BRIEF REPORT

Laurence Senn
Philippe Eggimann
Riadh Ksontini
Andres Pascual
Nicolas Demartines
Jacques Bille
Thierry Calandra
Oscar Marchetti

Caspofungin for prevention of intra-abdominal candidiasis in high-risk surgical patients

L. Senn · A. Pascual · J. Bille ·
T. Calandra · O. Marchetti (✉)
Infectious Diseases Service,
Department of Medicine,
Centre Hospitalier Universitaire Vaudois
(CHUV) and University of Lausanne
(UNIL), Rue du Bugnon 46,
1011 Lausanne, Switzerland
e-mail: Oscar.Marchetti@chuv.ch
Tel.: +41-21-3141010
Fax: +41-21-3141018

P. Eggimann
Adult Intensive Care Service,
Centre Hospitalier Universitaire Vaudois
(CHUV) and University of Lausanne
(UNIL), Lausanne, Switzerland

R. Ksontini · N. Demartines
Visceral Surgery Service,
Centre Hospitalier Universitaire Vaudois
(CHUV) and University of Lausanne
(UNIL), Lausanne, Switzerland

J. Bille
Institute of Microbiology, Centre
Hospitalier Universitaire Vaudois (CHUV)
and University of Lausanne (UNIL),
Lausanne, Switzerland

Abstract *Purpose:* Thirty to forty percent of patients with recurrent gastrointestinal perforation/anastomotic leakage or acute necrotizing pancreatitis develop intra-abdominal invasive candidiasis (IC). A corrected *Candida* colonization index (CCI) ≥ 0.4 is a powerful predictor of IC. Fluconazole prevents intra-abdominal IC in this setting, but azole-resistant *Candida* species are emerging. The aim of this study was to explore the efficacy and safety of caspofungin for prevention of intra-abdominal IC in high-risk surgical patients. *Methods:* Prospective non-comparative single-center study in consecutive adult surgical patients with recurrent gastrointestinal perforation/anastomotic leakage or acute necrotizing pancreatitis. Preventive caspofungin therapy (70 mg, then 50 mg/day) was given until resolution of the surgical condition. *Candida* colonization index and CCI, occurrence of intra-abdominal IC and adverse events were monitored. *Results:* Nineteen patients were studied: 16 (84%) had recurrent gastrointestinal perforation/anastomotic leakage and 3 (16%) acute necrotizing pancreatitis. The median duration of preventive caspofungin therapy was 16 days (range 4–46). The colonization index decreased significantly during study therapy, and the CCI remained <0.4 in all patients. Caspofungin was successful for prevention of intra-abdominal IC in 18/19 patients (95%, 1 breakthrough IC 5 days after inclusion). No drug-related adverse event requiring caspofungin discontinuation occurred. *Conclusion:* Caspofungin may be efficacious and safe for prevention of intra-abdominal candidiasis in high-risk surgical patients. This needs to be further investigated in randomized trials.

Keywords Caspofungin · Prevention · Surgery · Pancreatitis · Candidiasis · Fungal infection

Background

Invasive candidiasis (IC) has emerged as a frequent complication in surgical critically ill patients [1, 2]. About one-third of patients with recurrent gastrointestinal perforations, anastomotic leakages or acute necrotizing pancreatitis develop intra-abdominal IC [3, 4]. *Candida* colonization is a major risk factor for IC in this setting

[5–7], and a corrected colonization index (CCI) ≥ 0.4 has been shown to predict IC with an efficiency of 100% [8].

Early identification of non-neutropenic patients at high risk of IC remains difficult and late therapy is associated with high morbidity and mortality. Few data are available on the utility of monitoring *Candida* colonization and/or non-invasive fungal markers [9–13]. Clinical prediction rules of the risk of IC have been investigated, but their role for guiding the decision to start antifungal therapy remains to be established [14, 15]. Fluconazole has been shown to prevent IC in high-risk surgical patients with a number needed to treat ranging between 3 and 10 [3, 12, 16–20]. In contrast, a study in ICU patients with persistent fever despite antibacterial therapy (incidence of IC 9%) failed to demonstrate the efficacy of empirical fluconazole therapy [21]. Based on a moderate to high level of evidence, guidelines from the Infectious Diseases Society of America (IDSA) recommend fluconazole for prevention of IC in high-risk surgical ICU settings [20, 22].

A broad use of azoles has been associated with a shift towards infections due to non-*albicans Candida* species with reduced antifungal susceptibility [23–26]. Preventive antifungal therapy should thus be used very selectively in patients at highest risk. Caspofungin, an approved agent for therapy of mucosal and invasive candidiasis, is active against azole-resistant *Candida* spp. [27]. As no experience on the role of echinocandins for prevention of intra-abdominal candidiasis in high-risk surgical patients is available, the aim of this study was to explore the efficacy and safety of caspofungin in this setting.

Patients and methods

Design

We conducted a prospective non-comparative single-center study between February 2006 and March 2007. The study was approved by the institutional ethical committee.

Patients' selection

Inclusion criteria were: (1) age ≥ 16 years, (2) recurrent gastrointestinal perforations/anastomotic leakage(s) after abdominal surgery or surgery for acute necrotizing pancreatitis during the preceding 7 days, and (3) written informed consent. Exclusion criteria were (1) documented IC at study entry, (2) ongoing antifungal therapy during >48 h, (3) severe hepatic insufficiency (Child–Pugh score >9), (4) caspofungin allergy, (5) pregnant or lactating woman, or (6) high probability of death within 72 h.

Preventive caspofungin therapy

A caspofungin loading dose (70 mg), was followed by 50 mg/day until resolution of the surgical condition defined by (1) recovery of gastrointestinal function and (2) no complication requiring surgical reintervention.

Clinical data

Demographic, clinical and laboratory data were collected at study entry and then twice weekly until end of follow-up, i.e., 1 week after end of study therapy or death.

Microbiological follow-up

Oral cavity, stool, urine, peritoneal fluid (at laparotomy or from surgical drains), and additional sites according to the underlying conditions were monitored for *Candida* colonization. *Candida* cultures on *Candida*-specific chromogenic plates (CAN2®, Biomerieux, France) were performed at study entry, twice during the first week, and then once weekly until end of follow-up. Colonization was assessed as weak, moderate, or heavy by semi-quantitative cultures using the clock-streak technique [5]. The colonization index (number of sites colonized/number of sites screened) and the CCI [(number of sites with heavy colonization/number of sites colonized) × colonization index] were calculated as previously reported [8]. Colonizing species were differentiated as *Candida albicans* and non-*albicans*.

Cultures of blood, urine, peritoneal fluid, surgical wounds, and other sites were performed as clinically indicated in the presence of symptoms/signs of infection. Invasive *Candida* isolates were identified to the species level and antifungal susceptibility was tested according to CLSI standards [28].

Definitions of *Candida* infections

IC was defined by: (1) intra-abdominal candidiasis including (1a) abscess with *Candida* isolated in pure or mixed culture or (1b) peritonitis in presence of fever, abdominal pain, tenderness on palpation, ileus, and leukocytosis ($>10 \times 10^9$/L) with isolation of *Candida* in the peritoneal fluid from laparotomy or drain effluents (in mixed bacterial and fungal cultures, *Candida* was regarded as pathogen when recovered from blood or in increasing amounts in serial cultures in absence of clinical improvement despite appropriate surgical and antibacterial treatment), (2) candidemia, i.e., positive blood cultures and clinical symptoms/signs of infection, (3) *Candida* urinary tract infection, i.e., $>10^5$ CFU/ml with pyuria and fever without other focus and/or with local symptoms/signs of

infection, (4) infection at another site, e.g., surgical wound infection with *Candida* isolated from a biopsy specimen or a purulent discharge.

Endpoints

The primary endpoint was the absence of breakthrough intra-abdominal IC during and within 1 week after discontinuation of preventive caspofungin therapy. Secondary endpoints were (1) absence of breakthrough extra-abdominal IC, (2) survival, (3) *Candida* colonization indices, and (4) drug-related adverse events according to the National Cancer Institute criteria [29].

Statistics

No sample size calculation had been performed for this observational non-comparative single-center exploratory study. Continuous variables and proportions of *Candida* colonization at start and end of preventive therapy were compared by non-parametric paired Wilcoxon signed rank test and Fisher's exact test, respectively. The correlation of continuous variables was studied by the non-parametric Spearman rank test.

Results

Clinical characteristics

Nineteen patients were included in the study. Demographics and clinical characteristics are shown in Table 1. All patients had abdominal surgery before inclusion: explorative laparotomy with/without gut resection and/or peritoneal lavage, or pancreatic necrosectomy. Fourteen (74%) patients required additional abdominal surgery after study entry.

Candida colonization

Data on *Candida* colonization are summarized in Table 2. Colonization index and CCI at baseline and at end of preventive caspofungin therapy are shown in Fig. 1. No patient developed a CCI ≥0.4 during preventive therapy. A decline of the colonization index was correlated with the duration of preventive caspofungin therapy (Spearman correlation coefficient $r = -0.46$, $P = 0.049$).

Success of preventive caspofungin therapy

Caspofungin was successful for prevention of intra-abdominal IC in 18/19 patients (95%). Only one

Table 1 Patients demographics and clinical characteristics

Patients	19
Gender: male/female	16/3
Age	69 (40–84)
Underlying surgical conditions	
Gastrointestinal perforation/anastomotic leakage	16 (84%)
Necrotizing pancreatitis	3 (16%)
Number of abdominal surgical interventions[a]	
Before inclusion	2 (1–6)
During preventive caspofungin therapy	1 (0–6)
Antibiotic therapy at baseline	19 (100%)
Hospitalized in ICU	14 (74%)
APACHE[b] II score at ICU admission	17 (10–30)
SAPS[c] II score at ICU admission	45 (31–65)
Mechanical ventilation	10 (53%)
Days of ICU stay	
Before inclusion	3 (0–14)
Overall	13 (3–56)
Days of preventive caspofungin therapy	16 (4–46)
Days of follow-up after study entry	28 (6–182)
Days of hospital stay	
Before inclusion	10 (1–43)
Overall[d]	37 (17–194)

Data are median (range), unless specified otherwise
[a] Explorative laparotomy with/without gut resection and/or peritoneal lavage, or pancreatic necrosectomy for therapy of recurrent gastrointestinal perforations/anastomotic leakage(s) or for acute necrotizing pancreatitis
[b] Acute physiology and chronic health evaluation
[c] Simplified acute physiology score
[d] In 14 patients who survived and were discharged

breakthrough IC (mixed intra-abdominal abscess due to *Enterococcus* spp., *C. glabrata* and *C. lipolytica*) occurred in a patient with ischemic colitis and recurrent intestinal perforations, who died from an intra-abdominal bleeding 5 days after study inclusion (no autopsy performed). However, as no intra-abdominal sampling for culture was available at baseline, an IC ongoing at study entry could not be ruled out. At the time of diagnosis, the *C. glabrata* isolate was susceptible to fluconazole and caspofungin (MIC 8 and 0.16 mg/l) and the *C. lipolytica* isolate had a reduced susceptibility to fluconazole (MIC 16 mg/l) and was susceptible to caspofungin (MIC 0.25 mg/l). The patient was colonized at study entry and remained colonized at time of death by a non-*albicans Candida* spp. No extra-abdominal breakthrough IC occurred.

Survival

Fourteen patients (74%) survived. Causes of death were: (1) acute necrotizing pancreatitis with multiple organ failure, intestinal perforation and bacterial peritonitis ($n = 2$), (2) ischemic colitis with extended intestinal necrosis, multiple perforations and bacterial peritonitis ($n = 2$), and (3) intra-abdominal hemorrhage with concomitant breakthrough IC ($n = 1$, see above).

Table 2 *Candida* colonization

	At study entry	At end of preventive therapy[a]
Patients colonized with *Candida* spp.	17/19 (89%)	9/14 (64%)[b,c]
Number of screened sites per patient, median (range)	4 (3–5)	4 (0–5)
Number of colonized sites per patient, median (range)	2 (0–4)	1.5 (0–3)
Number of sites colonized/number of sites screened	34/68 (50%)	17/53 (32%)[d]
Oropharynx	13/18 (72%)	5/12 (42%)
Stools	7/7 (100%)	7/11 (64%)
Lower respiratory tract	7/9 (78%)	2/6 (33%)
Peritoneal fluid	6/17 (35%)	3/13 (23%)
Urine	1/17 (6%)	0/12 (0%)
Number of colonizing *Candida* isolates	39[e]	26[e]
Candida albicans	27/39 (69%)	19/26 (73%)
Non-albicans *Candida* species	12/39 (31%)	7/26 (27%)

[a] In patients who survived

[b] In 1 patient who was not colonized at baseline, colonization with a non-*albicans Candida* species was documented at 1 site (stool) during preventive therapy

[c] $P = 0.11$. In all patients, including those who died: 14/19 (74%)

[d] $P = 0.06$. In all patients, including those who died: 29/75 (39%)

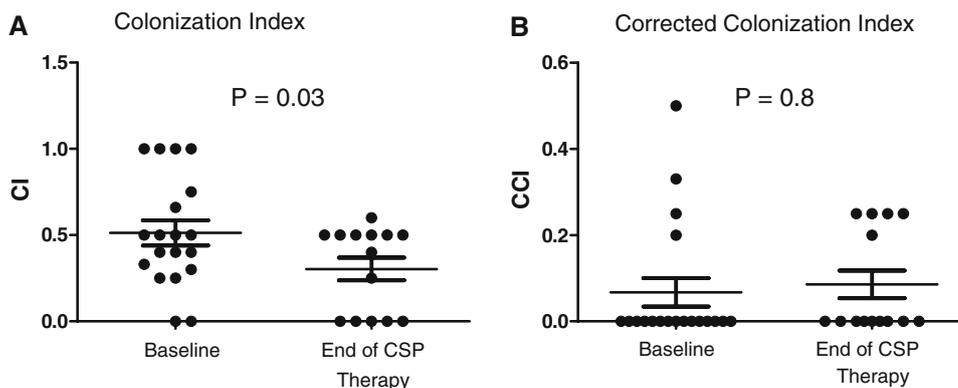[e] Four sites with ≥ 2 *Candida* species

Adverse events (AE)

No AE with probable or proven relationship with caspofungin was documented. AE possibly related to caspofungin were observed in 8 patients (42%): cholestasis in 7 (37%): grade 1 in 3, grade 2 in 1, and grade 3 in 3; hepatic cytolysis in 2 (32%), both grade 1; and skin rash in 2 (11%), both grade 1. However, all these patients were receiving simultaneously multiple co-medications, which may have been implicated in these AE. No AE required discontinuation of caspofungin.

Discussion

Based on a previous study conducted in our institution, we estimated that the risk of developing intra-abdominal IC in patients with recurrent gastrointestinal perforations, anastomotic leakages or acute necrotizing pancreatitis ranges 30–40% [3]. In this study of preventive caspofungin therapy in surgical patients enrolled on the basis of a high-risk clinical profile before the colonization status was known, this complication occurred in one single case (5%). This failure occurred despite in vitro susceptibility of the *Candida* isolates to caspofungin in a patient with a severe unresolved surgical condition complicated by intra-abdominal bleeding (primary cause of death) and bacterial co-infection, in whom an IC at baseline could not be ruled out. As expected from the drug safety profile, no AE requiring discontinuation of caspofungin was observed.

As in other studies in surgical patients with similar high-risk profiles [3, 5, 8, 16, 17, 30], most patients were colonized with *Candida* at baseline, but none with a CCI exceeding 0.4, a previously reported powerful predictor of

Fig. 1 Semi-quantitative assessment of the *Candida* colonization at baseline and at end of preventive caspofungin therapy in patients who survived. *Panel* **a** colonization index (CI = number of sites colonized/number of sites screened). *Panel* **b** corrected colonization index [CCI = (number of sites heavily colonized/number of sites colonized) × colonization index]. Each *symbol* represents a single patient. The *horizontal bars* represent the median values at each time point. Previous studies have suggested that a CCI ≥ 0.4 may predict IC with a positive predictive value of 100%

IC, which would have made them eligible for pre-emptive antifungal therapy [8, 11]. The *Candida* colonization index decreased at end of preventive therapy, and no patient developed a CCI exceeding 0.4. This finding is suggestive of a preventive action of caspofungin on the development of a heavy colonization, one of the initial steps in the pathogenesis of IC. No shift towards non-*albicans Candida* species occurred during preventive caspofungin therapy.

No experience is available on the efficacy of echino-candins, a new class of fungicidal drugs active against *Candida* species with decreased susceptibility to azoles, for prevention of IC. Despite limitations such as the open single-center non-comparative design and the small sample size, the observations of this proof-of-concept study suggest that caspofungin may be efficacious and safe for prevention of intra-abdominal candidiasis in surgical patients with a high-risk profile. This could be of particular interest in hospitals with a high prevalence of azole-resistant *Candida* species. The present exploratory results provide a stepping stone to future randomized studies designed to define the role of echinocandins for prevention of IC in such a high-risk setting, and to assess its impact on morbidity, mortality, and pharmaco-economic issues. Whether other antifungals licensed for therapy of IC, such as liposomal amphotericin B or voriconazole, may also be efficacious for prevention of IC needs to be investigated. Moreover, the utility of monitoring *Candida* colonization and of clinical prediction rules for guiding the decision to start pre-emptive antifungal therapy remains to be defined. Waiting for all these additional data, fluconazole remains the recommended first-line choice for a prevention based on straightforward clinical criteria.

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