ORIGINAL ARTICLE

Anidulafungin versus Fluconazole for Invasive Candidiasis

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ABSTRACT

BACKGROUND

Anidulafungin, a new echinocandin, has potent activity against candida species. We compared anidulafungin with fluconazole in a randomized, double-blind, noninferiority trial of treatment for invasive candidiasis.

METHODS

Adults with invasive candidiasis were randomly assigned to receive either intravenous anidulafungin or intravenous fluconazole. All patients could receive oral fluconazole after 10 days of intravenous therapy. The primary efficacy analysis assessed the global response (clinical and microbiologic) at the end of intravenous therapy in patients who had a positive baseline culture. Efficacy was also assessed at other time points.

RESULTS

Eighty-nine percent of the 245 patients in the primary analysis had candidemia only. *Candida albicans* was isolated in 62% of the 245 patients. In vitro fluconazole resistance was infrequent. Most of the patients (97%) did not have neutropenia. At the end of intravenous therapy, treatment was successful in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole (difference, 15.4 percentage points; 95% confidence interval [CI], 3.9 to 27.0). The results were similar for other efficacy end points. The statistical analyses failed to show a "center effect"; when data from the site enrolling the largest number of patients were removed, success rates at the end of intravenous therapy were 73.2% in the anidulafungin group and 61.1% in the fluconazole group (difference, 12.1 percentage points; 95% CI, -1.1 to 25.3). The frequency and types of adverse events were similar in the two groups. The rate of death from all causes was 31% in the fluconazole group and 23% in the anidulafungin group (P=0.13).

CONCLUSIONS

Anidulafungin was shown to be noninferior to fluconazole in the treatment of invasive candidiasis. (ClinicalTrials.gov number, NCT00056368).

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N Engl J Med 2007;356:2472-82. Copyright © 2007 Massachusetts Medical Society. **I**NVASIVE CANDIDIASIS IS AN IMPORTANT cause of complications and death in hospitalized patients.¹⁻⁴ Current choices for treatment include fluconazole, caspofungin, voriconazole, and amphotericin B.⁵⁻⁸ These agents were developed through prospective, randomized trials in which amphotericin B deoxycholate was used as the comparison agent.⁶⁻⁹ Although caspofungin has been shown to be noninferior to amphotericin B, dose-limiting nephrotoxicity contributed to a worse outcome in the amphotericin B group.⁷

Echinocandins have emerged as important agents for the treatment of invasive candidiasis.^{9,10} Fluconazole and echinocandins have favorable safety profiles.¹¹⁻¹³ Anidulafungin, a new echinocandin with activity against candida species,¹⁴⁻¹⁶ was found to be efficacious in the treatment of invasive candidiasis in a phase 2 study.¹⁷ We conducted a randomized, double-blind, multicenter trial comparing anidulafungin with fluconazole for the treatment of candidemia and other forms of invasive candidiasis.

METHODS

CONDUCT OF THE STUDY

The protocol was approved by the institutional review board at each of the 47 participating institutions. All patients or their legal representatives provided written informed consent before enrollment. The study began in March 2003 and ended in October 2004. An independent data safety monitoring board oversaw the study. All authors had complete and unfettered access to the study data, participated in the collection and analysis of the data, wrote the manuscript, and vouch for the completeness and accuracy of the data and analysis presented.

PATIENTS

Patients 16 years of age or older who had candidemia (defined as at least one positive blood culture) or other forms of invasive candidiasis (defined as a positive culture obtained from a sterile site) within 96 hours before enrollment were eligible for the study. Inclusion criteria were one or more of the following: fever, hypothermia, hypotension, local signs and symptoms, or radiologic findings of invasive candidiasis. Exclusion criteria were more than 48 hours of systemic antifungal therapy for the current episode, prophylactic administration of any azole for more than 1 week within 30 days before enrollment, refractory candida infection, elevated levels of hepatic enzymes, *Candida krusei* infection, or osteomyelitis, endocarditis, or meningitis due to candida species. Removal of central venous catheters was recommended for all patients with candidemia.

STUDY DESIGN

In this double-blind, noninferiority study, patients were stratified according to scores on the Acute Physiology and Chronic Health Evaluation (APACHE II) instrument (≤ 20 or >20, with higher scores indicating more severe disease) and absolute neutrophil count (≤500 or >500 per cubic millimeter) at enrollment and randomly assigned to a study drug. Randomization was performed in centrally balanced, permuted blocks within each stratum in a 1:1 ratio. Patients were randomly assigned to receive either intravenous anidulafungin (200 mg on day 1 and then 100 mg daily) or intravenous fluconazole (800 mg on day 1 and then 400 mg daily). The dose of fluconazole was adjusted for patients who had a creatinine clearance of 50 ml per minute or less or were receiving hemodialysis. Study drugs were administered for 14 to 42 days and for at least 14 days after a negative blood culture and improvement in signs and symptoms. All patients could receive oral fluconazole (400 mg daily) at the investigators' discretion after at least 10 days of intravenous therapy if the patients were able to tolerate oral medication, if they had been afebrile for at least 24 hours, if the most recent blood culture was negative for candida species, and if there was clinical improvement. Signs and symptoms were assessed at baseline, daily during treatment, at the end of intravenous therapy, at the end of oral therapy, and 2 weeks and 6 weeks after the end of all antifungal therapy. Laboratory values were obtained periodically.

EVALUATION OF EFFICACY

The primary efficacy analysis of global response at the end of intravenous therapy assessed the modified intention-to-treat population. A global response was considered successful if there was both clinical success (defined as the resolution of signs and symptoms of invasive candidiasis and no need for additional systemic antifungal therapy) and microbiologic success (defined as the eradication of candida species present at baseline, as determined on follow-up culture, or the presumed eradication, if culture data were not available for a patient with a successful clinical response). Secondary analyses included the global response at the end of all study therapy (intravenous and oral) and at follow-up visits at 2 weeks and 6 weeks, the per-patient and per-pathogen microbiologic response at all time points, and death from all causes. Failure of response was defined as no significant improvement in signs and symptoms; death due to invasive candidiasis; persistent or recurrent candidiasis or a new candida infection; or any indeterminate response, including loss to follow-up or death that was not attributed to candidiasis.

STATISTICAL ANALYSIS

The intention-to-treat population included all patients who received at least one dose of study medication. Safety analyses were conducted in this population. The modified intention-to-treat population included all patients who received at least one dose of study medication and had a positive culture for candida species within 96 hours before enrollment.

The primary analysis in this noninferiority trial was a two-step comparison of the rate of global success between the two study groups at the end of intravenous therapy. A two-sided 95% confidence interval was calculated for the true difference in efficacy (the success rate with anidulafungin minus that with fluconazole). In the first step, noninferiority was considered to be shown if the lower limit of the two-sided 95% confidence interval was greater than –20 percentage points. In the second step, if the lower limit was greater than 0, then anidulafungin was considered to be superior in the strict sense to fluconazole.

Assuming a success rate of 70% at the end of intravenous therapy for both anidulafungin and fluconazole, the number of patients required to establish noninferiority with 90% power was 111 in each study group. Assuming that 10% of patients would be excluded because of the absence of a positive baseline culture, we planned to enroll 248 patients.

SAS software (version 8.2, SAS) was used to generate summary tables. All data available for each time point were included, with no substitutions for missing data. Missing data were treated as missing, and if they were missing because of a lack of clinical or microbiologic response, or both, the data were considered to be indeterminate. Kaplan–Meier survival estimates were calculated, and differences between the two treatments were assessed by means of the log-rank test. All reported P values are two-sided and unadjusted for multiple comparisons. A multivariate logistic-regression analysis of the global response at the end of intravenous therapy was performed to adjust for differences in particular characteristics between the groups at baseline (i.e., immunosuppressive therapy, diabetes mellitus, prior azole therapy, positivity for *C. glabrata* at baseline, and removal of the central catheter).

An analysis for a "center effect" was performed with the use of the Cochran-Mantel-Haenszel test. Post hoc analyses for this effect were also performed by grouping centers into fewer strata and performing both the Cochran-Mantel-Haenszel and Breslow-Day tests. The following grouping strategies were used for these analyses: the center enrolling the highest number of patients versus all other centers pooled, and any center that had 5% or more of the total modified intention-to-treat population versus small centers, those with less than 5% of the total modified intention-to-treat population as divided into two subgroups, U.S. centers and non-U.S. centers. Finally, a third analysis for the center effect was performed with the use of a logistic-regression model, and other categorical modeling techniques (CATMOD procedure, SAS) were applied to each of these grouping strategies to include center, treatment assignment, and interaction (between treatment and center) effects.

RESULTS

BASELINE CHARACTERISTICS

Of a total of 261 patients enrolled, 256 were included in the intention-to-treat population and 245 in the modified intention-to-treat population. In the modified intention-to-treat population, 127 patients were assigned to anidulafungin and 118 were assigned to fluconazole. (For a clinical flow chart, see Fig. 1 in the Supplementary Appendix, available with the full text of this article at www. nejm.org.) Characteristics of patients and the course of therapy are shown in Table 1. The two study groups did not differ significantly in demographic characteristics, duration of treatment, frequency of switch to oral fluconazole, or exposure to oral fluconazole.

MICROBIOLOGIC FINDINGS

The distribution of candida species was similar in the anidulafungin group and the fluconazole group (Table 1). The most frequently occurring species was *C. albicans*, occurring in 61.6% of patients. *C. glabrata* was isolated in 15.7% of those in the anidulafungin group and 25.4% of those in the fluconazole group (P=0.08). The minimal inhibitory concentrations (MICs) of anidulafungin and fluconazole for baseline clinical isolates are shown in Table 2.¹⁸ For all but 10 isolates (5 obtained from patients in each study group) of a total of 242 isolates of all candida species (95.9%), the MIC of fluconazole was less than 16 μ g per milliliter.

EFFICACY

Successful global responses at all time points in the modified intention-to-treat population are shown in Figure 1. For the primary end point of global response at the end of intravenous therapy, a successful outcome was achieved in 96 of 127 patients in the anidulafungin group (75.6%), as compared with 71 of 118 patients in the fluconazole group (60.2%) (difference, 15.4 percentage points; 95% confidence interval [CI], 3. 9 to 27.0); therefore, anidulafungin met the prespecified criteria for noninferiority to fluconazole. Since the confidence interval for the difference excluded 0, there was a significantly greater response rate in the anidulafungin group (P=0.01). Concordant results were obtained for the intention-totreat population. Differences between the two groups remained significant (P=0.04; odds ratio, 1.8; 95% CI, 1.0 to 3.2) in a multivariate logisticregression model of global response at the end of intravenous therapy, after adjusting for the baseline characteristics of immunosuppressive therapy, diabetes mellitus, prior azole therapy, presence of C. glabrata, and catheter removal.

Of the 47 participating centers, 1 center enrolled 25 patients (10% of the modified intentionto-treat population). Of the 15 patients at this site who were assigned to anidulafungin, 14 (93.3%) had a successful global response, whereas 5 of the 10 patients receiving fluconazole (50%) had a successful response. There were no significant differences in baseline characteristics between this site and the other sites, except that patients in the fluconazole group were slightly older than those enrolled at the other sites and more patients in the anidulafungin group had *C. albicans*. The Cochran–Mantel–Haenszel test, the Breslow–Day test, logistic-regression analyses, and CATMOD models did not show any evidence of a center effect on the results of the primary analysis. However, if data for the 25 patients at this single center were removed from the primary analysis, the success rate would change to 73.2% for anidulafungin versus 61.1% for fluconazole (difference, 12.1 percentage points; 95% CI, –1.1 to 25.3), and anidulafungin would be statistically noninferior to fluconazole, rather than superior in the strict sense to fluconazole.

Among patients with candidemia only (89% of all patients), a successful response at the end of intravenous therapy occurred in 88 of 116 patients (75.9%) in the anidulafungin group and 63 of 103 (61.2%) in the fluconazole group (difference, 14.7 percentage points; 95% CI, 2.5 to 26.9; P=0.02). The proportion of patients with other forms of invasive candidiasis who had a successful response was higher in the anidulafungin group (8 of 11 patients [72.7%]) than in the fluconazole group (8 of 15 patients [53.3%]). Among those with a baseline APACHE II score of 20 or lower, more patients in the anidulafungin group (82 of 101 [81.2%]) had a successful response at the end of intravenous therapy than in the fluconazole group (60 of 98 [61.2%]). Among the few patients with a baseline APACHE II score higher than 20, the proportion of those with a successful response was similar in the two groups. Thirty-three patients in each group received oral fluconazole; 31 (93.9%) in the anidulafungin group and 28 (84.8%) in the fluconazole group were successfully treated. Anidulafungin showed better efficacy than fluconazole at the end of all therapy and at the 2-week follow-up. At the 6-week follow-up, the proportion of patients in the anidulafungin group who had a successful response was greater than that in the fluconazole group, but statistically, the value met only noninferiority criteria.

Microbiologic and global per-pathogen responses at the end of intravenous therapy are shown in Table 3. Microbiologic success was observed for 88.1% of all baseline pathogens in specimens obtained from patients in the anidulafungin group and for 76.2% of pathogens in specimens obtained from patients in the fluconazole group (P=0.02). The response rate for *C. albicans* in the anidulafungin group was 95.1%, as compared with 81.4% in the fluconazole group (P=0.01).

Table 1. Characteristics of the Modified Intention-to-Treat Population.*					
Characteristic	Anidulafungin Group (N=127)	Fluconazole Group (N=118)	P Value		
Sex — no. (%)			1.00		
Male	65 (51)	60 (51)			
Female	62 (49)	58 (49)			
Age — yr			0.29		
Mean	57.0±17.0	59.2±16.5			
Range	16-89	24–91			
Race or ethnic group — no. (%)†			0.59		
White	92 (72)	87 (74)			
Black	23 (18)	25 (21)			
Other	12 (9)	6 (5)			
Coexisting disease — no. (%)					
Diabetes mellitus	44 (35)	30 (25)	0.13		
Renal failure or insufficiency	47 (37)	42 (36)	0.89		
Hemodialysis	20 (16)	18 (15)	1.00		
Peritoneal dialysis	3 (2)	2 (2)	1.00		
Bacterial sepsis‡	58 (46)	49 (42)	0.52		
Neoplastic disease	28 (22)	27 (23)	0.88		
Disorder requiring transplantation	7 (6)	5 (4)	0.77		
Risk factors for invasive candidiasis — no. (%)					
Central venous catheter	99 (78)	92 (78)	1.00		
Broad-spectrum antibiotics	88 (69)	82 (70)	1.00		
Recent surgery	53 (42)	51 (43)	0.90		
Recent hyperalimentation	31 (24)	31 (26)	0.77		
Immunosuppressive therapy	18 (14)	27 (23)	0.10		
Prior azole prophylaxis§	7 (6)	2 (2)	0.17		
Apache II score					
≤20 — no. (%)	101 (80)	98 (83)	0.52		
>20—no. (%)	26 (21)	20 (17)	0.51		
Mean (median)	15.0±7.7 (14)	14.4±6.8 (13)			
Range	2–42	3–36			
Absolute neutrophil count — no. (%)					
>500/mm³	124 (98)	114 (97)	0.71		
≤500/mm³	3 (2)	4 (3)			
Site of infection — no. (%)					
Blood only	116 (91)	103 (87)	0.41		
Other sterile site only¶	7 (6)	11 (9)	0.33		
Both	4 (3)	4 (3)	1.00		
Duration of intravenous treatment — days					
Mean (median)	13.5 (14)	12.1 (11)	0.10		
Range	1–33	1–37			
Switch to oral fluconazole — no. (%)**	33 (26)	33 (28)	0.77		

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Table 1. (Continued.)					
Characteristic	Anidulafungin Group (N=127)	Fluconazole Group (N=118)	P Value		
Duration of exposure to oral fluconazole — days					
Mean (median)	9.2 (7)	7.97 (5)	0.46		
Range	1–32	2–33			
Total (intravenous and oral) exposure to study drug — days					
Mean (median)	15.9 (15)	14.4 (14)	0.12		
Range	1-43	1–42			
Baseline candida pathogen — no. (%)					
Candida albicans	81 (64)	70 (59)	0.51		
C. glabrata	20 (16)	30 (25)	0.08		
C. parapsilosis	13 (10)	16 (14)	0.44		
C. tropicalis	15 (12)	11 (9)	0.54		
Other candida species	6 (5)	3 (3)	0.50		

* Plus-minus values are means ±SD.

† Race or ethnic group was self-reported, if possible, or as shown in the medical record.

 \pm Patients were included if bacterial sepsis occurred within 1 month before randomization.

§ Prior azole prophylaxis was defined as low-dose fluconazole (<200 mg daily) for less than 7 days.

¶ Other sterile sites were defined as peritoneal, intraabdominal, and pleural fluid; pelvis; and pancreas.

Both sites were defined as blood plus bile, pleural fluid, skin, peritoneal fluid, or kidney.

** All patients could switch to oral fluconazole (400 mg daily) at the investigator's discretion after at least 10 days of intravenous therapy if they were able to tolerate oral medication, had been afebrile for at least 24 hours, had cultures that were negative for candida species, and had improvement in signs and symptoms of candida infection.

In the anidula fungin group, the eradication rate for C. parapsilosis, for which the MIC of anidulafungin was highest, was lower than for other candida species. There was no apparent trend toward an association between the MIC of fluconazole for baseline isolates and the rate of eradication. Among fluconazole recipients, success rates were similar whether the MIC of fluconazole was less than 16 μ g per milliliter or 16 μ g per milliliter or more (75.7% and 80.0%, respectively); however, only five isolates had MICs of fluconazole equal to or greater than 16 μ g per milliliter: one isolate of C. albicans and three isolates of C. glabrata (MIC, 32 μ g per milliliter for each) and one isolate of C. glabrata (MIC, 128 μ g per milliliter). Fluconazole eradicated 60.9% of isolates of C. glabrata for which MICs of fluconazole were less than 16 μ g per milliliter and 75.0% of isolates of C. glabrata for which MICs of fluconazole were 16 μ g per milliliter or more.

As compared with fluconazole recipients, anidulafungin recipients had a higher rate of successful global response for every pathogen except *C. parapsilosis*. The difference in the global response rate between the two groups was most striking for *C. albicans* (81.1% of those in the anidulafungin group were successfully treated, vs. 62.3% of those in the fluconazole group; P=0.02). Successful global response rates for *C. glabrata* were similar in the two groups (56.3% in the anidulafungin group and 50.0% in the fluconazole group). Reasons for treatment failure are shown in Table 4.

In 187 of the 202 patients who had an intravascular catheter (92.6%), the catheter was removed (96.0% in the anidulafungin group vs. 89.0% in the fluconazole group). Among patients with an intravascular catheter that was not removed before the administration of study medication, 3 of 4 patients (75.0%) in the anidulafungin group and 3 of 11 (27.3%) in the fluconazole group had a successful response at the end of intravenous therapy.

At the end of intravenous therapy, persistent infection was documented in 8 patients (6.3%) in the anidulafungin group and 17 (14.4%) in the fluconazole group (P=0.06); in all these patients except 1 in the fluconazole group, the catheter was removed. Among anidulafungin recipients who had persistently positive cultures, three had

Table 2. In Vitro Susceptibility of Clinical Isolates to Anidulafungin				
and Fluconazole in the Modified Intention-to-Treat Population.*				

Organism and Antimicrobial Agent	MIC₅₀	MIC ₉₀	MIC Range
All candida species (242 isolates)†			
Anidulafungin	0.008	0.50	≤0.002 to 2.00
Fluconazole	0.25	8.00	≤0.06 to >128.0
Candida albicans (140 isolates)			
Anidulafungin	0.004	0.015	≤0.002 to 0.06
Fluconazole	0.25	1.00	≤0.06 to >128.00
C. glabrata (44 isolates)			
Anidulafungin	0.03	0.06	≤0.002 to 0.12
Fluconazole	4.00	16.00	0.12 to 128.00
C. parapsilosis (26 isolates)			
Anidulafungin	1.00	2.00	0.03 to 2.00
Fluconazole	0.25	1.00	≤0.06 to 1.00
C. tropicalis (24 isolates)			
Anidulafungin	0.015	0.060	≤0.002 to 0.12
Fluconazole	0.25	1.00	≤0.06 to 2.00

* Minimum inhibitory concentrations (MICs) were determined according to the reference method (approved standard, M27-A2) of the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards¹⁸) for broth-dilution antifungal susceptibility testing in yeasts. For echinocandins, the end point of 24 hours of incubation has been recommended as appropriate. Because of the trailing phenomenon observed with azoles, data obtained at this time point are also presented for fluconazole. MIC_{so} denotes the MIC required to inhibit 50% of isolates, and MIC_{so} the MIC required to inhibit 90% of isolates.

† Susceptibility testing was performed on all isolates collected during the study.

C. glabrata, two had *C. parapsilosis*, two had *C. albicans*, and one had *C. tropicalis*, whereas among fluconazole recipients with persistently positive cultures, nine had *C. albicans*, six had *C. glabrata*, and two had *C. parapsilosis* (see Table 1 in the Supplementary Appendix). In post hoc analyses, a higher proportion of patients in the anidulafungin group than in the fluconazole group had negative blood cultures at days 3 and 7, but the differences were not significant (see Table 2 in the Supplementary Appendix).

Late complications of invasive candidiasis were uncommon. Two patients (one in each group) had endophthalmitis, three (two in the anidulafungin group and one in the fluconazole group) had recurrently positive cultures, and one patient in the fluconazole group had hepatic candidiasis caused by *C. albicans*. The two patients with endophthalmitis had negative funduscopic examinations at baseline. Endophthalmitis was diagnosed at the 2-week follow-up in the patient in the anidulafungin group and on day 7 in the patient in the fluconazole group.

ADVERSE EVENTS AND DEATHS

The number of treatment-related adverse events was similar in the two groups (anidulafungin group, 59 events in 32 patients [24.4%]; fluconazole group, 64 events in 33 patients [26.4%]). Elevated levels of hepatic enzymes that were deemed



Figure 1. Global Response to Treatment for Prespecified Time Points in the Modified Intention-to-Treat Population.

A successful global response required both clinical success (defined as the resolution of signs and symptoms of invasive candidiasis and no additional systemic antifungal therapy) and microbiologic success (defined as the eradication of candida species present at baseline as determined on follow-up culture, or the presumed eradication if culture data were not available for a patient with a successful clinical response). P<0.02 for the comparison between the anidulafungin group and the fluconazole group at the end of intravenous therapy. P<0.02 for the comparison between the two groups at the end of all therapy and at the 2-week follow-up. At the end of intravenous therapy, 33 patients in each of the two groups (26% in the anidulafungin group and 28% in the fluconazole group) switched to oral fluconazole. For multiple comparisons of the secondary end points, 98.3% confidence intervals (CI) adjusted post hoc were 2.9 to 31.6 at the end of all therapy, 0.4 to 30.4 at the 2-week follow-up, and -3.4 to 27.0 at the 6-week follow-up. The dashed vertical line represents the prespecified margin for noninferiority.

Table 3. Microbiologic and Global Responses at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.*						
Candida Pathogen	Successful Microbiologic Response			Successful Global Response†		
	Anidulafungin Group	Fluconazole Group	P Value	Anidulafungin Group	Fluconazole Group	P Value
	no. of isolates/total no. (%)		no. of patients/total no. (%)			
Candida albicans	77/81 (95)	57/70 (81)	0.01	60/74 (81)	38/61 (62)	0.02
C. glabrata	15/20 (75)	18/30 (60)	0.37	9/16 (56)	11/22 (50)	0.75
C. parapsilosis	9/13 (69)	14/16 (88)	0.36	7/11 (64)	10/12 (83)	0.37
C. tropicalis	13/15 (87)	7/11 (64)	0.35	13/14 (93)	4/8 (50)	0.04
Other candida species	5/6 (83)	3/3 (100)	1.00	3/4 (75)	2/3 (67)	1.00
All candida species	119/135 (88)	99/130 (76)	0.02	92/119 (77)	65/106 (61)	0.01

* Patients may have had more than one pathogen at baseline, but the majority had a single pathogen (94% in the anidulafungin group and 90% in the fluconazole group). Of 227 patients with candidemia, 138 had multiple positive blood cultures at baseline. However, because the protocol did not require blood to be drawn for culture on the first day of administration of the study drug, the number of patients with multiple positive blood cultures is likely to be underestimated. † Patients included in this analysis had a single pathogen at baseline.

Table 4. Reasons for Failure of Global Response at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.					
Reason	Anidulafungin Group (N=31)	Fluconazole Group (N=47)	P Value		
Observed failure*	13	24	0.49		
Clinical success and microbiologic failure†	1	2	1.00		
Clinical failure and microbiologic success	4	6	1.00		
Clinical failure and microbiologic failure†	8	16	0.47		
Indeterminate‡	18	23	0.49		
Withdrawal from study or study medication	18	23	0.49		
Reason for withdrawal					
Adverse event∬	11	16	1.00		
Withdrawal of consent	4	4	0.71		
Investigator's discretion	3	3	0.68		
Death, not due to candidemia or invasive candidiasis	10	16	1.00		
Receipt of less than 3 doses of study medication	5	8	1.00		

* Observed failure of global response was defined as treatment failure declared by the investigator to be clinical failure, microbiologic failure as indicated by positive findings on culture, or both. All patients with observed failure had candidemia except two, one in each treatment group, in both of whom the clinical response was successful but the microbiologic response was not. The mean time to failure was 12.2 days in 13 patients (not including those with indeterminate response) in the anidulafungin group in whom true failure occurred at the end of intravenous therapy. The mean time to failure was 9.3 days in the 24 patients in the fluconazole group (not including those with indeterminate response) in whom failure occurred at the end of intravenous therapy.

† Among those in whom microbiologic failure occurred, 8 of 9 patients in the anidulafungin group and 17 of 18 in the fluconazole group had persistent infection. (For details, see the Supplementary Appendix.) The other two patients in whom microbiologic failure occurred had superinfections.

‡ For the primary efficacy analysis, indeterminate response was grouped with failure of global response. Patients could be considered to have an indeterminate response for more than one reason.

In the anidulafungin group, adverse events included renal failure, respiratory failure, elevated levels of liver enzymes, cardiac failure, hypoglycemia, and septic shock (each in one patient), multisystem organ failure (in three patients), and worsening sepsis (in two patients). In the fluconazole group, adverse events included worsening of metastatic lung cancer, worsening respiratory failure, respiratory failure, respiratory arrest, multisystem organ failure (each in one patient), elevated levels of liver enzymes (in two patients), worsening renal failure and sepsis (in one patient), septic shock (in two patients), lung cancer, bradycardia and flushing, cardiac arrest, renal failure and progression of prostatic cancer, rash, and bradycardia (each in one patient).

to be related to the study drug were more frequently observed in the fluconazole group (in nine patients [7.2%], vs. two patients in the anidulafungin group [1.5%], P=0.03). Treatment-related serious adverse events occurred in two patients in each study group: in the anidulafungin group, one patient had atrial fibrillation and one patient had seizures; in the fluconazole group, one patient had deep-vein thrombosis and one patient had increased levels of hepatic enzymes. Adverse events leading to discontinuation of the study drug occurred in 27 patients receiving fluconazole and 15 receiving anidulafungin (P=0.02). Many of these adverse events were not toxic effects commonly associated with fluconazole but, instead, were symptoms and signs compatible with worsening clinical status. (For details on adverse events, see Tables 3 through 6 in the Supplementary Appendix.) In the modified intention-to-treat population, more patients died in the fluconazole group (37 of 118 [31.4%]) than in the anidula fungin group (29 of 127 [22.8%], P=0.13). The median time to death was 21 days in the anidulafungin group and 14 days in the fluconazole group. Kaplan-Meier estimates of survival are shown in Figure 2.

DISCUSSION

We directly compared the efficacy of an echinocandin with that of an azole for the treatment of candidemia and other forms of invasive candidiasis. Fluconazole is one of the agents of first choice for the treatment of invasive candidiasis.



Figure 2. Kaplan–Meier Estimates of Survival in the Modified Intention-to-Treat Population.

The P value was calculated by means of the log-rank test.

The results of this study are consistent with those of a phase 2 trial of anidulafungin for invasive candidiasis, in which 80.9% of the 68 patients in the modified intention-to-treat population were considered to have a successful global response at the end of therapy.¹⁷ The success rate at the end of intravenous anidulafungin therapy in our trial was similar also to that reported for another echinocandin, caspofungin, in the primary treatment of invasive candidiasis.7 Response rates observed for fluconazole in our study are lower than those reported in a previous study,⁶ but they are similar to those recently reported in a randomized trial comparing fluconazole alone with fluconazole plus amphotericin B, in which the difference in success rates was based on differences in the rate of failure to clear the bloodstream.19

C. albicans and C. glabrata were the most common pathogens at baseline in our study, a finding that was similar to the baseline epidemiologic findings in other studies. MIC values for these and other species were also similar to those in previous studies.²⁰⁻²² The MICs of anidulafungin for C. parapsilosis and the MICs of fluconazole for C. glabrata were generally higher than those of either agent for C. albicans. The difference in perpathogen success rates was not a function of fluconazole resistance, since the majority of the isolates, including those of C. glabrata, were susceptible. Since echinocandins are rapidly fungicidal in vitro and in vivo against most candida species,^{11,16,20} the difference may reflect the concentration-dependent fungicidal effect of anidulafungin,¹⁶ as compared with the fungistatic effect of fluconazole.23,24 We were unable to test this hypothesis because daily blood cultures were not required by the protocol, and the post hoc analyses on days 3 and 7 failed to show a significant difference in blood culture negativity. Although the absolute difference in the rate of successful response against C. parapsilosis was not significant, echinocandins are generally less active against this species than against others, perhaps because of changes in the glucan synthase subunit Fks1.25,26

The limitations of this study include the small proportion of patients with neutropenia, the small proportion of those with noncandidemic invasive candidiasis, the exclusion of pediatric patients, and a possible center effect. Although extensive statistical analysis did not detect a center effect, one should nevertheless interpret the findings of superiority cautiously. The fact that the evidence for the superiority of anidulafungin was diminished by removal of the site with the highest enrollment suggests that there may be heterogeneity in the relative treatment difference or, simply, that the robustness of the findings is limited by the size of the sample. This trial was designed primarily as a noninferiority study, albeit with a prespecified two-step statistical analysis for superiority.²⁷⁻²⁹ In conclusion, this study shows that anidulafungin is not inferior to and possibly is more efficacious than fluconazole for the primary treatment of the candidemic form of invasive candidiasis, with a safety profile similar to that of fluconazole.

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APPENDIX

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