Role of liposomal amphotericin B (AmBisome®) in the prophylaxis of mycoses after liver transplantation

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Background

The incidence of invasive fungal infection (IFI) after liver transplantation (LTx) ranges from 5 to 42% [1]. *Candida albicans* and *Aspergillus fumigatus* are the most common pathogens in liver graft recipients, who are more susceptible to IFIs than any other type of solid organ transplant recipient. Onset of fungal infection is mainly within the first two months after LTx which is associated with a high mortality of up to 100% for systemic aspergillus infection [2,3]. The high rate of IFI in liver transplant patients is related to difficulties in establishing an early diagnosis, lack of effective therapy in many situations, difficult management of certain antifungal drugs, and limited data on effective regimens for antifungal prophylaxis [2,4].

However, amphotericin B is still the gold standard for the treatment of IFI, but its use is limited by adverse effects, mainly nephrotoxicity [5]. All of the current antimycotics cause various adverse effects. Simultaneous administration of fluconazole with cyclosporine or tacrolimus might cause increased trough levels of cyclosporine and tacrolimus by inhibition of cytochrome P450 3A [6,7]. New therapeutic approaches using immunomodulators (e.g. interferon-γ) are under investigation as adjuvants for antimycotic therapy [8].

A new potential alternative to amphotericin B is the liposomal formulation Ambisome®, a small unilammellar liposome preparation (diameter 45-80 nm) containing amphotericin B in the bilayer, which shows reduced toxicity and elevated peak plasma level compared with conventional amphotericin B without loss of the broad-spectrum antifungal activity of amphotericin B [9,10]. These attributes make liposomal amphotericin B attractive for prophylactic use in liver transplantation.

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Patients and Methods

88 liver transplantations were performed in 81 patients with a median age of 52 (2-70) years between September 1994 and November 1998 including seven retransplantations. All 81 liver recipients received liposomal amphotericin B as antimycotic prophylaxis. Initial immunosuppression consisted of cyclosporine A-based regimen in 11 patients and 70 patients received a tacrolimus-based regimen. The target range for cyclosporine was 150-250 µg/L (EMIT®) and 5-15 µg/L (Protrac II®/MEIA II®) for tacrolimus.

Liposomal amphotericin B (Ambisome®, NeXstar Pharmaceuticals GmbH, Germany) was started at a dose of 1 mg/kg/day intravenously (iv) on the first postoperative day and was continued for seven days. All patients received cefotaxime 3x2 g/day iv perioperatively. Selective bowel decontamination was administered to all patients from the time when the patient was listed for LTx until discharge from hospital after LTx.

Screening for mycotic infections was performed as described previously [11]. IFI was defined as histologic evidence of tissue invasion on biopsy or autopsy, positive culture from a deep tissue compartment (e.g. blood, cerebrospinal fluid, peritoneal fluid) or biopsy specimen, positive cultures from multiple sites (three or more), such as urine, wound, and other sites, presence of budding yeast, hyphae, or positive culture from a bronchoalveolar lavage specimen with clinical and/or radiological evidence of pneumonitis [12].

Four of 81 (4.9 %) patients developed IFI after LTx including three cases of aspergillosis and one *Candida* sepsis. The three patients with invasive aspergillosis died due to rapid *Aspergillus* pneumonia, invasive aspergillosis with fungal endocarditis, or disseminated aspergillosis. Except the fulminant pneumonia, aspergillosis was diagnosed post mortem. All three patients with *Aspergillus* infection had poor liver function prior to or after transplantation and underwent hemofiltration for acute renal failure. The patient with *Candida albicans* sepsis starting on day 4 recovered under increased dosage of liposomal amphotericin B. All four patients had received liposomal amphotericin B (1 mg/kg/day) as antimycotic prophylaxis during the first week after LTx (Table 1).

Discussion

First reports on antimycotic prophylaxis in liver transplant recipients occurred in the early 1990´s. Mora *et al.* used amphotericin B at a dosage of 10 mg/day iv over

Table 1. Characteristics of liver recipients who developed deep fungal infection.

Patient, Child-Pugh - Classification	42 yom, C	59 yof, C	22 yom, C	60 yom, B
Indication for LTx	cirrhosis (alcohol)	hyperacute liver failure	cirrhosis (HBV/HDV)	cirrhosis (HCV)
Relevant history preLTx	esophageal bleeding (PVT due to TIPS)	ARF => HF until death, coma	pPVT	
LTx	emergency OLTx	auxiliary LTx (S I-IV)	OLTx	OLTx
Primary graft function Retransplantation	PF no	PDF no	reLTx for PNF pod 3, rereLTx for PDF pod 22	reLTx for PNF pod 5
Immunosuppression	CyA, ATG, P	Tac, P	Tac, MMF, P	Tac, MMF, PMP 500 mg pod 14-16
Pathogen	*Candida albicans*	*Aspergillus fumigatus*	*Aspergillus* spp	*Aspergillus* spp
Diagnosis of DFI	blood, bile, BAL	BAL pod 8	post mortem (DA)	post mortem (DA)
Clinical signs	fever, leukocytosis pod 4	deteriorated pulmonary gas exchange pod 7, pneumonia and pulmonary bleeding pod 8	ARF => HF pod 2-17, fever pod 22	ARF => HF pod 1-19, fever, brain edema, multiple ischemic areas and small hemorrhages in CT-scan pod 16
Therapy	Ambisome 3 mg/kg/d, flucytosin 150 mg/kg/d		Ambisome 1 mg/kg/d, vancomycin, meropenem	piperacilline/tazobactam, switched to meropeneme
Outcome	alive, follow-up 4 years	died pod 9	died pod 24	died pod 19

Abbreviations: HBV (hepatitis B virus infection), HDV (hepatitis D virus infection), HCV (hepatitis C virus infection), OLTx (orthotopic liver transplantation), pPVT (partial portal vein thrombosis), TIPS (transjugular portosystemic stent shunt), PF (primary function), PDF (primary dysfunction), PNF (primary nonfunction), CyA (cyclosporin A), ATG (antithymocyte globulin), P (prednisolone), MP (methylprednisolone), DFI (deep fungal infection), BAL (broncho alveolary lavage), ARF (acute renal failure), pod (postoperative day), HF (hemofiltration), DA (disseminated aspergillosis)

10 to 15 days in liver recipients that were considered at high risk of developing fungal infection on intensive care. The fungal infection rate was 7.5% with an overall mortality rate of 1.3%, and no patient suffered from *Aspergillus* infection [13,14]. In another study, prophylactic administration of conventional amphotericin B at a dosage of 0.5 mg/kg/day resulted in 3/55 cases of invasive aspergillosis after LTx [15]. A randomized double-blind, placebo-controlled study including 77 liver graft patients showed a significant lower incidence of deep fungal infections in patients receiving liposomal amphotericin B (1 mg/kg/day) for the first 5 days after transplantation. Also, antimycotic prophylaxis was less expensive by $5000 than treatment of proven invasive fungal infections in the patients receiving placebo [16]. However, in our series liposomal amphotericin B (1 mg/kg/day) was not sufficient to prevent systemic aspergillosis.

Besides the approach of antimycotic prophylaxis, early detection of invasive aspergillosis is a major goal to reduce the high mortality of invasive aspergillosis. A recently developed sandwich ELISA detecting *Aspergillus* galactomannan (Platelia, Sanofi-Pasteur, France) appears to be useful for early diagnosis [17,18].

A comparison of four study periods in the time from 1988 to 1994 demonstrated a major shift in the microbial etiologies of infections, particularly of pneumonitis after LTx. While the overall incidence of pneumonia decreased from 34 to 15 %, the incidence of fungal pneumonia increased from 9 to 37 %. This changing pattern of microbial etiologies is suggested to be caused by the use of modern immunosuppressive agents [19]. However, patient survival and quality of life improved since the introduction of cyclosporine A and other new immunosuppressives. Comparing major infectious complications and outcomes between cyclosporine and tacrolimus in liver recipients revealed no significant difference for deep fungal infections [20].

Reflecting the patients preoperative status, all patients with deep fungal infection had advanced end stage liver disease. Primary non-/dysfunction, complicated hyperacute liver failure, retransplantation, early acute renal failure requiring hemofiltration, long-term mechanical ventilation, and antibiotic therapy for infection of unknown origin were risk factors present in the three patients, who died of aspergillosis. These findings are in accordance to previous reports on risk factors for deep fungal infection in liver recipients [1,4, 21].

In summary, liposomal amphotericin B in a dose of 1 mg/kg/day iv could be used as a potent prophylaxis to prevent *Candida* infection in the early phase after LTx. However, higher dosage of liposomal amphotericin B are required to prevent aspergillosis. Patients at risk of acquiring invasive aspergillosis should possibly be given 3 mg/kg/day iv (1 mg/kg/day conventional amphotericin B). This is the suggested therapeutic dosage for treatment of invasive mycosis [22-24]. Prophylactic administration of liposomal amphotericin B (3 mg/kg/day) should be continued until the risk factors like graft non-/dysfunction, retransplantation, fulminant hepatic failure, acute renal failure, and long-term mechanical ventilation are controlled.

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