A Prospective, Open-label Study to Assess the Safety, Tolerability and Efficacy of Anidulafungin in the Treatment of Invasive Candidiasis in Children 2 to <18 Years of Age

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Background: Treatment with an echinocandin is recommended as first-line therapy for patients with invasive candidiasis (ICC) including candidemia. Little is known about the efficacy and safety of anidulafungin in children with ICC.

Methods: Eligible patients with ICC 2 to <18 years old were enrolled into this prospective, open-label, noncomparative, international study (NCT00761267) and received anidulafungin for 10–35 days (3 mg/kg on day 1, 1.5 mg/kg daily thereafter). Safety was assessed through week 6 follow-up. Efficacy, measured by global response (based on clinical and microbiologic responses), was assessed at end of intravenous treatment (EOIVT), end of treatment, weeks 2 and 6 follow-up.

Results: Forty-nine patients (n = 19, 2 to <5 years; n = 30, 5 to <18 years) received ≥1 dose of anidulafungin (median 11 days; range 1–35 days) and were assessed for safety. Among 48 patients with a *Candida* species isolated, *C. albicans* (37.5%), *C. parapsilosis* (25.0%), *C. tropicalis* (14.6%) and *C. lusitaniae* (10.4%) were the most frequent *Candida* spp. All patients reported ≥1 treatment-emergent adverse event, with diarrhea (22.4%), vomiting (24.5%) and pyrexia (18.4%) being most frequent. Five patients discontinued treatment because of adverse events, of which 4 discontinuations were considered related to anidulafungin. All-cause mortality was 8.2% (4/49) by EOIVT and 14.3% (7/49) by week 6 follow-up. None of 7 deaths during the study period were considered treatment related. Global response success rate was 70.8% at EOIVT.

Conclusions: These data support the use of anidulafungin as a treatment option for ICC in children 2 to <18 years old at the studied dose.

Key Words: anidulafungin, invasive candidiasis, candidemia, pediatric

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Infection with *Candida* spp. is one of the most important causes of nosocomial infections among pediatric patients.[1] Incidence rates for *Candida* spp. vary according to study design and reporting methods: 0.06–0.3 per 1000 inpatient-days (median age: 50 months) in a case-control study,[2] 0.28 per 1000 patient-days in another case-control study in premature infants and children up to age 17 years[3] and 0.81 per 1000 admissions in a prospective surveillance study.[4] All-cause mortality for pediatric candidemia exceeds 15% in the United States versus 5.9% for matched patients without candidemia.[5]

Infectious Disease Society of America and European Society of Clinical Microbiology and Infectious Diseases guidelines for the prevention and treatment of invasive candidiasis (ICC) in children primarily rely on extrapolation from adult studies, as safety and efficacy data for antifungal agents in pediatric patients are lacking.[6] Amphotericin B, echinocandins and azoles can be used for the treatment of ICC in children.[6,7] Anidulafungin is an echinocandin antifungal drug indicated in adults for the treatment of candidemia and other forms of *Candida* infections (intraabdominal abscess and peritonitis) and esophageal candidiasis.[8] It is currently approved in 95 countries for the treatment of ICC in adults. Little is known about the efficacy and safety of anidulafungin for the management of ICC in children.

An open-label, noncomparative, multicenter international study (NCT00761267) was conducted to evaluate the safety, efficacy and pharmacokinetics of anidulafungin for the treatment of ICC in pediatric patients 1 month to <18 years old. Herein we report safety, tolerability and efficacy data in patients 2 to <18 years old. Data for patients 1 month to <2 years old and pharmacokinetics data will be published separately.

METHODS

Patients

Eligible patients (2 to <18 years old) were required to meet clinical criteria and have a confirmed diagnosis of ICC (positive culture for *Candida* spp. from a normally sterile site obtained within 96 hours before enrollment). Patients could be enrolled with

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Availability of data and material: Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the United States and/or the European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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mycologic evidence highly suggestive of *Candida* spp. but were discontinued from treatment if culture confirmation of *Candida* spp. was not obtained within 96 hours after treatment initiation. Full inclusion and exclusion criteria are detailed online (Text, Supplementary Digital Content 1, http://links.lww.com/INF/D350). A total of 69 sites participated in the study, and patients were enrolled from 20 sites across 8 countries.

Study Design

All study patients received anidulafungin as a single intravenous (IV) loading dose of 3 mg/kg on day 1, followed by a 1.5 mg/kg IV once-daily maintenance dose. Anidulafungin was administered for a minimum of 10 days to a maximum of 35 days, with an option to switch to oral fluconazole therapy (6–12 mg/kg/d) after day 10, if prespecified criteria were met (Text, Supplementary Digital Content 1, http://links.lww.com/INF/D350). The maximum total treatment duration of anidulafungin plus oral fluconazole was 49 days.

Treatment (anidulafungin alone or anidulafungin followed by oral fluconazole) was required for a minimum of 14 days after the last negative culture (the second of 2 negative cultures, separated by at least 24 hours) and resolution of signs and symptoms attributable to infection. Safety and efficacy were evaluated at the end of IV therapy (EOIVT) and end of all therapy (EOT) and at follow-up visits at 2 and 6 weeks after the last dose of study treatment.

The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines established by the International Council on Harmonisation. The final protocol, amendments and informed consent documentation were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees of the investigational centers. Written consent, and assent where applicable, was obtained for all patients.

Endpoints

The primary objective of this study was to assess the safety and tolerability of anidulafungin in children with ICC. All patients who received at least 1 dose of anidulafungin were evaluated for safety through the week 6 follow-up visit. Safety evaluation included monitoring of adverse events (AEs), clinical laboratory assessments, vital signs, temperature and physical examination. AEs were categorized as mild, moderate or severe. Serious AEs (SAEs) were those which were life-threatening, required hospitalization or resulted in persistent or significant disability/incapacity, a congenital anomaly/birth defect or death.

Secondary endpoints included efficacy, measured by global response in the modified intention-to-treat (MITT) population (patients who received ≥1 dose of anidulafungin had microbiologically confirmed *Candida* infection) at the following study time points: EOIVT, EOT, the week 2 follow-up visit and the week 6 follow-up visit. Global response was derived programmatically from a combination of the investigator's assessment of clinical and microbiologic response and was classified as Success, Failure or Indeterminate. Global response was considered Success if there were both clinical success (resolution of signs and symptoms of ICC and no need for additional systemic antifungal therapy) and microbiologic success (eradication of *Candida* spp. present at baseline as determined on follow-up culture or presumed eradication if culture data were not available and the patient had a successful clinical response). Other secondary endpoints included rates of relapse (any baseline *Candida* spp. isolated after eradication or culture data are not available for a patient with a clinical response of failure after a previous response of success) and new infection (patient classified as clinical failure with the emergence of new *Candida* spp. at the original site of infection or at a distant site of infection) at weeks 2 and 6 follow-up visits and all-cause mortality.

Statistical Analysis

No formal statistical analysis was planned. Statistical evaluations were primarily descriptive with frequencies and/or percentages presented for categorical data. All patients who received at least 1 dose of study treatment were included in the safety analysis. Efficacy endpoints were assessed in the MITT population.

RESULTS

Patient Characteristics and Baseline Demographics

In this analysis, 49 patients (n = 19, 2 to <5 years; n = 30, 5 to <18 years) received anidulafungin (median 11 days; range 1–35 days) and were assessed for safety (Table 1). Overall, 25 of 49 patients (51.0%) switched to oral fluconazole [n = 10/19 (52.6%), 2 to <5 years old; n = 15/30 (50.0%) 5 to <18 years old]. The median time that patients were switched to oral fluconazole was 12 days (range 10−22 days), and the median dose of fluconazole was 7.8 mg/kg/d.

Forty-eight patients (98%) had microbiologically confirmed *Candida* infection (MITT population) (Table 1). For a majority of patients (n = 46, 95.8%), the site of infection was the blood, and central venous catheter involvement was reported in 31 patients (64.6%) (Table, Supplementary Digital Content 2, http://links.lww.com/INF/D351). The most frequently reported risk factors for *Candida* infection were the use of a central venous catheter and the use of broad-spectrum antibiotics, in 79.2% and 70.8% of patients, respectively (Table, Supplementary Digital Content 2, http://links.lww.com/INF/D351).

Safety

All patients reported at least 1 treatment-emergent AE, with diarrhea (22.4%), vomiting 24.5%) and pyrexia (18.4%) being most frequent (Table 2). Table (Supplemental Digital Content 3, http://links.lww.com/INF/D352) presents treatment-emergent

TABLE 1. Baseline Characteristics of Safety Population

Characteristics	Age Group		
	2 to <5 yr (n = 19)	5 to <18 yr (n = 30)	Overall (N = 49)
Sex (male), n (%)	11 (57.9)	17 (56.7)	28 (57.1)
Race, n (%)			
White	15 (78.9)	20 (66.7)	35 (71.4)
Black	1 (5.3)	0 (0.0)	1 (2.0)
Asian	2 (10.5)	4 (13.3)	6 (12.2)
Other	1 (5.3)	6 (20.0)	7 (14.3)
Mean age, yr (SD)	3.1 (0.7)	10.7 (3.7)	N/A
Anidulafungin treatment	n = 19	n = 30	n = 49
Median days (range)	11.0 (1–28)	11.0 (1–35)	11.0 (1–35)
Fluconazole treatment	n = 10	n = 15	n = 25
Median days (range)	9.0 (4–16)	7.0 (1–52)	N/A
Baseline pathogen*, n (%)	n = 18	n = 30	n = 48
Candida albicans	10 (55.6)	8 (26.7)	18 (37.5)
C. parapsilosis	2 (11.1)	10 (33.3)	12 (25.0)
C. tropicalis	1 (5.6)	6 (20.0)	6 (12.5)
C. lusitaniae	1 (5.6)	4 (13.3)	5 (10.4)
C. glabrata	2 (11.1)	1 (3.3)	3 (6.3)
C. guilliermondii	2 (11.1)	1 (3.3)	3 (6.3)
C. famata	1 (5.6)	0 (0.0)	1 (2.1)
C. haemulonii	1 (5.6)	0 (0.0)	1 (2.1)

*As per local laboratory data.
N/A indicates not available; SD, standard deviation.

TABLE 2. Incidence of Treatment-emergent AEs of All Causalities (Affecting >10% of Safety Population)

AE, n (%)	Age Group 2 to <5 yr (n = 19)	5 to <18 yr (n = 30)	Overall (N = 49)
Vomiting	7 (36.8)	5 (16.7)	12 (24.5)
Diarrhea	2 (10.5)	9 (30.0)	11 (22.4)
Pyrexia	3 (15.8)	6 (20.0)	9 (18.4)
Epistaxis	3 (15.8)	5 (16.7)	8 (16.3)
Headache	1 (5.3)	6 (20.0)	7 (14.3)
Abdominal pain	3 (15.8)	3 (10.0)	6 (12.2)
Alanine aminotransferase increased	2 (10.5)	3 (10.0)	5 (10.2)
Hypotension	2 (10.5)	3 (10.0)	5 (10.2)

If the same patient in a given treatment had more than one occurrence in the same preferred event category, only the most severe occurrence was recorded. Includes AEs occurring during the treatment period and up to 30 d after last dose of study treatment.

AE indicates adverse event.

AEs that were less common (affecting >5% and <10% of the safety population). No clinically relevant differences in reported AEs were noted in patients who received anidulafungin only compared with patients who received anidulafungin plus oral fluconazole (Table, Supplementary Digital Content 4, http://links.lww.com/INF/D353). Eighteen patients (36.7%) experienced AEs considered by the investigator to be possibly related to treatment. The most frequent treatment-related AEs were diarrhea, vomiting, increased alanine aminotransferase and increased aspartate aminotransferase, occurring in 3 patients each, and pyrexia, leukopenia and increased transaminases, occurring in 2 patients each; all other treatment-related AEs occurred in 1 patient each. All of the treatment-related AEs were mild or moderate in severity with the exception of 5 severe AEs which occurred in 1 patient each: neutropenia, gastrointestinal hemorrhage, increased transaminases, hyponatremia and myalgia. Overall, 5 patients (10.2%) discontinued treatment because of AEs, and in 4 patients the AEs (increased transaminases, increased alanine/aspartate aminotransferases, vomiting and pruritus generalis) were considered related to anidulafungin treatment (8.2%). None of the severe AEs led to discontinuation of anidulafungin with the exception of increased transaminases for 1 patient. Two patients (4.1%) underwent infusion rate reduction or temporary discontinuation because of AEs. The infusion rate of anidulafungin was reduced for 1 patient because of venous access irritation, and fluconazole treatment was interrupted in another patient because of gastrointestinal bleeding. SAEs were observed in 23 patients (46.9%) with 2 SAEs reported as related to anidulafungin treatment (increased transaminases and gastrointestinal hemorrhage).

All-cause mortality was 8.2% (4/49) by EOIVT and 14.3% (7/49) by week 6 follow-up. Of the 7 deaths during the study, none were considered to be treatment-related. One death was considered to be related to ICC. This patient (*C. albicans* at baseline) discontinued anidulafungin treatment after 1 dose because of pruritus generalis, subsequently received IV fluconazole and micafungin and died of septic shock (day 20). The remaining deaths were related to other conditions, including acute respiratory failure, acute respiratory distress syndrome, intracranial hemorrhage, progression of medulloblastoma, sepsis and septic shock. The 1 patient who died of sepsis had positive blood cultures for *Stenotrophomonas maltophilia* but no *Candida* growth at the time of death. For the patient who died of septic shock (day 1), death was assessed by the investigator to be related to previous septic shock resulting from neutropenia caused by chemotherapy treatment.

TABLE 3. Anidulafungin Global Response Success Rates by Age Group (MITT Population)

Endpoint, n/N (%)	Age Group 2 to <5 yr (n = 18)	5 to <18 yr (n = 30)	Overall (N = 48)
EOIVT	14/18 (77.8)	20/30 (66.7)	34/48 (70.8)
EOT	14/18 (77.8)	21/30 (70.0)	35/48 (72.9)
Response by site of infection at EOIVT			
Blood only	13/16 (81.3)	20/29 (69.0)	33/45 (73.3)
Blood/other sterile site	0/1 (0.0)	-	0/1 (0.0)
Other sterile site	1/1 (100.0)	0/1 (0.0)	1/2 (50.0)
Response by neutrophil count at EOIVT			
≤500/mm^3	2/3 (66.7)	3/6 (50.0)	5/9 (55.6)
>500/mm^3	11/13 (84.6)	14/19 (73.7)	25/32 (78.1)

Global response of failure from a prior visit is carried forward.

EOIVT indicates end of intravenous treatment; EOT, end of treatment; MITT, modified intention-to-treat.

Efficacy

The overall global response success rate was 70.8% at EOIVT (Table 3). In a sensitivity analysis at EOIVT (excluding indeterminate and missing data), the global response success rate was 93.3% in patients 2 to <5 years old and 87.0% in those 5 to <18 years old. Global response success rates according to age group, site of infection and baseline neutrophil count are shown in Table 3. Among the 2 most commonly reported baseline pathogens, *C. albicans* and *C. parapsilosis*, the overall global response success rates at EOIVT were 61.1% and 83.3%, respectively (Table, Supplementary Digital Content 5, http://links.lww.com/INF/D354).

There were no new *Candida* infections reported at the week 2 and week 6 follow-up visits in either age group. There were also no relapses of *Candida* infection reported at the week 2 follow-up visit. At the week 6 follow-up visit, 1 patient in the 2 to <5 years age group was reported to have a relapse of *C. albicans* infection and 2 patients in the 5 to <18 years age group were reported to have relapse of *Candida* infection (*C. parapsilosis*, culture data not available for the second patient who had a clinical response of failure and was assessed as relapsed infection because of response definitions).

In patients who achieved negative blood culture for *Candida* spp., the median time from first dose of study treatment to first negative blood culture for *Candida* spp. was 3.0 days (range 2−37 days). One patient did not achieve first negative blood culture until 37 days because no blood culture was obtained at EOIVT (assessed at presumed eradication).

Microbiology Findings

Microbiologic response of success (eradication plus presumed eradication) was observed in 14 of 18 patients (77.8%) for *C. albicans* and 11 of 12 (91.7%) patients for *C. parapsilosis* at EOIVT (Table, Supplementary Digital Content 5, http://links.lww.com/INF/D354). For those *Candida* spp. for which interpretive criteria were available, there were no isolates resistant to anidulafungin (Table, Supplementary Digital Content 6, http://links.lww.com/INF/D355). The remaining spp., for which interpretive criteria were not available, included 6 *C. lusitaniae* [anidulafungin minimum inhibitory concentration $(MIC)_{50/90}$ 0.125/0.25µg/mL] and 1 *Kodamaea ohmeri* (anidulafungin $MIC_{50/90}$ 0.25/0.25).

DISCUSSION

In this report of the safety and efficacy of anidulafungin in pediatric patients 2 to <18 years old with ICC, treatment with

anidulafungin appeared effective and the safety profile was consistent with the known safety profile of anidulafungin and previous data from adult studies.[9,10]

The most common AEs were diarrhea (22.4%), vomiting (24.5%) and pyrexia (18.4%). In adults with ICC, the most common AEs reported with anidulafungin treatment were diarrhea (10.2%), hypokalemia (9.0%) and pyrexia (8.6%).[9] Although the patient numbers in this study were small, anidulafungin was generally well tolerated. In line with the adult population, reported AEs were consistent with the known safety profile for anidulafungin and the pattern of events expected for the patient population.[9,10]

Of the 7 deaths reported in this analysis (7/49; 14.3%), none were considered related to study treatment. Mortality rates for ICC can be difficult to examine in pediatric patients because of the complexity and severity of underlying conditions. Increased mortality rates have been observed in children with ICC compared with controls in the intensive care unit setting.[11,12] Numerically lower all-cause mortality rates were observed in the 2 to <5 years old group in this study (10.5%) compared with those 5 to <18 years old (16.7%). A greater proportion of patients in the 5 to <18 years old group had an intensive care unit stay for >4 days compared with patients 2 to <5 years old, which could reflect more serious underlying conditions in the older age group. In addition, an increased frequency of non-*albicans* spp. was also noted in the older age group, which may be an additional factor in the mortality rates observed. Previous studies have identified higher mortality rates for non-*albicans* spp. including *C. tropicalis*.[13,14] In this study, 3 of 6 patients with baseline pathogen of *C. tropicalis* died; however, these deaths were related to other conditions and were not associated with ICC. Overall, no new safety concerns were identified for anidulafungin in this study, though safety conclusions are limited by the small numbers of patients in each age group.

The overall global response success rate at EOIVT in this pediatric population with invasive candidemia (70.8%) was similar to that previously observed in the adult registration study of anidulafungin (75.6%)[15] and a recent pooled analysis (76.4%) of adult patients.[9] We note that the patient numbers vary slightly between age groups in this study and overall are small, which could influence the differences in response and mortality rate between age groups.

Although some aspects of pediatric and adult ICC are similar, studies have identified differences in *Candida* spp. distribution and prognostic outcomes according to age group.[16–18] *C. albicans* and *C. parapsilosis* were the most common baseline pathogens in this study. Compared with *C. albicans*, microbiologic and global success rates were higher in patients with a baseline pathogen of *C. parapsilosis*, for which microbiologic success was achieved in all but 1 patient (although study numbers are small). Among all baseline *Candida* spp., only 3 patients at EOIVT/EOT visits were assessed as global response of failure, 1 each for *C. albicans*, *C. parapsilosis* and *C. tropicalis*. The primary difference in overall success rates among baseline pathogens was probably associated with the higher rates of indeterminate responses for *C. albicans* (22%–28%) and *C. tropicalis* (50%) compared with *C. parapsilosis* (8.3%). For those *Candida* spp. for which interpretive criteria were available, there were no study isolates resistant to anidulafungin. $MIC_{50/90}$ values for anidulafungin against *Candida* spp. recovered in this current study and were generally consistent with those previously reported.[19]

Though this current study is one of the largest pediatric studies of antifungal agents,[20] its main limitation is that it is an open-label, noncomparative study with a small sample size, which is particularly notable when stratifying patients according to age, baseline pathogen or risk factor. Also, most qualifying infections were candidemia (blood only), and therefore comparisons with other tissue sites were limited. The study, however, was designed primarily to provide descriptive data to assess the safety and tolerability of anidulafungin in pediatric patients at the chosen therapeutic dose. The study was not powered to statistically evaluate efficacy.

In conclusion, the data from this study support the use of anidulafungin as a treatment option for ICC in children 2 to <18 years old at the studied dose (3 mg/kg loading dose on day 1, followed by 1.5 mg/kg maintenance dose daily thereafter).

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APPENDIX: THE ANIDULAFUNGIN A8851008 PEDIATRIC STUDY GROUP:

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