LETTER

Low Dosage Liposomal Amphotericin B in the Treatment of *Candida* Infections in Critically Ill Patients

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Candida spp. is the most common cause of fungal infections and an important pathogen causing nosocomial bloodstream infections with significant morbidity and mortality, especially in critically ill patients [1-3]. Based on *in vitro* studies, amphotericin B has the broadest spectrum of activity and may treat a wide range of *Candida* infections. At least one large randomized double-blind clinical study has shown liposomal amphotericin B (L-AMB) to be non-inferior to micafungin in the treatment of candidemia. In this study micafungin (100 mg/ day) was compared with liposomal amphotericin B (3 mg/kg/day) in 531 patients with invasive candidiasis (mostly candidemia) [4]. Although L-AMB has been licensed at 3-5 mg/kg per day, the optimal dosage of this compound in the treatment of candidemia is unclear. The efficacy of L-AMB in *Candida* infections was also investigated in two other studies (pre-clinical 104-00 and 104-10) [5]. Clinically and mycologically, L-AMB was comparable to conventional amphotericin B in the treatment of candidiasis when clinical success and mycological eradication rates, respectively, were assessed. In that study L-AMB was administrated once daily over 30-60 minutes at doses ranging from 0.2 to 3 mg/kg/day.

In two prospective, parallel comparative multicenter trials two dosages of L-AMB (1 mg/kg/day vs 3 mg/kg/day) were compared in the empirical treatment of febrile neutropenia not responding to 96 hours of systemic broad-spectrum antibiotic treatment. Efficacy assessments indicated success in 58% of patients treated with low-dose and 64% with higher-dose, respectively [6].

Based on pharmacodynamic data, *in vitro* experiences and clinical observations, L-AMB 1-3 mg/kg/daily is safe, well tolerated and produces plasma concentrations significantly greater than the typical minimum inhibitory concentration (MIC) values for all *Candida* species for the entire dosing interval [7,8]. Based on these concepts we evaluated the efficacy and tolerability of L-AMB at the dosage of 2 mg/kg/daily in critically ill patients admitted to Intensive Care Unit (ICU) with candidemia.

Success was defined as: 1) absence of all clinical signs and symptoms present at baseline; 2) absence of any new signs and symptoms that may be observed during the episode of candidemia or alternative explanation for persistent or relapsing clinical signs and symptoms present at baseline or during the episode of candidemia such as clearly detectable bacteria (i.e. positive blood cultures) and 3) eradication of the fungal infection (negative cultures) or negative blood cultures for *Candida*. No systemic antifungal agent, other than the study drug, was administered for the episode of candidemia.

It was not recommended to declare failure (and therefore change of treatment) before giving at least 5 days of antifungal therapy.

The study did not achieve the planned enrollment of 39 subjects because it was interrupted for low recruitment. Here we would like to report on the 8 subjects enrolled and treated. The study was approved by the local Ethic Committees and all patients signed an informed consent. All subjects were Caucasian, with an age ranging from 45 to 76 years (mean 62.4). APACHE II scores ranged from 8 to 25 (mean 18.6). All subjects received 2 mg/kg/day of L-AMB for a mean duration of 12.2 days.

The *Candida* species isolated were: *C. albicans* (4), *C. parapsilosis* (2) and *C. glabrata* (2). The MIC of L-AMB ranged from 0.25 to 1.0 μg/ml.

Central venous catheters were removed in all patients within 48 hours, after the yeast identification.

Overall, 6 of 8 patients (75%) achieved treatment success at the end of therapy. The 4 subjects available for follow-up assessment were still cured at the second and fourth weeks after end of therapy. Only 2 patients failed treatment: 1 had recurrence of candidemia due to *C. parapsilosis* and 1 interrupted treatment for persistence of positive urine cultures for *C. albicans*, after urinary catheter removal and was treated with another antifungal. No drug-related adverse events were reported. All subjects had hypoalbuminemia, related to the underling conditions and most subjects also had electrolyte abnormalities, particularly hypocalcemia and hypokalemia. Two patients died for cardiocirculatory arrest, considered unrelated to study drug.

The results of this Phase II, open-label, pilot study of L-AMB (2 mg/kg/day) as a treatment for candidemia in non-neutropenic subjects cannot lead to any conclusions because of the small number of patients. However, it may constitute the rationale for further studies aimed at rationalizing dosages and improving our understanding of treatment of candidemia.

TRANSPARENCY DECLARATIONS: In the past 5 years, M.B. has been an advisor/consultant for Gilead Scienses, Merck Sharp and Dohme, Novartis, Pfizer and Schering Plough. He has been paid for talks on behalf of Angelini, Astellas, Astra Zeneca, Aventis, Bayer, Cephalon, Glaxo SmithKline, Gilead Sciences, Jansen Cilag, Merck Sharp and Dohme, Novartis, and Pfizer. The other authors declare that they have no competing interests.

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