

Prophylactic Fluconazole in Liver Transplant Recipients

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Among persons who receive solid organ transplants, liver transplant recipients have the highest incidence of invasive fungal infection; however, no anti-fungal prophylaxis has been proven to be effective.

Objective: To evaluate the efficacy and safety of prophylactic fluconazole in liver transplant recipients.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: University-affiliated transplantation center.

Patients: 212 liver transplant recipients who received fluconazole (400 mg/d) or placebo until 10 weeks after transplantation.

Measurements: Fungal colonization, proven superficial or invasive fungal infection, drug-related side effects, and death.

Results: Fungal colonization increased in patients who received placebo (from 60% to 90%) but decreased in patients who received fluconazole (from 70% to 28%). Proven fungal infection occurred in 45 of 104 placebo recipients (43%) but in only 10 of 108 fluconazole recipients (9%) ($P < 0.001$). Fluconazole prevented both superficial infection (29 of 104 placebo recipients became infected [28%] compared with 4 of 108 fluconazole recipients [4%]; $P < 0.001$) and invasive infection (24 of 104 placebo recipients became infected [23%] compared with 6 of 108 fluconazole recipients [6%]; $P < 0.001$). Fluconazole prevented infection by most *Candida* species, except *C. glabrata*. However, infection and colonization by organisms intrinsically resistant to fluconazole did not seem to increase. Fluconazole was not associated with any hepatotoxicity. Patients receiving fluconazole had higher serum cyclosporine levels and more adverse neurologic events (headaches, tremors, or seizures in 13 fluconazole recipients compared with 3 placebo recipients; $P = 0.01$). Although the overall mortality rate was similar in both groups (12 of 108 [11%] in the fluconazole group compared with 15 of 104 [14%] in the placebo group; $P > 0.2$), fewer deaths related to invasive fungal infection were seen in the fluconazole group (2 of 108 patients [2%]) than in the placebo group (13 of 104 patients [13%]) ($P = 0.003$).

Conclusions: Prophylactic fluconazole after liver transplantation decreases fungal colonization, prevents superficial and invasive fungal infections, and has no appreciable hepatotoxicity. Although fluconazole prophylaxis is associated with fewer deaths from fungal infection, it does not improve overall survival. Patients receiving prophylactic fluconazole require close monitoring of serum cyclosporine levels to avoid neurologic toxicity.

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Because of the relatively high incidence and severity of fungal infections (1), prophylaxis with antifungal drugs is frequently used in recipients of certain solid organ transplants. Oral prophylaxis with such agents as nystatin, clotrimazole, and amphotericin B and intravenous prophylaxis with low doses of amphotericin B have produced inconsistent results, and their beneficial effects remain largely unproved (1). Consequently, no approach for prevention of fungal infections in solid organ transplant recipients has been uniformly accepted or recommended.

The triazole antifungal drug fluconazole was found to be safe and effective for preventing superficial and invasive *Candida* infection in recipients of bone marrow transplants (2, 3). The exact role of fluconazole in solid organ transplant recipients and other surgical patients, however, has not been clearly established. Therefore, we performed a double-blind, placebo-controlled trial of prophylactic fluconazole in patients undergoing solid organ transplantation. Liver transplant recipients were chosen for the trial because they have the highest incidence of fungal infection among solid organ transplant recipients (1, 4).

Methods

Patients

Patients were eligible for the study if they were undergoing orthotopic liver transplantation, were 13 years of age or older, had no clinical evidence of fungal infection at study entry, had received no systemic antifungal therapy in the 2 weeks before randomization, and were not allergic to imidazole or azole antifungal agents. Women were required to have a negative result on a pregnancy test. Informed consent was obtained from patients or their relatives in a manner approved by the University of California, Los Angeles (UCLA), Human Subject Protection Committee.

Transplantation Procedures

The surgical procedures and post-transplantation management used in liver transplant recipients at the UCLA Medical Center have previously been published (5, 6). Baseline immunosuppression therapy usually consisted of cyclosporine, azathioprine,

and corticosteroids. Acute rejection documented by liver biopsy was treated with boluses of intravenous corticosteroids. Episodes of rejection refractory to corticosteroids were treated with OKT3.

Immediately before transplantation, patients received oral neomycin and erythromycin for decontamination of the gastrointestinal tract. Perioperative intravenous antibacterial prophylaxis was given for 24 hours and consisted of ampicillin-sulbactam alone, vancomycin with ceftizoxime, or an aminoglycoside (for patients who were allergic to penicillin). During surgery, the abdominal cavity was irrigated with a solution of 25 mg of amphotericin B in 1000 mL of sterile water. Nystatin and oral antibiotics were not used for bowel decontamination to prevent infection after transplantation. Antiviral prophylaxis consisted of 100 days of intravenous ganciclovir or high doses of acyclovir (6, 7). Twice-weekly trimethoprim-sulfamethoxazole or pentamidine once every 2 weeks (for patients who were allergic to sulfa drugs) was used for *Pneumocystis carinii* prophylaxis.

Study Drugs and Design

In a double-blind fashion, eligible patients were randomly assigned to receive prophylactic fluconazole or placebo. A 1:1 computer-generated randomization schedule was used. Fluconazole or placebo was started preoperatively on the day of surgery; patients in the treatment group received 400 mg of fluconazole as a single daily dose. The study drug was initially administered intravenously over a period of 1 hour. After transplantation, fluconazole was given by mouth as four 100-mg capsules when patients were able to receive oral medications. The daily dose of fluconazole was decreased by 50% for a creatinine clearance of 20 to 50 mL/min and by 75% for a creatinine clearance less than 20 mL/min. The intravenous placebo was normal saline (0.9% sodium chloride). Placebo capsules consisted of lactose, corn starch, and magnesium stearate.

Because most fungal infections occur in the first 2 to 3 months after liver transplantation (1, 4, 6), prophylaxis with the study drug was continued for 10 weeks after transplantation. If the patient required another transplantation during the study period, prophylaxis was given for an additional 10 weeks from the date of the repeated procedure. Prophylaxis was discontinued if a documented invasive fungal infection developed, a serious adverse side effect definitely related to the study drug occurred, or the patient was unable to continue in the study because of noncompliance or death. Patients who developed a documented superficial fungal infection could be treated with topical clotrimazole while continuing to receive the study drug. Similarly, treatment with the study drug was continued when empirical therapy with intravenous amphotericin B was administered for suspected but undocumented systemic fungal infection.

Laboratory Procedures

Complete blood counts, prothrombin times, blood urea nitrogen levels, serum creatinine and electrolyte determinations, and liver function studies (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin levels) were obtained at study entry, twice weekly during the study, and at the end of prophylaxis to assess patients for drug-related side effects. Serum cyclosporine levels determined by high-pressure liquid chromatography were measured 24 to 48 hours after transplantation and at least once per week for the duration of the study (8). Before the study, a serum pregnancy test was done on all women of childbearing age. Patients were examined at least twice weekly for clinical symptoms and signs of adverse effects related to the study drug.

Surveillance cultures of the oropharynx, axillae, inguinal skin folds, urine, and stool or perirectal area were done at study entry, once weekly during the study, and at the end of prophylaxis to determine the presence of fungal colonization. Blood cultures for fungus were also performed at study entry. Cultures of blood and other suspected sites of fungal infection were obtained during the study whenever a patient's clinical condition suggested the possibility of infection.

Definitions of Fungal Colonization and Infection

Fungal colonization was defined as the presence of a fungus in one or more surveillance cultures in the absence of any clinical symptoms or signs of infection. Superficial fungal infections were diagnosed by the isolation of a fungus from the skin, oropharynx, vagina, gastrointestinal tract, wounds, or urine in association with signs of inflammation, ulcerations, plaques, or exudates that could not be explained by other pathogens. Invasive fungal infections were diagnosed by the presence of fungus in the blood, pulmonary tissue or secretions, sinuses, peritoneal cavity, or other organ structures in association with symptoms and signs of infection that could not be explained by other pathogens.

Data Collection and Statistical Analysis

All reviews, classification of infections, and data entry were done blindly before the statistical analyses were performed. Similarly, all side effects or adverse events that occurred during the study were recorded and classified blindly by the investigators as unrelated, possibly related, or probably related to the study drug.

All statistical tests were performed as two-tailed tests. The Fisher exact test was used to compare

differences in proportion. The equality of two distributions was compared by using the Wilcoxon rank-sum test. Bivariate comparisons of times to specific events were performed by using Kaplan-Meier estimates of survival distributions and the Gehan generalized Wilcoxon test (9). The SAS procedure LIFETEST (SAS Institute, Cary, North Carolina) was used for these comparisons (10). Estimates of relative risk and multivariable analyses were done by using the Cox proportional hazards model (11). If fungal infection occurred in at least 20% of patients undergoing liver transplantation (estimated incidence), then each study group (placebo and fluconazole) would need to include 102 patients to demonstrate a reduction in proven fungal infection to 7% (power, 0.8; $P = 0.05$). All patients were included in the efficacy analysis (modified intention-to-treat analysis) except 24 patients who did not receive the study drug after transplantation.

Role of the Funding Source

The study sponsor (Pfizer, Inc., New York, New York) provided both fluconazole and placebo. The study design was developed jointly by Pfizer, Inc., and the authors. The study sponsor also provided clinical research associates and statisticians for the collection and analysis of data. The decision to submit the manuscript for publication was made by the authors.

Results

Patient Characteristics

From May 1992 to September 1993, 291 adults and children were hospitalized for orthotopic liver transplantation at the UCLA Medical Center. Two hundred thirty-nine patients were eligible for the study (Figure 1). Only 3 eligible patients declined to participate. The other 236 patients were randomly assigned to receive placebo or fluconazole. Twenty-four patients (13 placebo recipients and 11 fluconazole recipients) were excluded from analysis after randomization and after receiving a single preoperative dose of the study drug because it was found that they did not meet the inclusion criteria. Reasons for exclusion were cancellation of transplantation because of metastatic tumor (7 cases), inadequate donor organ (6 cases), or severe pulmonary hypertension (1 case); death in the operating room during transplantation (4 cases); pregnancy (1 case); age younger than 13 years (1 case); long-term dialysis (1 case); preoperative blood culture that was positive for *Candida glabrata* (1 case); and previous enrollment in the study (2 cases). No patients were excluded because of noncompliance with the study medication. Of the 4 patients who died during sur-

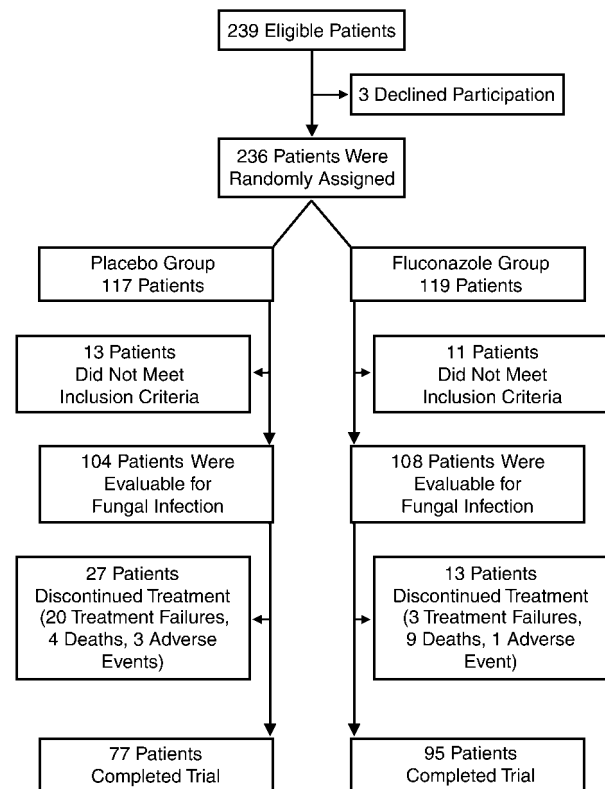


Figure 1. Profile of patients.

gery, 3 were receiving placebo and 1 was receiving fluconazole. Death during surgery was caused by hemorrhage (1 case) and hemodynamic complications of severe liver disease (3 cases).

The characteristics of the remaining 212 patients are summarized in Table 1. The 104 patients who received placebo and the 108 patients who received fluconazole were similar in terms of demographic characteristics and risk factors for fungal infection (4, 12–15).

The median number of on-study days was 72 for both placebo recipients (range, 5 to 130 days) and fluconazole recipients (range, 19 to 218 days). The median duration of intravenous dosing of the study drug was 10 days (range, 3 to 57 days) in the placebo group and 12 days (range, 3 to 79 days) in the fluconazole group. The median duration of oral dosing of the study drug was 64 days for both placebo recipients (range, 2 to 121 days) and fluconazole recipients (range, 1 to 210 days).

Fungal Infections

Types of proven fungal infections and their causative organisms are summarized in Tables 2 and 3. Proven fungal infection occurred in 45 of 104 placebo recipients (43%) but only 10 of 108 fluconazole recipients (9%) ($P < 0.001$). Both superficial and invasive fungal infections occurred less frequently in the patients receiving prophylactic fluconazole.

Table 1. Patient Characteristics

Characteristic	Placebo Group	Fluconazole Group
Patients, n (%)	104	108
Median age (range), y	49 (15–75)	53 (19–74)
Sex, n (%)		
Male	56 (54)	61 (56)
Female	48 (46)	47 (44)
Underlying disease, n (%)		
Alcoholic liver disease	30 (29)	25 (23)
Chronic hepatitis C	21 (20)	24 (22)
Chronic hepatitis B	5 (5)	6 (6)
Chronic non-A, non-B hepatitis	13 (12)	9 (8)
Cryptogenic cirrhosis	10 (10)	12 (11)
Primary biliary cirrhosis	10 (10)	10 (9)
Sclerosing cholangitis	5 (5)	12 (11)
Fulminant hepatic failure	4 (4)	3 (3)
Hepatocellular carcinoma	3 (3)	4 (4)
Other*	3 (3)	3 (3)
United Network Organ Sharing classification, n (%)		
1 (life support in intensive care)	10 (10)	12 (11)
2 (continuous hospitalization)	17 (16)	20 (19)
3 (continuous medical care)	77 (74)	76 (70)
4 (stable at home)	0 (0)	0 (0)
Antibiotic therapy within 4 weeks of transplantation, n (%)	19 (18)	19 (18)
Corticosteroid therapy within 4 weeks of transplantation, n (%)	11 (11)	10 (9)
Pretransplantation renal failure, n (%)†	20 (19)	20 (19)
Fungal colonization at baseline/cultured at baseline, n/n (%)	62/104 (60)	74/106 (70)
Repeated transplantation, n (%)	16 (15)	16 (15)
Other abdominal surgery during study, n (%)	28 (27)	22 (20)
Cytomegalovirus disease after transplantation, n (%)	5 (5)	5 (5)
Initial immunosuppressive agents, n (%)		
Cyclosporine, azathioprine, and corticosteroids	92 (88)	97 (90)
Cyclosporine plus corticosteroids	1 (1)	2 (2)
Tacrolimus plus corticosteroids	1 (1)	0 (0)
OKT3 plus other agents	10 (10)	9 (8)
Rejection episodes, n (%)		
0	68 (65)	65 (60)
1	22 (21)	29 (27)
>1	14 (13)	14 (13)
Treatment for rejection, n (%)		
None	68 (65)	65 (60)
Pulse corticosteroids once	18 (17)	22 (20)
Pulse corticosteroids more than once	10 (10)	8 (7)
OKT3 plus other agents	8 (8)	13 (12)

* Placebo group: Budd–Chiari syndrome, Wilson disease, isoniazid hepatotoxicity; fluconazole group: polycystic liver disease (2 cases), chronic rejection.

† Serum creatinine concentration > 177 $\mu\text{mol/L}$ (2.0 mg/dL).

Kaplan–Meier estimates of the percentage of patients in each group who did not have a proven fungal infection also showed that fluconazole effectively prevented fungal infection ($P < 0.001$) (Figure 2).

Fluconazole prevented most types of *Candida* infection except that caused by *C. glabrata* (Table 3). However, *C. glabrata* infection occurred in fewer fluconazole recipients (6 cases) than placebo recipients (12 cases). Of note, only 1 case of *C. krusei* infection occurred during the study, in a patient receiving prophylactic fluconazole who developed oropharyngeal candidiasis caused by *C. krusei* and *C. glabrata*. Two cases of disseminated coccidioidomycosis occurred in the placebo group, but none occurred in the fluconazole group. Invasive aspergillosis involving the lungs, sinuses, or central nervous

system occurred in 4 placebo recipients and 1 fluconazole recipient.

Four patients in both study groups were given empirical intravenous amphotericin B for treatment of suspected systemic fungal infection. Infection was suspected in these patients because of persistent fever and overall clinical deterioration despite antibiotic therapy. Six of the eight patients improved; two placebo recipients died, but a fungal infection was never documented.

The incidence of fungal infection in each treatment group was also evaluated in patients with the highest risk for fungal infection. Risk factors for fungal infection were identified by using stepwise regression analysis with the Cox proportional hazards model. The factors included in this analysis were type of study drug (fluconazole or placebo), age, sex, presence of underlying disease, United Network Organ Sharing classification, previous antibiotic or corticosteroid therapy within 4 weeks of transplantation, pretransplantation renal failure (serum creatinine concentration $\geq 176.8 \mu\text{mol/L}$ [$\geq 2.0 \text{ mg/dL}$]), baseline fungal colonization, repeated transplant, other abdominal surgery during the study, initial immunosuppressive agents used, number of rejection episodes, number of treatments received for rejection, use of OKT3, and cytomegalovirus disease. Assignment to placebo, a United Network Organ Sharing classification of 1, baseline fungal colonization, and repeated transplantation were found to be significant risk factors (Table 4). Other studies have also identified these variables as risk factors for fungal infection in liver transplant recipients (12–15).

Seventy placebo recipients and 81 fluconazole recipients had one or more significant risk factors and were therefore considered at high risk for fungal infection. Proven fungal infection occurred in 38 of 70 high-risk placebo recipients (54%) but only 9 of 81 high-risk fluconazole recipients (11%) ($P < 0.001$) (Figure 2). Similarly, the incidences of both superficial fungal infection (24 of 70 placebo recipients [34%]) compared with 4 of 81 fluconazole re-

Table 2. Incidence of Proven Fungal Infections

Variable	Placebo Group	Fluconazole Group
Patients, n	104	108
Patients with proven fungal infection, n (%)*	45 (43)	10 (9)†
Patients with superficial infection of mucocutaneous site, gastrointestinal tract, wound, or urinary tract, n (%)	29 (28)	4 (4)†
Patients with invasive infection of blood, lungs, intra-abdominal site, sinuses, or multiple organs, n (%)	24 (23)	6 (6)†

* Eight placebo recipients had separate proven superficial and invasive infections.
† $P < 0.001$ compared with placebo.

Table 3. Types of Organisms Causing Fungal Infection

Organism	Superficial Infection*		Invasive Infection†		Total Infections	
	Placebo Group	Fluconazole Group	Placebo Group	Fluconazole Group	Placebo Group	Fluconazole Group
	←----- n ----->					
<i>Candida albicans</i>	27	3	11	1	38	4
<i>Candida tropicalis</i>	1	0	3	0	4	0
<i>Candida lusitanae</i>	0	0	1	0	1	0
<i>Candida guilliermondii</i>	0	0	0	1	0	1
<i>Candida parapsilosis</i>	1	0	0	0	1	0
<i>Candida species</i>	0	0	0	1	0	1
<i>Candida krusei</i>	0	1	0	0	0	1
<i>Candida glabrata</i>	7	3	5	3	12	6
<i>Coccidioides immitis</i>	0	0	2	0	2	0
<i>Aspergillus species</i>	0	0	4	1	4	1
<i>Trichophyton rubrum</i>	4	0	0	0	4	0
Total	40	7	26	7	66	14

* Eleven placebo recipients and two fluconazole recipients had superficial infection with more than one organism.

† Two placebo recipients and one fluconazole recipient had invasive infection with more than one organism.

cipients [5%]; $P < 0.001$) and invasive fungal infection (21 of 70 placebo recipients [30%] compared with 5 of 81 fluconazole recipients [6%]; $P < 0.001$) were significantly lower in high-risk patients receiving prophylactic fluconazole. In contrast, among low-risk patients without any significant risk factors for fungal infection, invasive fungal infection developed in only 3 of 34 placebo recipients (9%) and 1 of 27 fluconazole recipients (4%) ($P > 0.2$). Superficial fungal infections occurred in 5 of 34 low-risk patients (15%) and none of the 34 low-risk fluconazole recipients (0%) ($P = 0.03$).

Fungal Colonization

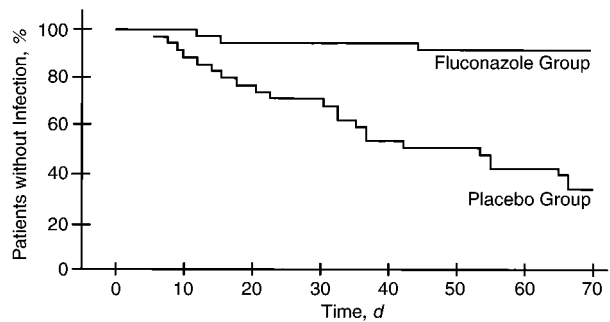
The effects of prophylactic fluconazole on fungal colonization are shown in **Table 5**. Colonization with fungus increased in placebo recipients but decreased in fluconazole recipients. At week 8 of the study period, 90% of placebo recipients and only 28% of fluconazole recipients had fungal colonization ($P < 0.001$). Fluconazole was especially effective in eliminating colonization with *C. albicans*: At week 8, 44 of 58 placebo recipients were colonized (76%) compared with only 2 of 83 fluconazole recipients (2%) ($P < 0.001$). Fluconazole also decreased colonization by all other *Candida* species except *C. krusei* and *C. glabrata*. However, no increased colonization with *C. krusei*, *C. glabrata*, or *Aspergillus* species was associated with prophylactic fluconazole.

Clinical and Laboratory Side Effects

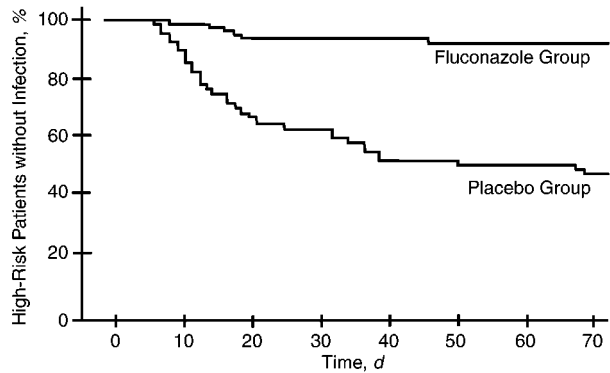
Adverse clinical events or laboratory abnormalities that were possibly or probably related to the study drug occurred in 28 of 104 placebo recipients (27% [95% CI, 18% to 35%]) and 43 of 108 fluconazole recipients (40% [CI, 31% to 49%]) ($P = 0.05$). Gastrointestinal symptoms and neurologic

events were the most common side effects. Diarrhea, nausea, vomiting, or abdominal pain occurred in 23 placebo recipients (22% [CI, 14% to 30%]) and 29 fluconazole recipients (27% [CI, 18% to 35%]). Neurologic events were the only clinical side effects that were more common in the fluconazole group than in the placebo group. These events occurred in 13 fluconazole recipients (12% [CI, 6% to 18%]) and 3 placebo recipients (3% [CI, 0% to 6%]) ($P = 0.01$) and included headaches (8 fluconazole recipients and 3 placebo recipients), seizures (5 fluconazole recipients), and tremors (1 fluconazole recipient). Skin rash, palpitations, dry mouth, altered taste, and anorexia were the other clinical side effects attributed to the study drug in the placebo group. Skin rash (2 cases), elevated serum cyclosporine levels (2 cases), fever (1 case), dry mouth (1 case), anorexia (1 case), and altered mental status (1 case) were the other side effects in the fluconazole group. Three placebo recipients (2 with diarrhea and 1 with palpitations) and 1 fluconazole recipient with nausea were withdrawn from the study.

An elevated serum cyclosporine level was the only laboratory abnormality that occurred more frequently in the fluconazole group. In patients who received prophylactic fluconazole compared with those who received placebo, median trough serum cyclosporine levels were higher at 1 week (320 ng/mL compared with 271 ng/mL; $P = 0.004$), 2 weeks (383 ng/mL compared with 324 ng/mL; $P = 0.02$), and 4 weeks (311 ng/mL compared with 250 ng/mL; $P = 0.06$) after transplantation. Differences in serum levels of bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase between the placebo and fluconazole groups were not statistically significant or clinically important. Therapy with the study drug was never discontinued because of concern about hepatotoxicity.



Fluconazole Group, n	108	107	102	100	99	98	98	97
Placebo Group, n	104	95	77	73	64	63	61	59



Fluconazole Group, n	81	80	75	73	73	72	72	71
Placebo Group, n	70	62	46	42	35	35	34	32

Figure 2. Time to development of any proven fungal infection in all patients (top) and in high-risk patients (bottom). Survival distributions of time to development of proven superficial or invasive fungal infection in fluconazole and placebo recipients were derived by using Kaplan-Meier product-limit estimates. High-risk patients are defined as those with a United Network Organ Sharing classification of 1, baseline fungal colonization, and repeated transplantation. For the difference in time of onset of proven fungal infection between fluconazole and placebo recipients, $P < 0.001$ in all patients and all high-risk patients.

Survival

Fifteen placebo recipients (14%) and 12 fluconazole recipients (11%) died during the study. Although the overall mortality rate was similar in the placebo and fluconazole groups, prophylactic fluconazole was associated with fewer deaths from fungal infection. Thirteen deaths in the placebo group (13 of 104 patients [13%]) but only 2 deaths in the fluconazole group (2 of 108 patients [2%]) were related to invasive fungal infection ($P = 0.003$). Organisms that caused fatal infection in the placebo group were *C. albicans* (7 cases), *C. tropicalis* (1 case), *C. glabrata* (1 case), *C. albicans* plus *Aspergillus* species (1 case), *Aspergillus* species alone (2 cases), and *Coccidioides immitis* (1 case). The two fatal infections in the fluconazole group were caused by *Candida guilliermondii* plus *Candida glabrata* and by *Aspergillus* species. The other causes of death in the fluconazole group were bacterial infection (3 cases), hemorrhage (2 cases), liver graft fail-

ure (2 cases), pseudomembranous colitis (2 cases), and central pontine myelinolysis (1 case). Liver graft failure (1 case) and cerebral infarctions (1 case) were the other causes of death in the placebo group.

Discussion

Few large, well-controlled, randomized clinical trials have demonstrated the benefit of any antifungal agent for prevention of serious fungal infection in recipients of liver and other solid organ transplants (1, 4). Oral formulations of nystatin, clotrimazole, or amphotericin B and low doses of intravenous amphotericin B have been used most frequently for prophylaxis. However, the incidence of documented fungal infection in liver transplant recipients has been reported to be as high as 22% to 42% despite the use of oral nystatin (4, 12–14). Similarly, although oral clotrimazole and oral amphotericin B may decrease fungal colonization and superficial infection in transplant recipients, they have never been shown to be effective prophylaxis against invasive systemic infection (1, 4, 16, 17). Some researchers have claimed that low doses of intravenous amphotericin B (10 mg/d) effectively reduce the incidence of fungal infection after liver transplantation; however, these claims are based on retrospective analyses using historical controls rather than results from randomized trials (18). Failed prophylaxis with low-dose amphotericin B has also been reported (19). In a recent small study of liver transplant recipients, intravenous liposomal amphotericin B was shown to be effective prophylaxis against *Candida*-related peritonitis (20); however, because this drug is expensive and toxic and must be administered intravenously, it is not an optimum agent for prophylaxis.

Our study demonstrates that fluconazole can prevent superficial and invasive fungal infection in a large group of high-risk liver transplant recipients. Prophylactic fluconazole was associated with decreased fungal colonization and fewer deaths related to fungal infection. Similar results have been reported in recipients of bone marrow transplants, whose risk factors for fungal infection (neutropenia

Table 4. Significant Risk Factors for Fungal Infection*

Risk Factor	Hazard Ratio (95% CI)	P Value
Assignment to placebo	8.3 (4.0–17.1)	<0.001
United Network Organ Sharing classification 1 (life support in intensive care)	3.5 (1.7–7.0)	<0.001
Fungal colonization at baseline	2.3 (1.2–4.3)	0.01
Repeated transplantation	3.7 (2.0–6.8)	<0.001

* Stepwise regression analysis using the Cox proportional hazards model.

Table 5. Fungal Colonization at Baseline and during Prophylaxis*

Variable	Patients Cultured	Any Fungus	P Value	<i>Candida albicans</i>	P Value	<i>Candida krusei</i>	P Value	<i>Candida glabrata</i>	P Value	Other <i>Candida</i> Species†	P Value	<i>Aspergillus</i> Species	P Value
	n	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Baseline													
Placebo group	104	62 (60)		52 (50)		0 (0)		17 (16)		18 (17)		0 (0)	
Fluconazole group	106	74 (70)	0.149	62 (58)	>0.2	1 (1)	>0.2	15 (14)	>0.2	19 (18)	>0.2	1 (1)	>0.2
Week 2													
Placebo group	98	84 (86)		69 (70)		1 (1)		18 (18)		24 (24)		1 (1)	
Fluconazole group	102	49 (48)	<0.001	22 (22)	<0.001	3 (3)	>0.2	26 (25)	>0.2	11 (11)	0.015	3 (3)	>0.2
Week 4													
Placebo group	84	76 (90)		63 (75)		1 (1)		15 (18)		25 (30)		1 (1)	
Fluconazole group	98	35 (36)	<0.001	7 (7)	<0.001	2 (2)	>0.2	21 (21)	>0.2	12 (12)	0.005	2 (2)	>0.2
Week 6													
Placebo group	77	70 (91)		60 (78)		0 (0)		21 (27)		16 (21)		0 (0)	
Fluconazole group	91	30 (33)	<0.001	4 (4)	<0.001	4 (4)	0.126	19 (21)	>0.2	12 (13)	>0.2	4 (4)	0.126
Week 8													
Placebo group	58	52 (90)		44 (76)		0 (0)		15 (26)		16 (28)		0 (0)	
Fluconazole group	83	23 (28)	<0.001	2 (2)	<0.001	2 (2)	>0.2	13 (16)	0.197	12 (14)	0.085	2 (2)	>0.2
Week 10													
Placebo group	60	47 (78)		39 (65)		1 (2)		7 (12)		9 (15)		1 (2)	
Fluconazole group	85	29 (34)	<0.001	1 (1)	<0.001	0 (0)	>0.2	18 (21)	0.181	13 (15)	>0.2	0 (0)	>0.2

* Colonization was defined as isolation of fungus from any surveillance culture site in absence of symptoms or signs of infection. P values were determined by the two-tailed Fisher exact test.

† *Candida tropicalis*, *C. pseudotropicalis*, *C. lusitanae*, *C. lipolytica*, and *C. guilliermondii*.

and graft-versus-host disease) differ considerably from those of liver transplant recipients (2, 3).

Three smaller controlled trials have evaluated prophylactic fluconazole in liver transplant recipients. In a trial done at several hospitals in Spain, oral fluconazole, 100 mg/d, was more effective than oral nystatin for reducing *Candida* colonization and superficial infection (21). No benefit could be shown for prevention of invasive candidiasis, which occurred infrequently in both groups of patients (3% of fluconazole recipients and 9% of nystatin recipients). Similarly, Meyers and colleagues (22) found that a combination of fluconazole (400 mg/d), clotrimazole, and nystatin was more effective than clotrimazole plus nystatin for prevention of superficial fungal infection. Invasive fungal infection occurred in only one placebo recipient during the entire study. In a third trial, which reported no clear distinction between superficial and invasive fungal infection, the incidence of fungal infection was 38% in patients who received prophylactic nystatin and 7% in patients who received prophylactic fluconazole (400 mg/d) (23). These trials probably did not show a benefit of prophylactic fluconazole for prevention of invasive fungal infection because of smaller sample size and a low incidence of invasive infection among controls.

The 43% incidence of proven fungal infection among the placebo recipients in our study is relatively high. Several factors may have contributed to this high incidence. First, many patients undergoing liver transplantation at UCLA are high-risk patients who, in some cases, have been denied a transplant at another center. In our study, 71% of patients

(151 of 212) had one or more risk factors for fungal infection (4, 12–15). Second, patients were not excluded from the study because of critical condition or poor prognosis. Third, the placebo recipients did not receive nystatin or any type of selective bowel decontamination for prevention of infection. Although the efficacy of selective bowel decontamination for prevention of fungal infection has not been proven in any large randomized, controlled study, a low incidence of invasive fungal infection has been reported in liver transplant recipients who receive selective bowel decontamination after transplantation (15).

The potential hepatotoxicity of azole antifungal agents has been a concern in liver transplant recipients (24). In our study, fluconazole prophylaxis was never discontinued because of possible hepatotoxicity. Patients receiving prophylactic fluconazole experienced a higher incidence of adverse neurologic events; however, fluconazole recipients also had higher median serum levels of cyclosporine during the first month after transplantation. Therefore, this apparent neurotoxicity may have been related to the increased serum cyclosporine levels rather than to fluconazole itself (25). Like other azole compounds, fluconazole may increase serum levels of cyclosporine by inhibiting the cytochrome P-450 enzyme system (26). Serum cyclosporine levels must be closely monitored in liver transplant recipients who are receiving fluconazole and cyclosporine. During our study, attempts were made to maximize immunosuppression and prevent rejection in the first month after transplantation by maintaining serum trough cyclosporine levels in a higher range of 200 to 350

ng/mL. Because of the double-blind design of our study, researchers adjusted cyclosporine doses without knowledge of the patient's study group. This blinding, together with the attempts to keep serum cyclosporine levels in a higher range, may have contributed to the higher cyclosporine levels and more frequent adverse neurologic events in the fluconazole group.

Another concern about the use of prophylactic fluconazole is the emergence of resistant organisms. An increase in *C. krusei* and *C. glabrata* infections has been associated with the use of prophylactic fluconazole in some retrospective studies of recipients of bone marrow transplants and of other oncology patients from single centers (27–29). In our study, three fluconazole recipients developed invasive *C. glabrata* infection and one recipient had superficial *C. krusei* infection. However, colonization or infection by *C. krusei*, *C. glabrata*, or other organisms intrinsically resistant to fluconazole did not increase. These results are similar to those of other randomized, controlled trials of fluconazole prophylaxis in bone marrow transplant recipients and patients with leukemia (2, 3, 30). As fluconazole prophylaxis is used more extensively in solid organ transplant recipients, the possible emergence of fluconazole-resistant organisms will need to be closely monitored.

Our study did not specifically address the relative efficacy of universal antifungal prophylaxis for all transplant recipients compared with preemptive prophylaxis for only high-risk patients with identifiable risk factors for invasive fungal infection. However, the low incidence of invasive fungal infection in patients who had no predictive risk factors for fungal infection at the time of or immediately after transplantation suggests that fluconazole prophylaxis could be targeted to only high-risk patients. Our data should not be used to define high risk in other samples because the number of outcome events in our study was relatively small and the number of potential predictors in the model, many of which were correlated, was large. In addition, our analysis does not address the threshold of risk at which prophylaxis becomes most cost-effective. This issue should be the subject of future investigation.

Because the most serious cases of fungal infection in our study occurred in the initial 6 weeks after transplantation (Figure 2), it may be more cost-effective to limit the duration of prophylaxis to 6 weeks rather than the 10 weeks used in this study. In addition, we chose to use a 400-mg dose of fluconazole because this dose has been shown to be effective in previous studies (2, 3). Whether a lower dosage of fluconazole (100 to 200 mg/d) would be as effective and less expensive for prevention of invasive fungal infection in recipients of liver and

other solid organ transplants is unknown and requires further study.

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These dried brown leaves, gentlemen, come from the Peruvian bush *Erythroxylon coca*. I do not present them as a panacea, but I do assert that they possess very great virtues in cases of melancholia, morbid depression of spirits whether rational or irrational, and the restless uneasiness of mind that so often accompanies fever: it brings about an euphory, a sense of well-being far more lucid, far superior in every way to that produced by opium; and it does so without causing that unhappy addiction we are all so well acquainted with. Admittedly, it does not procure sleep as opium does—a most unhealthy sleep, I may add—but on the other hand the patient does not *require* sleep: his mind rests of itself in a remarkable calm clarity.

Patrick O'Brian
The Commodore
 New York: W.W. Norton; 1994:98-9

Submitted by:
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