M27-A. Wayne, PA: NCCLS, **1997**.
 29. Villanueva A, Gotuzzo E, Arathoon A, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med* **2002**; 113:294–9.
 30. Barbaro G, Barbarini G, DiLorenzo G. Fluconazole vs. flucytosine in the treatment of esophageal candidiasis in AIDS patients: a double-blind, placebo-controlled study. *Endoscopy* **1995**; 27:377–83.