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Antifungal prophylaxis in liver transplant recipients: a randomized placebo-controlled study

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Abstract The aim of this study was to evaluate the efficacy of two antifungal prophylaxis regimens in liver transplant recipients. One hundred and twenty-nine consecutive recipients were randomized to receive sequential treatment with intravenous liposomal amphotericin B + oral itraconazole, intravenous fluconazole + oral itraconazole, or intravenous and oral placebo. Frequency and incidence of mycotic colonization, local and systemic infection of mycotic origin, causes of death, and possible risk factors for mycotic infection were evaluated. The incidence of mycotic colonization was higher in the placebo group ($P < 0.01$), but there was no significant difference in the incidence of infection between the three groups. Pre-transplant colonization, severity of liver disease, and graft rejection were all risk factors for the development of fungal infection. The routine use of antifungal prophylaxis for all liver transplant recipients does not seem to be justified.

Keywords Liver transplant
Mycosis · Prevention and control · Antifungal agents

Introduction

The incidence of systemic fungal infections has increased substantially over the last few years, the greatest increase occurring among patients undergoing surgery and at intensive care units (ICUs) [20, 21]. Over the last ten years, orthotopic liver transplantation (OLT) has become an elective procedure for many patients with chronic liver disease and a consistent option for those with acute liver failure. However, despite the considerable advances that have been made with regard to surgical techniques, postoperative management, and medical and immunosuppressive protocols, the problem of infection still represents a major concern [14] that can still seriously jeopardize the successful outcome of a liver transplant. Although the identification of procedure-specific risk factors, implementation of appropriate prevention strategies, and improvements in therapeutic protocols have made it possible to reduce infection-related mortality in many centers from more than 50% to less than 10% [24], the incidence of infectious diseases is still considerable among OLT recipients. About two-thirds experience at least one episode of infection [24], whereas the reported incidence of fungal infections varies

from 20–42% [5, 15], which is higher than with other solid organ recipients [10] and is associated with a very high rate of mortality (50–75%) [24].

Although antibacterial chemoprophylaxis has long been an undisputed practice, the use and purpose of administering antifungal drugs perioperatively in order to prevent mycotic infections among the critically ill is still a subject of debate because it may encourage more widespread drug resistance [20]. In the case of OLT recipients, the rationale for perioperative use of antifungal drugs is objectively well founded (the high mortality rate, diagnostic difficulties, the possibility that a mycotic infection may delay or postpone another necessary medical treatment, and the high cost of the drugs) [16], but a number of important aspects are still unclear, such as what substances to use, their efficacy, the duration of administration, and the cost/benefit ratio.

Many drugs have been used to prevent fungal infections among OLT recipients. Liposomal amphotericin B [19] and fluconazole [25] are both effective in short- and long-term prevention of fungal infections, whereas itraconazole, a promising azolic antifungal agent, has not yet been tested.

The aim of this placebo-controlled study was to compare the efficacy of two antifungal prophylactic regimens including the two most effective and frequently used intravenous drugs (liposomal amphotericin B and fluconazole) administered sequentially with oral itraconazole in a population of OLT recipients during the first month after surgery.

Patients and methods

The study was undertaken after approval by our hospital's Ethics Committee. One hundred and thirty-one consecutive patients undergoing OLT at our institution between January 1999 and August 2000 were asked to participate in the study, all of whom gave their express written consent to the management of their data in accordance with the Italian Privacy Law. Exclusion criteria were previous systemic antifungal therapy during the 2weeks prior to OLT and any allergic episode to the administered drugs.

The anesthesia technique was the same for all patients, and a veno-venous bypass between the portal and inferior vena cava area and the superior vena cava was used in all cases. Upon completion of surgery, all patients were transferred to the ICU, where they were weaned from ventilatory support.

Immunosuppression

The immunosuppressive protocol included:

1. Oral cyclosporinA at a dose of 15mg/kg, which was started on the day of surgery and titrated in order too maintain blood trough levels of 200–250ng/dl for the first 3months.
2. Steroids (10mg/kg methylprednisolone intraoperatively, tapered by 50% daily to 20mg/day prednisolone for the first month after transplantation, followed by 10mg/day for the second month and 4mg/day for the third).
3. Azathioprine (1mg/kg per day, provided the platelet count was greater than 60,000).

In the case of rejection, three 1-gram boluses of methylprednisolone were administered; if the rejection was corticoresistant, the therapy was converted to 0.1mg/kg per day tacrolimus with a target blood level of 8–10ng/dl. If resistance persisted, a 14-day cycle of monoclonal antibodies was given (Orthoclone).

Antibacterial prophylaxis

Perioperative antibacterial prophylaxis consisted of 1g + 2g i.v. ampicillin-sulbactan twice daily for 48h; patients allergic to penicillin received clindamycin and aztreonam.

Antiviral prophylaxis

Antiviral prophylaxis included 5mg/kg per day ganciclovir i.v. until discharge, and then 3g/day p.o. for 3months. HBV+ patients were given passive immunoprophylaxis with specfic anti-HB immunoglobulins at a dose of 10,000U during the anhepatic phase, followed by 10,000U/day for 6days; the protocol was completed by administering 100mg/day lamivudine for 5years.

Study design

Immediately before surgery, each OLT recipient was randomly assigned to one of the following groups:

GroupA

1mg/kg per day liposomal amphotericin B (AmBisome) i.v. (administered over 180min) for 7days, and then 200mg itraconazole p.o. for 3weeks.

GroupB

400mg/day fluconazole i.v. for 7days, and then 200mg itraconazole p.o. for 3weeks.

GroupC

placebo (i.v. for 7days and p.o. for 3weeks).

The randomization was based on the drawing of envelopes containing a drug code. The placebo consisted of saline and vitamin tablets. Antifungal mycotic prophylaxis commenced at the beginning of the surgical procedure.

If a microbiologically proven mycotic infection was found or even suspected during the study period, 3–5mg/kg per day liposomal amphotericin B i.v. was started.

Microbiological surveillance

Samples were taken from wound, gut, throat, blood, bile, drain fluids, urine, and respiratory system secretions (bronchoalveolar lavage when intubated) before the surgical procedure (except for the wound samples) and twice weekly during the postoperative follow-up.

Definitions

In accordance with the criteria proposed by Castaldo et al. for OLT recipients [4],

- *colonization* was defined as the isolation or identification of a mycotic species from a single superficial site (urine, stool, sputum, throat/oropharynx, or skin/wound) or positive serological test results not associated with any clinical or other evidence of invasive disease;

- *mycotic infection* was defined as: (a) histological evidence of tissue invasion at biopsy or autopsy; (b) a positive culture from a deep tissue specimen, such as blood, peritoneal fluid, or biopsy specimen; (c) positive cultures from multiple peripheral sites (three or more); and (d) the presence of budding yeast, pseudohyphae, or a positive culture from a bronchoalveolar lavage specimen with clinical and/or radiological evidence of pneumonitis;
- *disseminated mycotic infection* was defined as biopsy-proven tissue invasion from multiple sites or the isolation of fungal species from two or more sites.

Fungal infections playing a major contributory role in a patient's death were considered as being a cause of death itself. Concomitant infections with different genera were considered separate episodes.

All adverse effects were recorded and their relationship with the study drugs assessed by the treating medical staff. Known risk factors for mycotic infection (Table 1) were evaluated 30days after transplantation.

The results were statistically analyzed using Statistical Packages for Social Sciences software version 7.0 (SPSS, Chicago, Ill.). Data are expressed as mean values ± SD. The study groups were compared using Pearson's $\chi 2$-test and the analysis of variance. Logistic regression analysis was used to estimate the relationship between study group variables and a set of predicted variables. Differences with a P-value of less than or equal to 0.05 were considered statistically significant.

Results

During the study period, 136 OLTs were carried out on 131 recipients. As two of the patients met the exclusion criterion of pre-transplant antifungal therapy and five were re-transplantation cases, the analysis was based on 129 subjects divided as follows:

Table 1. Risk factors for mycotic infection: review of the literature

Author	Risk factors
Winston et al. 1999 [25]	UNOS class 1 Pre-transplant colonization Re-transplant
Nieto-Rodriguez et al. 1996 [8]	Hyperglycemia Exposure to >3 antibiotics
Collins et al. 1994 [5]	Renal insufficiency Re-transplant Need for substantial intra-operative transfusions Re-intervention
Castaldo et al. 1991 [4]	Re-transplant Urgent surgery Need for substantial intra-operative transfusions Biliary reconstruction using Roux's loop Antibiotic therapy
Tollemar et al. 1990 [17]	Male gender Re-transplant Long duration of transplant Need for substantial intra-operative transfusions

GroupA

(i.v. liposomal amphotericin B/oral itraconazole): 42 patients

GroupB

(i.v. fluconazole/oral itraconazole): 43 patients

GroupC

(placebo): 44 patients.

The types and preoperative severity of liver diseases requiring the transplants are shown in Table 2 together with the patients' demographic and clinical data. Before surgery, there were 55 patients (42.6%) with colonization by fungi: 17 in groupA, 18 in groupB, and 20 in groupC. During the study, 63 patients (48.9%) showed colonization by fungi (15 in groupA: 23.8%, 18 in groupB: 28.6%, and 30 in groupC: 47.6%), and 22 (17%) had mycotic infections (seven in groupA: 31.8%, six in groupB: 40.9%, and nine in groupC: 27.3%). The mycotic infection was disseminated in ten patients (7.8%: three in groupA: 30%, four in groupB: 50%, and four in groupC: 20%). In two cases, infection was diagnosed outside of the ICU.

The clinical and microbiological spectra of the fungal isolations are shown in Tables 3 and 4. There were no differences between the two study regimens in terms of the prevention of colonization or single or disseminated infection; the only significant difference between these groups and the placebo group was colonization (Table 3).

Eight (6.2%) of the 129 patients died during the study: three in groupA, two in groupB, and three in groupC. A mycotic disease was diagnosed in five of these patients: one in groupA (*Candida glabrata*), two in groupB (*Aspergillus niger* and *Candida pelliculosa*), and two in groupC (*Candida albicans* and *Candida glabrata*). The other causes of death were multi-organ failure (groupA) and sudden spontaneous subarachnoid hemorrhage (groupC).

As shown in Table 5, the factors associated with a higher probability of developing mycotic infection were baseline fungal colonization, a severe liver disease indicating transplantation, and graft rejection.

Costs

The mean cost per patient of drugs used throughout the study was Euro 190.02 (groupB) and Euro 1588.3 (groupA).

Toxic effects

Two patients in groupA complained of pain in the lumbar region during the course of liposomal

Table 2. Demographic and clinical characteristics of the study population (group A: i.v. liposomal amphotericin B + oral itraconazole; group B: i.v. fluconazole + oral itraconazole; group C: i.v. and oral placebo)

Characteristic	Group A	Group B	Group C
Pre-operative			
Patients (*n*)	42	43	44
Mean age (range), years	46.2 (21–63)	50.3 (19–62)	51.5 (31–60)
Gender, m/f	22/20	27/16	33/11*
Liver disease, *n* (%)			
Cancer on post-viral cirrhosis	11 (26.2)	13 (30.3)	8 (18.2)
Post-viral cirrhosis	21 (50)	22 (51.2)	22 (50)
Ethanol cirrhosis	3 (7.2)	2 (4.7)	1 (2.3)
Acute/sub-acute hepatitis	4 (9.6)	3 (6.9)	2 (4.5)
Other	2 (4.7)	1 (2.3)	9 (20.4)
Re-OLT	1 (2.3)	2 (4.6)	2 (4.6)
Child class, *n* (%)			
A	0	0	0
B	22 (52.3)	15 (34.9)	15 (34)
C	17 (40.5)	22 (51.1)	27 (61.4)
NC	3 (7.2)	6 (14)	2 (4.6)
Intra-operative			
Cold ischemia (mean ± SD), (min)	547.3 ± 128.0	519.6 ± 197.3	543.0 ± 86.5
Duration of surgery (mean ± SD), min	369.5 ± 58.8	393.8 ± 100.4	392.3 ± 66.9
Transfused blood units (mean ± SD), *n*	4.5 ± 4.2	6.7 ± 6.3	5.4 ± 4.7
Post-operative			
Duration of postoperative ventilation (mean ± SD, range), h	12.1 ± 42.1(0–128)	11.6 ± 37.9(0–180)	11.9 ± 38.3(0–151)
ICU stay (mean), days	3.9	4.2	3.9
Abdominal re-interventions, *n* (%)	4 (9.5)	3 (6.9)	3 (6.8)
Re-transplants, *n* (%)	1 (2.3)	2 (4.6)	2 (4.5)
Simultaneous bacterial infection, *n* (%)	4 (9.5)	9 (20.9)	8 (18.2)
Pre-transplant mycotic colonization, *n* (%)	17 (49.4)	18 (41.8)	20 (45.4)
Patients with rejection episodes, *n* (%)			
0	36 (85.6)	38 (88.4)	38 (86.4)
1	4 (9.6)	4 (9.3)	5 (11.4)
>1	2 (4.8)	1 (2.3)	1 (2.2)

*$P < 0.05$ vs. group A

amphotericin B; no other clearly drug-related side effect was recorded.

Discussion

The optimal approach to preventing mycotic infections is still an open question: although the strategies for aspecific prophylaxis by means of environmental and nursing measures are now quite well defined and do not differ between transplant patients and other subjects at risk, the use of drugs to prevent fungal infections remains a subject of debate. Moreover, only a few randomized clinical studies have demonstrated the real efficacy of antifungal chemoprophylaxis in liver transplant patients. The oral administration of nystatin in the context of a selective intestinal decontamination protocol did not significantly change the incidence of fungal infections [2], and the same was found when oral amphotericin B was used [10]. It has been shown that the prophylactic use of intravenous amphotericin B can lead to a low incidence of post-transplant infections [6], but these were retrospective observations of non-randomized patients, and intravenous amphotericin B is also associated with possible toxic effects on the often already precarious renal function of OLT recipients.

Table 3. Clinical spectrum of mycotic isolations (group A: i.v. amphotericin B + oral itraconazole; group B: i.v. fluconazole + oral itraconazole; group C: i.v. and oral placebo)

Variable	Group A	Group B	Group C
Patients not infected or without colonization, *n* (%)	17 (40.6)	15 (34.9)	1 (2.3)[a,b]
Patients with mycotic colonization, *n* (%)	15 (35.7)	18 (41.9)	30 (68.2)
Patients with mycotic infections, *n* (%)	7 (16.6)	6 (13.9)	9 (20.5)
Patients with disseminated infection, *n* (%)	3 (7.1)	4 (9.3)	4 (9)
Total, *n* (%)	42 (100)	43 (100)	44 (100)

[a]$P < 0.01$ vs. group A
[b]$P < 0.01$ vs. group B

Table 4. Microbiological spectrum of mycotic infections

Mycetes	Colonization			Infection			Disseminated infection		
	Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C
	Number of cases								
Candida albicans	9	10	18	4	2	6	2	2	2
Candida glabrata	1	2	1	1	1	0	1	0	0
Candida krusei	0	1	1	0	0	0	0	0	0
Candida parapsilosis	0	1	2	0	1	1	0	0	1
Candida pelliculosa	2	0	2	1	0	1	1	0	0
Candida tropicalis	0	1	2	0	1	0	0	0	0
Aspergillus spp	0	2	0	0	2	0	0	0	0
Others	3	1	4	1	0	1	0	0	0

Some studies have found that liposomal amphotericin B can be efficacious. Tollemar et al. have demonstrated that its use at a dose of 1mg/kg for 5 consecutive days significantly prevents fungal infections in both the short and the long term [18, 19], but another study recorded the appearance of fungal sepsis or systemic aspergillosis in 4 of 58 recipients despite the fact that the drug was administered at the same dose for 1week [3].

It has recently been found that the prophylactic use of fluconazole leads to optimal results in the prevention of invasive fungal infections in OLT patients; furthermore, its limited toxicity and the fact that it can be administered orally make it very interesting [25].

In our study of a homogeneous population of OLT patients, we evaluated two protocols including the two intravenous drugs that have so far proved to have the best efficacy/toxicity ratio (liposomal amphotericin B and fluconazole), of which both were sequentially followed by a broad-spectrum azole derivative (itraconazole) whose prophylactic potential still needs to be defined. The use of an oral antifungal after the administration of intravenous drugs was dictated by the need to have a period of prophylaxis long enough (1month) to cover the time during which the risk of mycotic infection is high as a result of maximal immunosuppression. Itraconazole was chosen not only because of its broad spectrum [11] and the reduced frequency of resistant species [7], but also because of the interest in testing (albeit in combination with other substances of proven efficacy) the action of a drug whose prophylactic use has not been assessed previously in OLT patients.

The two study regimens were comparably efficacious, with no between-group differences found in terms of the incidences of colonization, organ infection, or disseminated infection, of which all were similar to those reported by others [13, 18, 19, 25]. As shown in Table 3, mycotic colonization was the only statistically significant difference between the two treatment groups and the placebo group, whereas the incidence of organ or disseminated infections was similar, a finding that is different from the results so far reported after the use of liposomal amphotericin B or fluconazole [18, 25].

We believe that this somewhat surprising result is due to some differences in the studied populations and transplant procedures. The general pre-transplant condition of our population was better than that of the patients involved in the study of liposomal amphotericin B by Tollemar et al. [18], because there were fewer patients on mechanical ventilation (0 vs 7) and fewer already in the ICU (1 vs 12). In terms of transplant procedures, our sample required fewer intra-operative transfusions (an overall mean of 5.5 ± 1.4vs 11 ± 2U), a shorter mean postoperative ICU stay (4 vs 6days), a shorter period of postoperative ventilation (28h vs 4days), and a smaller number of biliary reconstructions on Roux's loop (3 vs 22). Finally, we had fewer patients with colonization before transplantation (40.4 vs 60%).

Our sample also had fewer risk factors than the fluconazole-treated population studied by Winston et al. [25]: there was a lower frequency of pre-transplant renal insufficiency (1.5 vs 18.8%), re-transplants (3.8 vs 15%) and abdominal re-interventions during the course of the study (8.5 vs 23.6%), and a lower incidence of more than one rejection episode (3.1 vs 13%).

The risk factors present in a study population must always be considered in relation to post-transplant fungal infections [4, 5, 8, 17, 25], and the results of the logistic analysis of our data confirmed that pre-transplant colonization, the severity of the underlying liver disease, and rejection all play an important role in determining mycotic infections (Table 5). However, it also needs to be kept in mind that our data cannot be used

Table 5. Risk factors for mycotic infection in the study population

Risk factor	*P*
Child-Pugh class C	0.01
Pre-transplant mycotic colonization	< 0.01
Rejection of transplanted organ	0.01

to define precise categories in other environments insofar as each individual transplant center has its own particular environmental, operative, and epidemiological factors.

One of the concerns associated with the use of fluconazole is the possible selection of resistant mycotic species [8, 22, 23]: none of our recipients treated with this drug experienced mycotic diseases caused by known fluconazole-resistant micro-organisms (*Candida krusei, Candida glabrata*), nor was there any greater incidence of infection or colonization by these species. The use of oral itraconazole may have played an active role in this, despite the fact that some fluconazole-resistant strains of *Candida albicans* are cross-resistant to itraconazole [1]; another related factor may have been the relatively high fluconazole dose. Two cases of disease due to *Aspergillus spp* were recorded in the group of patients receiving fluconazole; this finding is in line with the fact that, unlike liposomal amphotericin B, it is not effective against this species.

Another question that still needs to be resolved is how long antimycotic prophylaxis should be administered. Periods of 10 or more weeks may be too long [12, 25]; we chose a period of 1month, which is in line with that used in similar studies [9, 13, 18, 19, 25], and our results confirm that this may be the period of choice under normal conditions.

Our study was not designed to compare the efficacy of an antifungal prophylactic therapy administered indiscriminately to all recipients with that of a preventive therapy reserved exclusively for patients with risk factors for mycotic infections. However, our finding that chemoprophylaxis did not have a significant effect on the prevention of mycotic infection suggests that (also for cost reasons) the administration of antifungal drugs should be limited to patients at risk.

In conclusion, our data show that the two studied antifungal prophylactic protocols were equivalent in terms of efficacy and tolerability in OLT patients, but substantially different in terms of costs. There was no significant difference in the incidence of simple or disseminated infections between the groups receiving prophylaxis and the placebo group, and so the routine use of antifungal prophylaxis for all liver transplant recipients does not seem to be justified. This confirms the need for every OLT center to identify its own recipient risk categories for mycotic infections and then define appropriate strategies to prevent such dangerous events.

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