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Rassegna

Review

Anidulafungina *versus* fluconazolo: approfondimento clinico sulle linee guida IDSA e ESCMID

Anidulafungin versus fluconazole: clinical focus on IDSA and ESCMID guidelines

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INTRODUCTION

The spectrum of disease of bloodstream infections by *Candida spp.* and invasive candidiasis is highly variable, ranging from aspecific symptoms to severe sepsis to organ specific signs or septic shock. The crude mortality rate ranges from 38% to 62% and up to 90% in patients with septic shock without source control with high attributable mortality [1-3]. Rate of positive blood cultures for Candida species raised fivefold in the past ten years placing this pathogen between the fourth and the sixth-leading cause of nosocomial bloodstream infections in United States and Europe, even though the sensitivity of culture has a great variability and non-culture tests may be needed to increase diagnosis [4-6]. *Candida albicans* is still the cause of approximately 50% of invasive candidiasis, but reports showed an increase in non-*albicans Candida* [7].

Echinocandins, fluconazole, voriconazole and liposomal amphotericin B were recommended by the 2009 IDSA guidelines with AI evidence for the treatment of candidemia, owing to data from at least one randomized trial [8]. However, echinocandins were favoured for patients with moderately severe to severe illness, reserving the use of fluconazole in selected situations, such as patients haemodynamically stable or without previous fluconazole exposure or with central nervous system disease [9]. A striking difference was highlighted by the 2012 ESCMID guidelines for the diagnosis and management of Candida disease in non-neutropenic adult patients, where fluconazole was downgraded to a CI recommendation ("marginal use"), with BI evidence for voriconazole and liposomal amphotericin B, maintaining AI ("strong support") for echinocandins [10, 11]. The added value of echinocandins after the publications of the two guidelines is shown by several reports [7, 12, 13]. In this perspective we briefly present and discuss the main clinical studies that supported the best treatment recommendation for echinocandins in invasive candidiasis and candidemia. We also discuss the possible reasons of the downgrading of fluconazole by the ESCMID guidelines.

Randomized controlled studies for echinocandins

Mora Duarte: caspofungin vs. amphotericin B deoxycholate [13]

This is a randomised double-blind trial comparing caspofungin (70 mg as loading dose, followed by 50 mg per day) with amphotericin B deoxycholate (0,6-1,0 mg/kg/die) for the treatment of 224 patients with invasive candidiasis, mostly candidemia. The most common Candida isolates were *C. albicans* (45%), followed by *C. parapsilosis, C. tropicalis* and *C. glabrata*.

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In the analysis of patients who met the prespecified criteria for evaluation, 80.7% of the caspofungin group and 64.9% of the amphotericin B group had successful outcomes at the end of intravenous therapy. The efficacy in patients with candidemia, as site of infection, was similar in the two groups (71,7% and 62,8% respectively) but caspofungin was better tollerated: the incidence of drug-related adverse events was significantly lower in the caspofungin group.

Reboli: anidulafungin vs. fluconazole [14]
Reboli et al. compared anidulafungin (200 mg on day 1 followed by 100 mg daily) with fluconazole (800 mg on day 1 and then 400 mg daily) in a randomised, double-blind, non-inferiority trial of treatment for invasive candidiasis (89% were candidemias) including 245 non-neutropenic patients.
The exclusion criteria were similar to the previous study and represented by: more than 48 hours of systemic antifungal therapy, fluconazole prophylaxis for >1 week within 30 days before enrollment, refractory Candida infection, elevated levels of hepatic enzymes or osteomyelitis, endocarditis, meningitis due to Candida species, in addition to *Candida krusei* infection (fluconazole is not active against *C. krusei*). At the end of intravenous therapy, treatment was successful in 75.6% of patients treated with anidulafungin and only 60.2% of those treated with fluconazole. Similar results were observed for secondary endpoints; the frequency and types of adverse events were similar in the two groups.
Moreover, some data were later available and showed that patients treated with anidulafungin had a faster time to negative blood cultures compared to fluconazole in *Candida albicans* infections (log-rank p <0.05, median times to negative blood culture 2 vs 5 days) and performed better if more severely sick [15]. In the *post hoc* analysis conducted on 163 patients anidulafungin had better results in more severely ill patients, with at least one criterion amongst APACHE II score ≥15, severe sepsis and/or admission in ICU: the global response was 70.8% vs. 54.1% for anidulafungin or fluconazole, respectively [16].

Pappas: micafungin vs. caspofungin [17]
This is a randomised, double-blind trial comparing two echinocandins (micafungin 100 or 150 mg/die and caspofungin at standard dosage) in 595 adults patients with candidemia (85% of cases) and other forms of invasive candidiasis. At the end of treatment, clinical success was observed in 76,4% of patients in micafungin 100 mg group, in 71,4% of micafungin 150 mg group and 72,3% of caspofungin group. There were no significant differences in mortality, relapsing and emergent infections, or adverse events between the study arms.

Kuse: micafungin vs. liposomal amphotericin [18]
This is a double-blind randomised, multinational, non-inferiority study (Phase III) comparing the efficacy of micafungin (100 mg/die) with liposomal amphotericin B (3 mg/kg/die) in the first-line treatment of 531 patients for invasive candidiasis/candidemia.
The success rates were similar in the two arms: 89,6% of patients (181) in the micafungin group and 89,5% (170) in amphotericin B group; the efficacy was consistent and independent of Candida species, site of infections, neutropenic status, APACHE II score and catheter removal. Micafungin had a low incidence of adverse events, including those leading to treatment discontinuation.

Rhunke: open study; anidulafungin in the ICU [19]
Anidulafungin was studied in a prospective, multicentre, phase IIIb study with an exploratory, open-label design by Ruhnke and colleagues to evaluate efficacy and safety of anidulafungin for the treatment of candidemia/invasive candidiasis in specific ICU patient populations, including at least one factor amongst the following: post-abdominal surgery, solid tumors, renal or hepatic failure, solid organ transplant, neutropenia and age ≥ 65 years.
Anidulafungin was administered at standard dosage for 10-42 days and after completing at least 10 days of treatment it was possible to switch to oral voriconazole or fluconazole, provided they had two consecutive negative blood cultures and resolution of signs and symptoms of disease.
The primary endpoint was global response (clinical and microbiological) at the end of treatment and secondary endpoints included global response at end of intravenous therapy and at two and six weeks post EOT (end of treatment), 90-day survival, and incidence of adverse events.
The primary analysis of efficacy was conducted in MITT population (modified intent-to-treat) on 170 patients, whilst the safety was evaluated in 216 patients. Predominant isolates were: *C.*

albicans (55.9%), *C. glabrata* (14.7%) and *C. parapsilosis* (10.0%). The mean duration of treatment in MITT population was 19,9 days (median, 18,5; range, 1-67), with a mean duration of anidulafungin therapy of 15,9 days (median, 14; range, 1-42).
At the end of treatment the global success was observed in 107 cases out of 154 patients included in the analysis (69,5%); these rates were 70,7% (111/157) at the end of intravenous treatment, 60,2% (77/128) and 50,5% (55/109) at 2 and 6 weeks post EOT respectively. The rates were high even in patients with septic shock (75%, 56% and 45,5; respectively).
The microbiological responses were similar to clinical outcomes.
No significant differences were observed in global and microbiological success rates amongst most patient populations, with the possible exception of those with neutropenia and solid organ transplants, where the response was lower.
Success rates did not change according to the Candida isolate (except for *C. tropicalis*), APACHE II score and presence of septic shock; the 90-day survival was 53,8%. Drug-related adverse events were observed in 33/216 patients (15,3%, mainly erythema and hypotension) and there were only four (1,9%) treatment-related adverse events.

The issue of anidulafungin and fluconazole

Echinocandins are now perceived as first-line antifungals in the treatment of candidemia [12, 14, 20]. In 2009, the IDSA guidelines recommended fluconazole with AI evidence due to the results of the Reboli trial where non-inferiority was met with anidulafungin (75.6% vs 60.2%) [14].
By a methodological point of view, a non-inferiority was demonstrated, meaning that the differences are not significant, but the Reboli trial clearly showed a lower time to clinical stability and reduced time to negative blood cultures in the anidulafungin arm, together with a higher response in the anidulafungin arm in patients more sick (70.8% vs 54.1%) or with *C. albicans* infections (81.1% vs 62.3%) [16,15]. Accordingly, the main difference between the North American and the European guidelines, even considering the different grade of recommendation, affects the scoring of the quality of the evidence for fluconazole, which is mostly based on the different considerations of the results of the Reboli trial [14].
Notwithstanding the non-inferiority, the IDSA guidelines stated that fluconazole should be reserved to less severe patients, without haemodynamic instability and/or not recently treated with fluconazole, or with *C. parapsilosis* infection, with a word of caution on fluconazole as compared to echinocandins.
The latest European guidelines (ESCMID) had a slightly different grading system, where A (good evidence from one or more randomized, controlled trials) refers to a strong support to clinical use ("Good evidence for the IDSA") and C marginally supports clinical use ("poor support for the IDSA guidelines") [10].
Accordingly, fluconazole has received a CI indication for treatment of candidemia and anidulafungin has maintained the AI as in the IDSA guidelines, similarly to the other echinocandins. The main question raised by some authors regarding the CI recommendation for fluconazole is how can a non-inferiority trial support AI for anidulafungin and CI for fluconazole, if the results are consistent with the non-inferiority?
However, besides the known fungistatic activity of fluconazole, the Reboli trial also reported higher response rate with anidulafungin compared to fluconazole in patients with *C. albicans* infections (81.1% vs. 62.3%), a result confirmed also in ICU patients in all Candida isolates, in the *post hoc* analysis [14].
Moreover, fluconazole was inferior in the subgroup of patients with higher APACHE II score, is marginally active against *C. glabrata* and is not active against *C. krusei*, which was excluded from the study per-protocol.
It is true that the European guidelines reinforced the available data on the better performance of echinocandins compared to fluconazole, also analyzing the Reboli data under the light of the inferiority of fluconazole in time-to-negative blood cultures and severely ill patients.
There were other papers supporting the low mortality with echinocandins: for example, Ortega reported a 10% mortality with caspofungin as a definite treatment of candidemia and the mortality was only 12% in patients with late-onset candidemia [12, 21].
The literature on anidulafungin is growing with case reports of efficacy, together with effective and timely cardiosurgery, of 200 mg daily of anidulafungin in patients with infective endocarditis by *C. glabrata,* a dosage perhaps supported by the IDSA guidelines, and data on pharmacokinetics of anidulafungin in patients

with septic shock and continuous veno-venous haemodialysis [22, 23]. Can the pharmacology support the best treatment recommendations for echinocandins? The echinocandins are concentration-dependent, active against biofilm-producing strains and fungicidal against *Candida spp*. (with the exception of *C. parapsilosis*), inhibiting the synthesis of β-1,3-glucan, with anidulafungin having the highest volume of distribution, as compared to fluconazole, a fungistatic, time-dependent antifungal without activity against biofilm-producing strains [24]. Fluconazole may be best used nowadays as a de-escalating antifungal, after clinical response and microbiological clearance has been achieved by first-line antifungals [13, 14, 19]. The safety profile of anidulafungin is well-recognized and it can be administered to patients with any degree of renal or hepatic impairment and does not require dose adjustements with comorbidities or any concomitant drugs [25, 26]. A recent Italian paper by Rosato published in 2013 confirmed the role *in vitro* of anidulafungin in biofilms and showed better performances in *C. albicans* and *C. tropicalis* with respect to *C. parapsilosis* [27]. In conclusion, the new ESCMID guidelines highlighted the efficacy of echinocandins in the treatment of candidemia and for the first time fluconazole was somehow down-graded. There is a growing body of evidence for the better efficacy of echinocandins in patients with candidemia or invasive candidiasis inside and outside the intensive care unit. However, the current view that fluconazole is especially useful in particular settings, for example in de-escalation treatment strategies after clinical and microbiological success with echinocandins, may be challenged by the results of a recent paper in patients with septic shock (28).

Keywords: anidulafungin, fluconazole, candidemia, echinocandin, guidelines.

SUMMARY

Invasive infections by *Candida spp.* play a major role in the management of the critically ill patient. Rates of positive blood cultures for *Candida* species have risen fivefold in the past ten years, placing this pathogen between the fourth and the sixth-leading cause of nosocomial bloodstream infections in the United States and Europe.
Candida albicans is still the cause of approximately 50% of invasive candidiasis, with heterogeneous epidemiology.
The echinocandin class, along with voriconazole and liposomal amphotericin B, was recommended by 2009 IDSA guidelines with AI evidence for the treatment of candidaemia, reserving the use of fluconazole in selected situations. Conversely fluconazole was downgraded to CI recommendation ("marginal use"), with BI evidence for voriconazole and liposomal amphotericin B, maintaining AI ("strong support") for echinocandins by 2012 ESCMID guidelines for the diagnosis and management of Candida disease in non-neutropenic adult patients. Our brief analysis of randomized trials, whereby recommendations are supported, aims to discuss the possible reasons for the different consideration of fluconazole by the two above mentioned guidelines.

RIASSUNTO

Le infezioni invasive da Candida spp. *rivestono un ruolo importante nella gestione dei pazienti critici. Negli ultimi dieci anni la prevalenza di emocolture positive è aumentata di cinque volte, posizionando questo patogeno al quarto e sesto posto delle infezioni nosocomiali del torrente circolatorio rispettivamente negli Stati Uniti e in Europa. Il 50% circa delle infezioni invasive da Candida è causato da* Candida albicans*, con variazioni epidemiologiche. La classe delle echinocandine ha un'evidenza di grado AI ("buona evidenza") nelle linee guida IDSA del 2009 per il trattamento della candidemia, insieme a voriconazolo e amfotericina B liposomiale, limitando l'uso del fluconazolo a situazioni particolari. Diversamente, le linee guida ESCMID del 2012 per il trattamento e la gestione delle infezioni da Candida negli adulti non-neutropenici, assegnano una raccomandazione di grado CI ("marginale evidenza") al fluconazolo mentre confermano il grado AI ("forte evidenza") alla classe delle echinocandine.*
Riportiamo una breve disamina dei trial randomizzati alla base di queste raccomandazioni, con l'intento di mettere in evidenza il substrato scientifico della eterogenea considerazione del fluconazolo nelle due linee guida esaminate.

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