Invasive candidiasis in patients with solid tumours treated with anidulafungin: efficacy analysis from six pooled studies

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INTRODUCTION

- *Candida* species are the most frequent cause of invasive fungal infection in patients with cancer[1] and patients with solid tumours are at increased risk of invasive candidiasis (IC).[2]
- An underlying pathology of solid tumours is the third-most common factor associated with IC, after surgery and medical care in the intensive care unit.[3]
- The Infectious Diseases Society of America guidelines recommend echinocandins as empiric treatment for suspected IC in adult patients in intensive care and in haematological settings.[4]
- Echinocandins are effective against a range of *Candida* species[5] and the class includes anidulafungin, which is approved in the United States and Europe for treatment of candidaemia and IC.
- Here, we report an analysis of anidulafungin treatment of IC in patients with past or present medical history of solid tumours.

METHODS

Setting

- Patient-level efficacy data were analysed from four anidulafungin open-label, non-comparative studies[6-9] and two double-blind, double-dummy, randomised studies that evaluated anidulafungin and caspofungin in patients with IC/candidaemia (Pfizer data on file) (**Table 1**). All studies had similar study protocols and endpoints, which permitted pooling of data.

Patients

- Male or female patients were included if they were aged ⩾18 years with culture-confirmed candidiasis (from blood, other sterile site or newly placed drains) within 96 h of study entry. Patients were also required to have clinical signs and symptoms of systemic *Candida* infection.
- Patients were excluded if they: had received >48 h of prior antifungal therapy; had prosthetic devices or vascular catheters at infection sites that could not be removed prior to or within 48 h of study entry; or had previously failed treatment for the current episode of candidaemia or IC.
- For the purpose of this analysis, patients were selected from the pooled database if they had a past (⩾6 months) or present (<6 months) history of solid tumours, prior to study entry.
- Solid tumour status was obtained by examining patient medical histories using the following search criteria: tumor, neopla* (neoplastic, neoplasia, neoplasm), mass, cancer, malign* (malignant, malignancy), growth, oncol* (oncology, oncological), carcinoma, adenocarcinoma and hepatoma.

Treatments

- In all six studies, patients received a single intravenous (IV) loading dose of 200 mg anidulafungin on Day 1, followed by 100 mg once daily.
- Patients could be switched to oral azole therapy after 5–10 days (**Table 1**) based on pre-specified criteria in the respective studies. IV anidulafungin and oral azole (if required) were maintained for ⩾14 days after the last positive culture.

Table 1. Prospective studies included in the analysis

Protocol/study	Region	Type of study	Indication
A8851011 (NCT00496197)[6,*,a]	USA, Korea	Open-label	Candidaemia and IC
A8851015 (NCT00548262)[6,*,a]	Latin America	Open-label	Candidaemia and IC
A8851016 (NCT00537329)[7,*,a]	Asia	Open-label	Candidaemia
A8851019 (NCT00689338)[8,*,b]	EU, Canada	Open-label	Candidaemia and IC
A8851021 (NCT00806351) (Pfizer data on file)[b]	EU, Russia	Double-blind, randomised	IC in neutropenic patients
A8851022 (NCT00805740) (Pfizer data on file)	USA, Canada, EU, Russia, Switzerland	Double-blind, randomised	*Candida* deep-seated tissue infection

*Switch to an oral azole (fluconazole or voriconazole) was permitted after: [a]⩾5 days of IV treatment or [b]⩾10 days of IV treatment
IC, invasive candidiasis; IV, intravenous

Endpoints

- The primary endpoint of the pooled analysis was global response success rate at the end of IV therapy (EOIVT) in the modified intent-to-treat (mITT) population, and included clinical and microbiological success.
- The mITT population included those who received ⩾1 dose of anidulafungin (ITT population) and had a confirmed diagnosis of candidaemia or a positive culture for *Candida* species.
- Global response success rate by baseline pathogen and site of infection were also evaluated.
- Secondary endpoints were global response success rate at end of all therapy (EOT), and all-cause mortality at Days 14 and 28. All studies also assessed safety.

Statistical analysis

- Analyses were for descriptive purposes. No hypotheses for efficacy endpoints were tested.
- Global response success rates were estimated with 95% confidence intervals for binomial proportion (Clopper-Pearson method).

RESULTS

- Out of 539 patients in the pooled database of six studies, 139 patients had confirmed IC and had a past or present medical history of solid tumours (26%). Baseline characteristics are shown in **Table 2**.

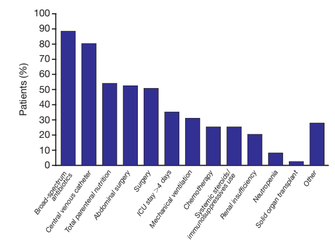
Table 2. Baseline characteristics

Characteristic	Total (N=139)
Sex (male), n (%)	73 (52.5)
Race, n (%)	
White	94 (67.6)
Black	15 (10.8)
Asian	23 (16.5)
Other	7 (5.0)
Mean age, years (SD)	63.1 (13.4)
18–44	13 (9.4)
45–64	58 (41.7)
⩾65	68 (48.9)
Mean APACHE II score (SD) (N=138)	14.9 (5.5)
APACHE II score ⩽20, n (%)	115 (82.7)
APACHE II score >20, n (%)	23 (16.5)
Baseline pathogen, n (%)*	
C. albicans	68 (48.9)
C. glabrata	30 (21.6)
C. tropicalis	22 (15.8)
C. parapsilosis	20 (14.4)
C. famata	2 (1.4)
C. kefyr	2 (1.4)
C. krusei	2 (1.4)
C. lusitaniae	1 (0.7)
C. sake	1 (0.7)
C. spp.	1 (0.7)
Other	4 (2.9)

N=139, unless stated
*Patients may be counted in >1 category
APACHE, Acute Physiology and Chronic Health Evaluation; SD, standard deviation

- The sites of infection at baseline were blood only (105/139, 75.5%), other sites (28/139, 20.1%) and blood plus other sites (6/139, 4.4%).
- Absolute neutrophil count was available for 88 patients; most (n=80) had >500 cells/μL.
- Overall, 54 patients switched from IV to oral therapy (fluconazole or voriconazole) after a median 8.0 days (range 4–34).
- The top five risk factors for IC included use of broad-spectrum antibiotics (88.5%), central venous catheter (80.3%), total parenteral nutrition (54.1%), abdominal surgery (52.5%) and surgery (50.8%) (**Figure 1**).

Figure 1. Risk factors for IC

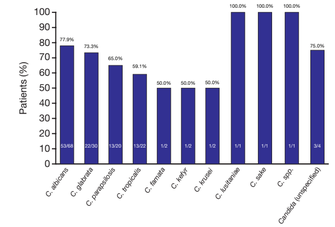


IC, invasive candidiasis; ICU, intensive care unit

Endpoints

- The global response success rate in the mITT population with solid tumours was 73.4% at EOIVT and 65.5% at EOT. Global response success rates by baseline pathogen are shown in **Figure 2** and **Table 3**.

Figure 2. Anidulafungin global response success rate at EOIVT by baseline pathogen



EOIVT, end of intravenous therapy

- Global response success rate by site of infection at EOIVT and at EOT are shown in **Table 3**.
- All-cause mortality was 14.4% (20/139) at Day 14 and 20.1% (28/139) at Day 28.
- Treatment-emergent adverse events of all causalities are shown in **Table 4**. The majority of adverse events were mild or moderate in severity (641/786; 81.6%).

Table 3. Anidulafungin global response success rate, global response by baseline pathogen and by site of infection in mITT population

	EOIVT	95% CI	EOT	95% CI
Global response, n/N (%)	102/139 (73.4)	66.0, 80.7	91/139 (65.5)	57.6, 73.4
Global response by baseline pathogen, n/N (%)				
C. albicans	53/68 (77.9)	68.1, 87.8	47/68 (69.1)	58.1, 80.1
C. glabrata	22/30 (73.3)	57.5, 89.2	21/30 (70.0)	53.6, 86.4
C. parapsilosis	13/20 (65.0)	44.1, 85.9	12/20 (60.0)	38.5, 81.5
C. tropicalis	13/22 (59.1)	38.5, 79.6	10/22 (45.5)	24.6, 66.3
C. famata	1/2 (50.0)	0.0, 100.0	1/2 (50.0)	0.0, 100.0
C. kefyr	1/2 (50.0)	0.0, 100.0	1/2 (50.0)	0.0, 100.0
C. krusei	1/2 (50.0)	0.0, 100.0	1/2 (50.0)	0.0, 100.0
C. lusitaniae	1/1 (100.0)	-	1/1 (100.0)	-
C. sake	1/1 (100.0)	-	1/1 (100.0)	-
C. spp.	1/1 (100.0)	-	1/1 (100.0)	-
Candida (unspecified)	3/4 (75.0)	32.6, 100.0	3/4 (75.0)	32.6, 100.0
Global response by site of infection, n/N (%)				
Blood only	79/105 (75.2)	67.0, 83.5	69/105 (65.7)	56.6, 74.8
Blood and other sterile site	2/6 (33.3)	0.0, 71.1	2/6 (33.3)	0.0, 71.1
Other sterile site	21/28 (75.0)	59.0, 91.0	20/28 (71.4)	54.7, 88.2

CI, confidence intervals; EOIVT, end of intravenous therapy; EOT, end of all therapy; mITT, modified intent-to-treat

Table 4. Incidence and severity of treatment-emergent adverse events during all treatment (IV anidulafungin + oral azole) by system organ class (MedDRA preferred terms) (N = 139)

Patients with adverse events, N (%)	**123 (88.5)**
Total events	**786**
Severity*: Mild/Moderate/Severe	349/292/145

Category	Events (any severity), n (%)	Severe events, n
Blood and lymphatic system	26 (18.7)	7
Cardiac	28 (20.1)	9
Ear and labyrinth	2 (1.4)	0
Eye	9 (6.5)	0
Gastrointestinal	64 (46.0)	12
General and administration site conditions	48 (34.5)	14
Hepatobiliary	11 (7.9)	3
Immune system	2 (1.4)	0
Infections and infestations	61 (43.9)	22
Injury, poisoning and procedural complications	13 (9.4)	3
Investigations	29 (20.9)	1
Metabolism and nutrition	44 (31.7)	3
Musculoskeletal and connective tissue	12 (8.6)	0
Neoplasms, benign, malignant and unspecified	15 (10.8)	13
Nervous system	20 (14.4)	3
Psychiatric	33 (23.7)	2
Renal and urinary tract	20 (14.4)	6
Reproductive system and breast	2 (1.4)	1
Respiratory, thoracic and mediastinal	46 (33.1)	18
Skin and subcutaneous tissue	20 (14.4)	2
Surgical and medical	4 (2.9)	1
Vascular	31 (22.3)	9

* If the same patient in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is taken. Patients are counted only once per treatment in each row
IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities

CONCLUSIONS

- In this population of patients with candidaemia/IC and solid tumours, anidulafungin had a global success response rate at EOIVT (73.4%) similar to that observed in the registrational study (75.6%).[10]
- The response rate was also high in patients infected by *C. parapsilosis*.
- Anidulafungin is effective for the treatment of candidaemia/IC in patients with solid tumours.

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DISCLOSURES

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