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Case collection study of the safety of AmBisome in association with voriconazole in the treatment of patients with invasive fungal infection

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Invasive fungal infections (IFIs) are potentially life-threatening complications of intensive chemotherapy, hematopoietic stem cell transplantation, hematological malignancies, solid tumors, or in critically ill patients Combination antifungal therapy has been proposed among other strategies as an approach to improve outcome as rescue treatment in high-risk patients[1]. The efficacy and safety of liposomal amphotericin B and voriconazole in monotherapy have been demonstrated in several clinical trials in patients with IFIs[2-5], however there are no data of the safety of both antifungal treatments in combination. In this report we present our experience of the combination of liposomal amphotericin B and voriconazole administered to high risk patients**.**

The objective of this small case collection study was to assess the safety of liposomal amphotericin B in combination with voriconazole in the treatment of proven, probable or possible invasive fungal infection (as defined by modified *EORTC* criteria)[6] in patients treated in the period of October 2003-November 2006 in 9 centres of Spain. Laboratory parameters (creatinine, bilirubin, alkaline phosphatase and liver enzymes), reported twice baseline value were considered as adverse events.

Thirteen patients were included in the study, seven of them were male and the overall age range was 14 to 71 years. Eight patients were oncohematologic and the remaining five cases were intensive care patients. None of the patients had previous IFIs.

Four hematologic patients presented with a proven IFI (*Aspergillus flavus, Fusarium* spp, *Scedosporium* spp, and *Candida* spp + unidentified mold), two patients presented with a probable IFI (*Fusarium oxysporum* and *Scesdosporium* spp) and two patients presented with a possible IFI (in one case cerebral toxoplasmosis was diagnosed in the necropsy study). Four intensive care patients presented with a proven infection (Candidemia) and the other patient had a probable IFI (*Aspergillus flavus* and *Aspergillus fumigatus* obtained from bronchial aspirated secretions).

All patients received antifungals prior to the administration of concomitant AmBisome and voriconazole. Eight patients were already receiving voriconazole when AmBisome was added and three patients were already receiving AmBisome when voriconazole was added. Doses of AmBisome ranged from 2 to 5.5 mg/kg/day with a median of 3.5 mg/kg/day. The daily dose of voriconazole ranged from 300 to 600 mg with a median of 400 mg. The combination was administered for a minimum of 6 days and a maximum of 50 days with a median duration of 17 days.

Hepatic function: Nine patients had hepatotoxicity (defined as increases in hepatic function tests to twice the baseline value) reported as an adverse event. Two of them were receiving potentially hepatotoxic concomitant medications. One of the nine patients presented with cholecystitis as the main underlying disease and one of the nine patients discontinued voriconazole treatment due to hepatotoxicity probably related to voriconazole.

Renal function: One patient experienced an increase in serum creatinine to twice baseline value, but the value returned to normal at the end of treatment. No clinically relevant increases in serum creatinine were observed at the end of treatment for any patient even in the eleven patients who were taken nephrotoxic drugs concomitantly.

Survival: Two patients died within 1 month after study drug discontinuation: one patient after 48 hours and one after 30 days. None of the deaths were related to the fungal infection.

Although not powered for efficacy, we observed that ten out of thirteen patients achieved complete response with the combination. All four patients with proven candidemia achieved complete response and six out of seven patients with proven/probable filamentous fungi achieved complete response. A partial response was observed in two patients, and one patient with cerebral toxoplasmosis remained stable (this patient died 2 days after the end of the observation period) (see table 1).

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Table 1 **Baseline characteristics and effectiveness results**

N	Underlying disease	Neutropenia	IFI	Prior antifungals	Duration combined treatment	Response at the end of treatment	Survival at 30 days
			PROVEN IFI: Candidemia				
1	Peritonitis	No	Fungemia *C. glabrata*	Fluconazole 800 mg, 8 d Caspofungin 50 mg, 20 d	28 d	Complete	No
2	Solid tumor	No	Fungemia *C. parapsilosis*	Voriconazole IV 600 mg, 6 d	12 d	Complete	Yes
3	Cholecystitis	No	Fungemia *C. albicans*	Fluconazole 400 mg, 3 d Voriconazole IV 600 mg, 3 d	14 d	Complete	Yes
4	Solid tumor	No	Fungemia *C. albicans*	Voriconazole IV 500 mg, 8 d	8 d	Complete	Yes
			PROVEN/PROBABLE: Filamentous fungi				
5	Acute lymphoblastic leukemia	Yes	Proven: *Aspergillus flavus*	Fluconazole 100mg, 26 d Voriconazole IV 400mg, 3 d	18 d	Complete	Yes
6	Atipic chronic myeloid Alo HPSCT/chronic GVHD	No	Probable: *Fusarium oxysporum*	Voriconazole IV 700mg, 3 d	21 d	Complete	Yes
7	Acute myeloid leukemia	Yes	Proven: Fungemia *Fusarium* sp.	Caspofungin 50mg, 28 d	50 d	Complete	Yes
8	Chronic lymphatic leukemia	No	Proven: Filamentous fungi and *Candida* spp	Fluconazole 200mg, 6 d AmBisome, 10 d	28 d	Complete	Yes
9	Abdominal septic shock	No	Probable: *Aspergillus fumigatus* and *A. flavus*	Caspofungin,15 d Voriconazole IV, 22 d	22 d	Partial	Yes
10	Acute mieloid leukemia	Yes	Probable: *Scedosporium prolificans*	Itraconazole, 8 d Caspofungin, 8 d Caspofungin+voriconazole, 5 d Voriconazole, 20 d	17 d	Completa	Yes
11	Acute lymphoblastic leukemia	Yes	Proven: *Scedosporium prolificans*	Itraconazole, 17 d Caspofungin, 5 d Caspofungin+voriconazole, 3 d Voriconazole, 15 d	21 d	Complete	Yes
			POSIBLE IFI				
12	NHL/Autologous transplant	No	Posible: Rx SNC	Caspofungin 50mg, 19 d AmBisome 3,5mg/kg/d 5 d	6 d	Stable	No
13	Acute myeloid leukemia	Yes	Posible: Rx CNS	Itraconazole 200mg, 16 d AmBisome 3mg/kg/d, 3 d, 5mg/kg/d, 12 d	11 d	Partial	Yes

Since this is a small collection of cases it is difficult to draw conclusions, but safety data presented in this report suggests that the combination of liposomal amphotericin B and voriconazole could be administered to high risk patients as rescue treatment. There are some in vitro data that show potential antagonism/indifference of the combination amphotericin and triazoles[7], but it seems that in ten of our thirteen cases no evidence of clinical antagonism was

observed. In addition, both antifungals have AI evidence for the treatment of invasive aspergillosis and also for the treatment of invasive candidiasis in neutropenic patients according to recent IDSA guidelines[1,8] therefore it seems appropriate to use both in combination.

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