

EFFICACY AND SAFETY OF ITRACONAZOLE PROPHYLAXIS FOR FUNGAL INFECTIONS AFTER ORTHOTOPIC LIVER TRANSPLANTATION: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND STUDY

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Background. There is significant morbidity and mortality related to fungal infections in the solid-organ transplant population.

Methods. A prospective, randomized, double-blind, placebo-controlled, restricted sequential design trial was performed in 71 adults undergoing orthotopic liver transplantation. Patients were randomly assigned to receive either itraconazole (5.0 mg/kg orally, preoperatively, 2.5 mg/kg orally, two times a day, postoperatively) or placebo. Therapy continued for a maximum of 56 days or until patient was discharged from hospital or met a predefined endpoint. Measurements included incidence of fungal colonization, superficial or systemic fungal infections requiring systemic therapy, adverse events, and mortality rate.

Results. This trial design supported the superiority of itraconazole in preventing fungal infections; nine patients in the placebo group (24%; 95% confidence interval, 0.118-0.412) and one patient in the itraconazole group (4%; 95% confidence interval, 0.001-0.204) developed fungal endpoints requiring therapy with amphotericin B ($P=0.04$, Fisher's exact test). At the time of enrolment, fungal colonization occurred in 40% and 37% of itraconazole and placebo patients ($P=0.43$), respectively. Adverse events were reported by 97% and 100% of the itraconazole and placebo groups, respectively, and one itraconazole and six placebo-group patients died within the study period. There was no relation to trial medication for serious adverse events.

Conclusion. Prophylaxis with itraconazole reduces fungal infections in patients undergoing orthotopic liver transplantation and is well tolerated.

There is a high incidence of fungal infections in solid-organ transplants, particularly in liver-transplant recipients. The diagnosis and treatment of fungal infections remain problematic, and they are associated with a high morbidity and

mortality rate (1-3). Currently, only one randomized, double-blind, placebo-controlled trial has demonstrated efficacy of fluconazole prophylaxis to reduce fungal infections in this patient population (4). Two other studies also demonstrated benefit; however, the design of these studies did not comply with level 1A evidence-based treatment decisions. Conversely, another trial demonstrated no benefit of fluconazole prophylaxis but used a smaller daily dose of fluconazole (100 mg) (5-7). There is no consensus regarding fungal chemoprophylaxis in the designated high-risk liver-transplant population (8). We therefore performed a randomized, placebo-controlled, restricted sequential trial to evaluate the efficacy and safety of the broad-spectrum triazole-itraconazole oral solution for antifungal prophylaxis in liver-transplant patients.

MATERIALS AND METHODS

Patients

Patients greater than 17 years of age undergoing orthotopic liver transplantation were enrolled. Patients were excluded if they were unable to receive medication enterally, were being treated or had signs or symptoms of a fungal infection at the time of transplantation, had known hypersensitivity to azole antifungals, had received systemic antifungal therapy within 2 weeks before study entry or topical intra-oral therapy within 1 week, had a previous fungal infection unresponsive to azole therapy, or were known to be HIV positive, pregnant, or lactating. Patients receiving the following medications within 1 month preceding study entry were not eligible or were withdrawn: isoniazid, rifabutin, rifampin, terfenadine, astemizole, loratadine, phenytoin, phenobarbital, carbamazepine, oral hypoglycemics, ddI, HMG-CoA reductase inhibitors, cisapride, oral midazolam, triazolam, or any investigational drug other than immunosuppressive agents.

Study Design

The protocol was approved by the University of Western Ontario Research Ethics Board for the Review of Health Sciences Research Involving Human Subjects. This study was designed as a prospective, randomized, double-blind, placebo-controlled, phase III, restricted sequential design trial. This design was chosen to generate a set of stopping rules to enable the early detection of any advantage to treatment (9).

After informed consent, the patients were randomized to receive either a bolus dose of itraconazole 5.0 mg/kg orally and preoperatively followed by 2.5 mg/kg, orally two times a day, postoperatively, or a placebo. Treatment continued until a fungal endpoint (Table 1) was reached or the patient was discharged from hospital or when a total of 56 days of treatment had occurred.

Blinding

Blinded medication kits in pairs of one treatment and one placebo group designation were numbered sequentially. The pharmacist as-

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977

TABLE 1. Definitions of fungal infection endpoints

1. Proven deep fungal infections required *one* of the following:
 - I) positive histology on biopsy from deep tissue
 - II) at least one positive blood culture for yeast to be further specified into three categories:
 - no clinical signs and symptoms (i.e., fever only) or
 - clinical signs and symptoms or
 - sepsis
 Candidemia was to be further specified according to
 - relation to catheters
 - acute or chronic disseminated candidosis - III) clinical signs and radiological lesions in combination with the presence of *Aspergillus spp* or other filamentous fungi in bronchoalveolar lavage fluid.
2. Suspected deep fungal infections required *one* of the following:
 - I) clinical signs and symptoms (with or without radiological lesions) with fever of unknown origin unresponsive to broad spectrum anti-bacterials.
 - II) highly suggestive radiological lesions for deep fungal infection, without mycological evidence by culture or histology (e.g., hepatosplenic candidosis and some types of pulmonary aspergillus)
 - III) clinical signs and symptoms (with or without radiological lesions), not highly suggestive of fungal infection but associated with a suggestive fungal isolation (e.g., from sputum or nasal cavities for aspergillosis)
3. Superficial fungal infections required clinical signs and symptoms of oral, esophageal, or vaginal candidosis plus positive mycology at the site of infection. Only superficial fungal infections treated with systemic antifungal medication were considered a fungal endpoint.
4. Fever of unknown origin requiring empiric treatment with IV amphotericin B defined by body temperature >38°C (oral or axillary measurement; >38.5°C rectal measurement) without clinical signs and symptoms, for at least 3 weeks, while receiving a broad spectrum antibiotic drug regimen.

signed each patient the next consecutive study-kit number upon randomization. All treatment assignment and study medications were blinded to all research and clinical staff, patients, and family members.

Efficacy Variables

The primary objective was to evaluate the efficacy of oral itraconazole prophylaxis as assessed by prevention of fungal infections and a reduction in morbidity or mortality. The definitions of the fungal infection endpoints are listed in Table 1.

The secondary objective was to assess the effects of itraconazole prophylaxis on fungal colonization, the incidence of fungal infections, the frequency of administration of intravenous amphotericin B, and the time to initiation of intravenous amphotericin B.

Safety

Patient tolerability and safety were assessed by monitoring laboratory data and adverse events. Any undesirable experiences, laboratory abnormalities, and intercurrent illnesses were recorded as adverse events. A serious adverse event (SAE) was defined as fatal or life threatening, disabling, requiring intervention to prevent permanent impairment or damage, or resulting in or prolonging inpatient hospitalization. Because of the nature of the transplant patient population being studied, the incidence of intercurrent illness and organ dysfunction was anticipated to be high. Therefore, a safety monitor-

ing group (SMG) reviewed safety reports for every five patient pairs. In the event that the SMG judged that a clinically significant imbalance in the severity or frequency of safety related abnormality existed between treatment groups, the SMG would recommend stopping the trial.

Itraconazole Drug Levels

Plasma samples were drawn at baseline, days 4 and 7, and weekly thereafter to assess plasma levels of itraconazole.

Sample-Size Calculations

The incidence of disseminated fungal infection posttransplantation was used as the primary outcome for the sample-size calculations. The frequency of fungal infection occurring within 56 days of transplantation in the placebo group was estimated at 25% (unpublished retrospective database from our institution over a 2-year period) as compared with 5% in the itraconazole group. For sample-size calculations, alpha equaled 0.05 and the power was set at 80%.

The upper boundary for rejection of the hypothesis of equal efficacy for itraconazole and placebo was defined by the equation $y=3.00+0.4078x$, where y is the number of pairs favoring itraconazole less the number of pairs favoring placebo, and x is the number of pairs in which either itraconazole or placebo of the pair reached a fungal infection endpoint. Crossing the upper boundary would automatically require that the study be stopped and would indicate the superiority of itraconazole. The lower boundary was defined by $y=x-4.10$; crossing the lower boundary would invoke the stopping rule and would indicate that itraconazole was inferior to placebo.

Statistical Methods

An intention-to-treat analysis was performed for all patients who received a transplant and at least one dose of medication. The sequential analysis was the primary efficacy outcome analysis. The primary and secondary outcomes were analyzed using Fisher's exact test (two-tailed). The impact of covariates was determined using the logistic regression on the primary outcome only. The Kaplan-Meier methodology was applied to time-dependent outcomes, and the cumulative probability of receiving systemic antifungal treatment was analyzed with life table analysis.

Time in trial, intensive care unit, and hospital were analyzed using analysis of variance (ANOVA). The number and percentage of febrile days were analyzed with the Wilcoxon rank sum test, and the number of immune modulators used was analyzed with the Chi-square test. Only descriptive analyses were performed for the safety outcomes. Adverse experiences occurring in 10% or more of the patients, regardless of treatment group, were analyzed to detect between treatment group differences using Fisher's exact test.

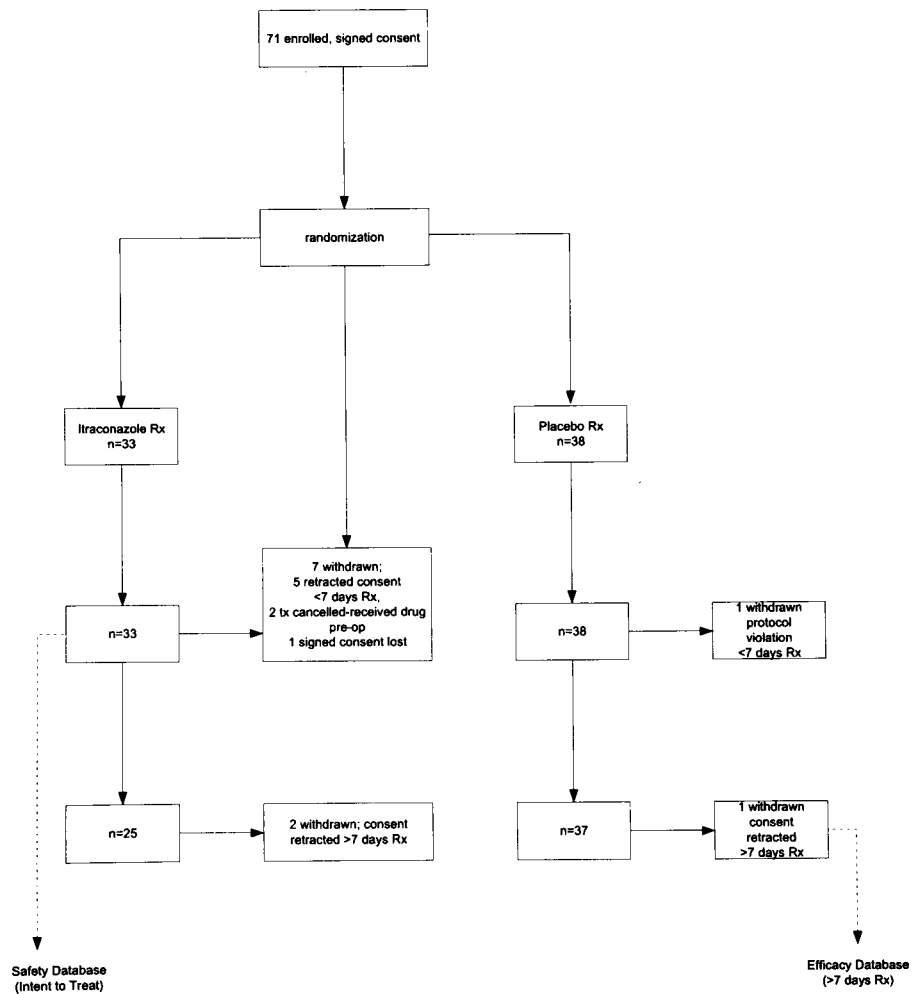
RESULTS

The disposition of the 71 patients enrolled in this trial is shown in Figure 1. There were 33 patients in the itraconazole group and 38 patients in the placebo group used for the intention-to-treat analysis (safety database) and 25 and 37 patients in the itraconazole and placebo groups, respectively, used for the efficacy analysis.

Mean age was 46 years, and 59% of the patients were male. At study entry, the Child's Turcot score was C in 46 patients (65%), B in 22 (31%), A in 2 (3%), and unknown in 1 patient. The most common underlying disease necessitating liver transplantation was hepatic cirrhosis ($n=49$, 69%). There were no significant differences in age, sex, underlying disease, or severity of liver disease between groups.

There were numerous possible predisposing factors for fungal infections upon entry into the trial. All patients had a central venous catheter, peripheral intravenous lines, and a

FIGURE 1. Enrollment and disposition of patients.



urinary catheter; three patients had implantation catheters, and one patient had a gallbladder catheter. Other catheters present in 17 patients included subhepatic drains, peritoneal drains, and dialysis catheters. The majority of patients (72%) had three catheters present, and 28% of patients had four or more catheters in situ.

Fungal colonization at entry was noted in 31 patients (44%), 17 in the itraconazole and 14 in the placebo groups ($P=0.34$, Fisher's exact test). Other predisposing factors were the use of parenteral nutrition (45% vs. 42%) and diabetes (12% vs. 11%) in the itraconazole and placebo groups, respectively. There were no differences in these factors in the two groups.

Immunosuppression

All patients received at least two immunosuppressive agents over the course of the trial; corticosteroids were administered to 94% and 100% of the itraconazole- and placebo-treated patients, respectively; cyclosporine was administered to 88% and 87% of itraconazole- and placebo-treated patients, respectively; azathioprine was administered to 73% and 84% of itraconazole- and placebo-treated patients, respectively.

Sequential Analysis

Patients were paired by the study statistician in an ongoing fashion for comparison of outcomes. Infections were di-

agnosed in seven placebo patients (itraconazole "wins"). One itraconazole patient placebo developed a fungal infection (placebo "win"); this patient failed to reach therapeutic drug levels of itraconazole (serum level <250 ng/mL). Fungal endpoints were reached in two additional placebo patients before the study was stopped. However, there were insufficient itraconazole patients to "pair" with these two. In summary, of the eight paired wins, seven favored itraconazole. Of the 10 fungal endpoints observed in total, 9 favored itraconazole. The sequential analysis of the final population is shown in Figure 2. The incidence of fungal endpoints is significantly lower in the itraconazole group (rate 0.04; 95% confidence interval 0.001–0.204) compared with the placebo group (rate 0.24; 95% confidence interval 0.118–0.412; $P=0.04$, Fisher's exact test).

Primary Efficacy Variables

No patients in either treatment group presented with proven deep fungal infection. Suspected deep fungal infection was diagnosed in six (16%) placebo patients and one (4%) itraconazole-treated patient; the incidence rate was not different between groups ($P=0.225$, Fisher's exact test). Superficial fungal infection necessitating systemic treatment was diagnosed in three (8%) placebo group patients and in no itraconazole patients ($P=0.141$, Fisher's exact test). The decision to treat for suspected deep fungal infection or superfi-

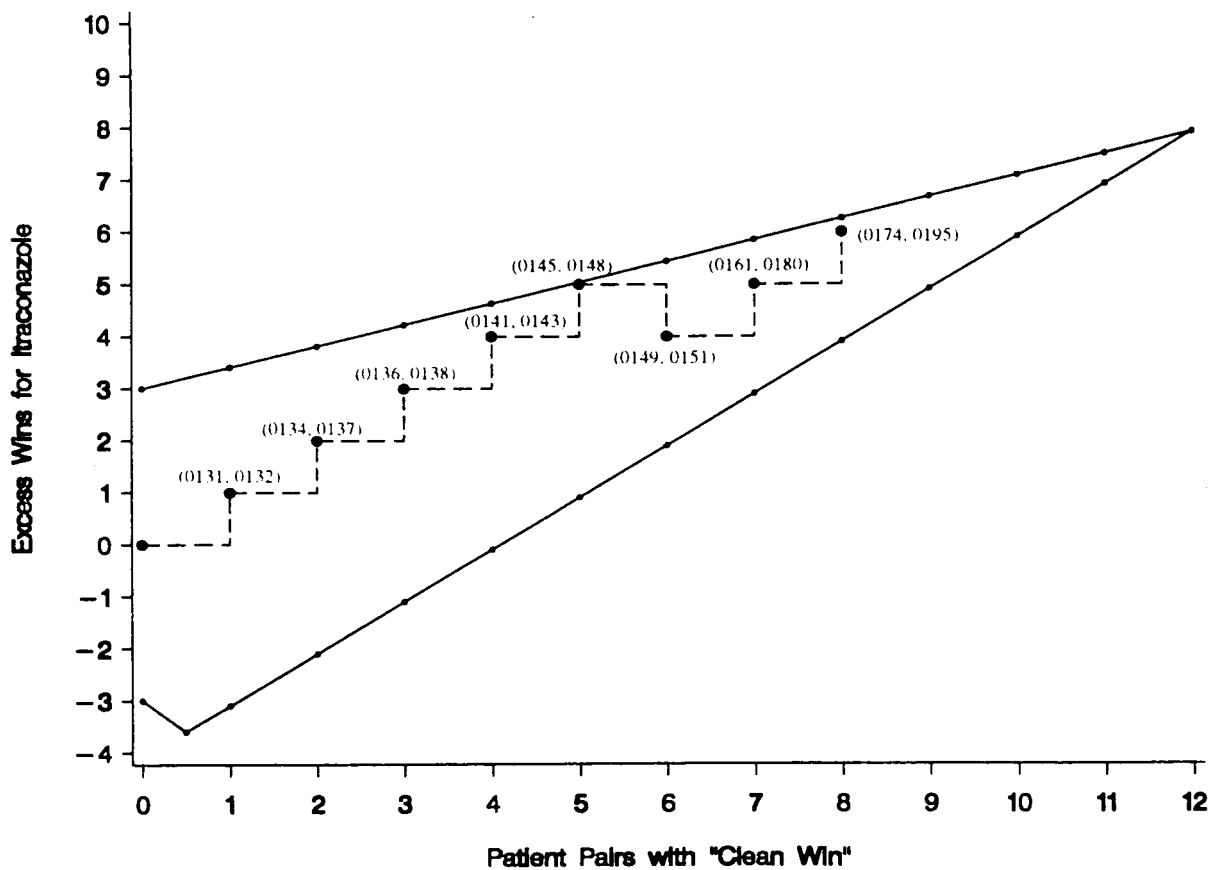


FIGURE 2. Sequential analysis of the final population. Interception of the top line of graph evoked the stopping rule of trial, indicating benefit of itraconazole prophylaxis. Numbers in parenthesis represent actual number assigned to patient and pairing of one itraconazole and one placebo patient.

cial fungal infection was at the discretion of the intensive care-transplant teams, according to the criteria defined in Table 1. All patients presented with a rising white blood cell count and changes in body temperature and were currently being treated with broad spectrum antibacterial therapy; 9 of 10 patients were also receiving vasopressor therapy (Table 2). The incidence of fungal infection requiring systemic treatment was significantly greater ($P=0.0396$) in the placebo patients (9%) as compared with the itraconazole patients (3%), although fungal colonization at the time of enrolment was similar between the two groups (itraconazole 40% vs. placebo 37%, $P=0.43$). Any patient colonized with a fungus at enrolment, regardless of treatment group, was 5.28 times more likely to reach the primary fungal endpoint ($P=0.037$). The cumulative probability of developing a fungal infection requiring systemic antifungal therapy over time after liver transplantation is displayed graphically in Figure 3. Log-rank analysis confirms that the probability of infection is markedly higher in the placebo group beyond the first 2 weeks of treatment as reflected in the time to systemic antifungal treatment ($P=0.038$).

Secondary Outcome Variables

All seven patients (1 placebo and 6 itraconazole) suspected of having deep fungal infection had positive mycologic cultures (Table 2). Three placebo-group patients were treated for documented superficial infection.

The logistic regression failed to confirm an association of the primary outcome with age, Child's Turcot score, the presence of parenteral nutrition, the presence of diabetes, or the primary reasons for transplant (i.e., underlying liver disease). The incidence of renal failure in either group was too low to determine whether renal failure was a risk factor for fungal infections. The only predictive factor of developing a fungal infection, in addition to the treatment group, was the presence of fungal colonization at entry of the study ($P=0.037$). Most patients achieved effective plasma levels of itraconazole (>250 ng/mL) with the exception of four patients. The single itraconazole group patient who reached a fungal endpoint had a subtherapeutic plasma level of itraconazole.

Tertiary Outcome Variables

There was no significant difference between groups comparing time in intensive care unit (itraconazole 28 ± 32 vs. placebo 24 ± 19 days), in hospital (itraconazole 6 ± 12 vs. placebo 6 ± 8 days), and time on trial treatment (itraconazole 13 ± 13 vs. placebo 13 ± 7 days).

Mortality

Six placebo-group patients (4 from chronic sepsis, 1 of massive hemorrhage, 1 from central pontine myelinolysis) and one itraconazole-group patient (massive hemorrhage-

TABLE 2. Culture summary of patients with fungal infection endpoint requiring systemic antifungal therapy

Patient no. (treatment group)	Fungal endpoint ^a	Organism	Site	Systemic antifungal therapy	Temp (°C), WBC, vasopressors used at endpoint	Outcome
131 (PL)	SDFI	<i>C. albicans</i>	Tracheal aspirate Nasal swab Mouth Stool Urine	Amphotericin B	35.4c, 4.1, dop,nor	Died Sepsis/MOF
0137 (PL)	SDFI	<i>C. albicans</i>	Tracheal aspirate Bronchial lavage Stool	Amphotericin B	38.4c, 24.0, dop,epi,nor	Died Sepsis/MOF
0138 (PL)	SDFI	<i>C. albicans</i>	Urine Vagina	Fluconazole IV	38.3ax, 17.6, dop	Died Sepsis
0141 (PL)	SDFI	<i>C. albicans</i>	Urine Stool Mouth Vagina	Amphotericin B Fluconazole po	38.1ax, 11.2, none	Alive
0148 (PL)	SDFI	<i>C. albicans</i>	Tracheal aspirate	Amphotericin B	39.3r, 23.6, dop	Died Sepsis/shock
0174 (PL)	SDFI	<i>C. glabrata</i>	Peritoneal fluid	Fluconazole po	38.4po, 12.2, dop	Alive
		<i>C. glabrata</i>	Peritoneal fluid	Fluconazole po		
0161 (PL)	SFI	<i>C. albicans</i>	Urine Stool Vagina Mouth Stool Nasal swab Sputum Urine	Fluconazole po	36.9ax, 12.4, dop	Alive
		<i>C. glabrata</i>	Nasal swab Vagina Stool Bronchial lavage			
0179 (PL)	SFI	<i>C. albicans</i>	Mouth Tracheal aspirate Nasal swab	Fluconazole po	38.6ax, 13.9, dop,nor	Alive
		<i>C. glabrata</i>	Urine Stool Vagina			
0196 (PL)	SFI	<i>C. albicans</i>	Mouth	Fluconazole po	35.7ax, 1.9, dop	Alive
0151 (ITR)	SDFI	<i>C. glabrata</i>	Nasal swab Mouth Tracheal aspirate Urine Vagina	Amphotericin B	35.2ax, 11.4, dop	Alive
		<i>C. albicans</i>	Stool Vagina Vagina			

^a Requiring systemic antifungal therapy; PL, placebo group; ITR, itraconazole group; WBC, white blood cell count; Temp, temperature; ax, axillary; po, oral; r, rectal; c, core; dop, dopamine; epi, epinephrine; nor, norepinephrine; MOF, multiorgan failure; SDFI, suspected deep fungal infection; SFI, superficial fungal infection.

intestinal infarction) died. Because of the very small numbers, this was not statistically significant. No relationship between death and the study medication was found.

Safety Evaluation

Adverse events were not significantly different between the two groups. Although nausea and vomiting contributed to poor drug tolerability in a few patients, there was no difference in the incidence between groups. Laboratory values were routinely abnormal (e.g., hepatic and renal param-

eters), but there were no significant differences between treatment groups implicating the transplant condition. Adverse events assessed as being related, or possibly related, to drug were reported in a total of 10 (30%) itraconazole patients and 11 (29%) placebo patients; these were predominately nausea, vomiting, and diarrhea in both treatment groups.

DISCUSSION

Systemic fungal infections remain a major challenge in transplant patients. The incidence of systemic fungal infec-

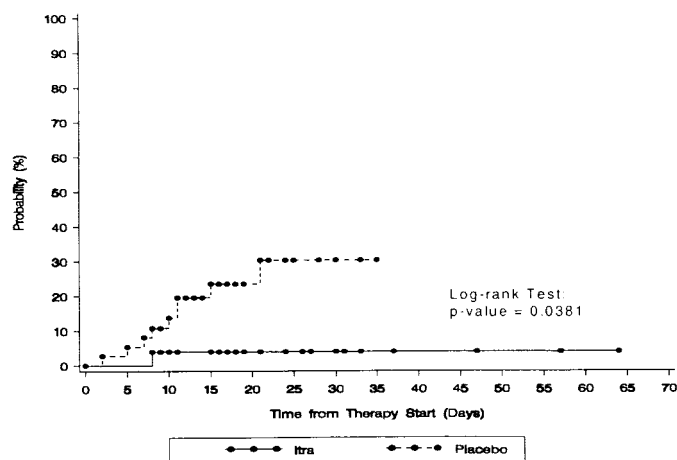


FIGURE 3. Cumulative probability of developing a fungal infection requiring systemic antifungal therapy over time; the probability of infection is markedly higher in the placebo group beyond the first 2 weeks of treatment.

tion ranges from 5% in renal transplant recipients to as high as 42% in liver-transplant recipients (3). Significant morbidity and mortality result from invasive fungal infections, and it is therefore prudent to develop antifungal prophylaxis protocols in high-risk patient populations (1, 2). Our study demonstrated that oral itraconazole administered as antifungal prophylaxis in the perioperative period significantly reduced the number of fungal infections requiring antifungal systemic therapy, with no evidence of hepatotoxicity or SAEs.

Chemoprophylaxis of transplant recipients with oral agents such as nystatin, clotrimazole, and amphotericin B have produced inconsistent results. Although clotrimazole and amphotericin B have shown to decrease fungal colonization and superficial infections, they have not reduced invasive fungal infections (10–13). Low-dose amphotericin B has been reported to reduce the incidence of fungal infections after liver transplantation, but this study is limited by its use of historic controls and the concern of its toxicity (14). Liposomal amphotericin B, on the other hand, reduces invasive fungal infections and is well tolerated in the liver population, however, its cost is a major drawback. Some authors argue the cost of treating fungal infections outweighs the added cost of antifungal prophylaxis with liposomal amphotericin B (15–18). Studies assessing antifungal prophylaxis with triazole preparations have yielded promising results. A randomized, double-blinded, placebo-controlled trial in liver transplant recipients by Winston et al. (4) demonstrated a significant reduction in superficial and invasive fungal infections as well as a reduction in deaths related to invasive fungal infections. A similarly designed trial by Lumbreras et al. (5) demonstrated a reduction in colonization and superficial fungal infections but had no effect on the incidence of invasive infections; however, the selected daily dose (100 mg) was less than the dose administered in the Winston trial (400 mg), and suboptimal plasma levels of fluconazole may explain the inability of this dose to prevent invasive fungal infections. Decruyenaere et al. (6) also demonstrated a reduction in invasive fungal infections in liver-transplant patients who received fluconazole prophylaxis; however, the trial de-

sign was suboptimal because it was a retrospective, nonrandomized, non–placebo-controlled trial design.

Itraconazole and fluconazole have similar spectra, but itraconazole has superior activity against *Aspergillus* species, which are important pathogens in liver-transplant patients (19). There is also concern regarding the emergence of resistant organisms associated with the use of prophylactic fluconazole as well as an increase in *C. krusei* and *C. glabrata* infections. Itraconazole may therefore be the more beneficial triazole agent for prophylaxis therapy. The efficacy of itraconazole prophylaxis has been demonstrated in other immunocompromised patient populations, and it has been demonstrated to be similar to fluconazole in reducing fungal colonization in liver-transplant patients (20–23). With the current clinical experience indicating that itraconazole is well tolerated with rarely reported cases of hepatotoxicity, we proceeded to study its efficacy in the liver-transplant population (24).

Liver-transplant recipients were chosen because they have the highest incidence of fungal infection among solid-organ transplant recipients (8). Quantification of risk factors in our study confirms that 93% of our population had multiple risk factors of developing systemic mycoses. All patients enrolled received at least two immune-modulating medications and multiple broad-spectrum antibiotics throughout the course of the study. Parenteral nutrition was administered in 44% of patients, 11% were diabetic, and the incidence of malnutrition was 67%. Furthermore, fungal colonization with *Candida albicans* or *Candida glabrata* was detected in 52% of itraconazole and 58% of placebo patients; 17% of these patients were positive at multiple culture sites. All patients who developed fungal endpoints in our study cultured *Candida* species (Table 2), suggesting that the origin of the fungal infections was likely the patient's own commensal flora. This finding is supported by other studies that have demonstrated patients with fungal colonization are at higher risk of developing invasive fungal infections (25–28).

This double-blind, placebo-controlled design included a range of defined fungal endpoints. The restrictive sequential design was chosen to enable the early detection of any advantage afforded by prophylaxis. As such, fungal endpoints were plotted in sequential-pairs fashion until one of the boundaries of the triangular graph was crossed (Fig. 2). At that point, the stopping rule was invoked, patient recruitment was discontinued, and the collected data was subsequently confirmed with patient's charts. This stopping-rule design allows for a clear efficacy result with a minimum number of patients enrolled. The cumulative probability of developing a fungal infection requiring systemic antifungal therapy was significantly higher in the placebo group beyond the first 2 weeks of treatment (Fig. 3). One drawback of this trial design was that patients were not stratified according to risk for developing fungal infection, and therefore we are unable to identify "high-risk" patients who would benefit more from antifungal prophylaxis as opposed to lower-risk patients who would benefit less from prophylaxis. For example, Laverdiere et al. (25) studied the impact of fluconazole prophylaxis on fungal colonization and infection rates in neutropenic patients and demonstrated a negative predictive value of 88% for development of an invasive fungal infection in patients with a colonization index less than 0.25. Such patients would not benefit from antifungal prophylaxis yet

would be at risk for potential toxicity of the antifungal agent as well as having the potential to develop resistant infections (29).

A total of 10 fungal endpoints were attained in our study, 9 in the placebo group and 1 in the itraconazole group ($P=0.0396$). No patients in either treatment group were classified as "proven deep fungal infection." This is likely a reflection of the extensive clinical fungal surveillance to which these patients were subjected. Strong clinical suspicion of deep fungal infection as previously defined fungal endpoints (Table 1), particularly with positive fungal cultures at several sites, resulted in withdrawal of the study medication and the immediate institution of systemic antifungal therapy. This is accepted clinical practice, and the indicated need for empiric antifungal therapy is a legitimate outcome measure (1). It is also interesting that the single patient in the itraconazole group who developed a suspected systemic infection requiring systemic therapy was one of four study patients who did not achieve an effective plasma level of itraconazole (250 ng/mL).

The frequency of adverse events was not different between the two treatment groups. Most adverse events can be readily linked to the postoperative transplant state, secondary to immunosuppressive therapy or the underlying disease. Withdrawal because of intolerability of the study medication occurred in five patients because of the unpleasant taste, four with itraconazole, and one with placebo. No patients were withdrawn from the study as a result of abnormal laboratory tests or evidence of hepatotoxicity. One death occurred in the itraconazole group unrelated to fungal infection, and five deaths occurred in the placebo group, three of which were directly attributed to systemic fungal infection resulting in multiorgan failure. There was no significant difference in overall mortality between the treatment groups.

Our study demonstrated that prophylaxis with itraconazole oral solution can safely reduce fungal infections in the liver-transplant population. Itraconazole may be the superior triazole agent for antifungal prophylaxis in the setting of solid-organ transplant patients because of its greater activity against *Aspergillus* species compared with fluconazole. Further studies are required to determine the "low-risk" patient who would not benefit from itraconazole prophylaxis to establish guidelines with respect to antifungal prophylaxis not only in liver-transplant patients but in other high-risk patients as well.

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