

# Intravenous and Oral Itraconazole versus Intravenous and Oral Fluconazole for Long-Term Antifungal Prophylaxis in Allogeneic Hematopoietic Stem-Cell Transplant Recipients

## A Multicenter, Randomized Trial

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**Background:** Allogeneic hematopoietic stem-cell transplant recipients often receive fluconazole or an amphotericin B preparation for antifungal prophylaxis. Because of concerns about fungal resistance with fluconazole and toxicity with amphotericin B, alternative prophylactic regimens have become necessary.

**Objective:** To compare the efficacy and safety of intravenous and oral itraconazole with the efficacy and safety of intravenous and oral fluconazole for long-term prophylaxis of fungal infections.

**Design:** Open-label, multicenter, randomized trial.

**Setting:** Five transplantation centers in the United States.

**Patients:** 140 patients undergoing allogeneic hematopoietic stem-cell transplantation.

**Intervention:** Itraconazole (200 mg intravenously every 12 hours for 2 days followed by 200 mg intravenously every 24 hours or a 200-mg oral solution every 12 hours) or fluconazole (400 mg intravenously or orally every 24 hours) from day 1 until day 100 after transplantation.

**Measurements:** Proven invasive or superficial fungal infection, drug-related side effects, mortality from fungal infection, and overall mortality.

**Results:** Proven invasive fungal infections occurred in 6 of 71 itraconazole recipients (9%) and in 17 of 67 fluconazole recipients (25%) during the first 180 days after transplantation (difference,

−16 percentage points [95% CI, −29.2 to −4.7 percentage points];  $P = 0.01$ ). Superficial fungal infections occurred in 3 of 71 itraconazole recipients (4%) and in 2 of 67 fluconazole recipients (3%). In a multivariable analysis using factors known to affect the risk for invasive fungal infection after hematopoietic stem-cell transplantation, prophylaxis with itraconazole was still associated with fewer invasive fungal infections (odds ratio, 0.300 [CI, 0.111 to 0.814];  $P = 0.02$ ) caused by either yeasts or molds. More fungal pathogens were found to be resistant to fluconazole than to itraconazole. Except for more frequent gastrointestinal side effects (nausea, vomiting, diarrhea, or abdominal pain) in patients given itraconazole (24% vs. 9%; difference, 15 percentage points [CI, 2.9 to 27.0 percentage points];  $P = 0.02$ ), both itraconazole and fluconazole were well tolerated. The overall mortality rate was similar in each group (32 of 71 patients in the itraconazole group [45%] vs. 28 of 67 patients in the fluconazole group [42%]; difference, 3 percentage points [CI, −13.2 to 19.8 percentage points];  $P > 0.2$ ), but fewer deaths were related to fungal infection in patients given itraconazole (6 of 71 [9%]) than in patients given fluconazole (12 of 67 [18%]) (difference, 9 percentage points [CI, −20.6 to 1.8 percentage points];  $P = 0.13$ ).

**Conclusion:** Itraconazole is more effective than fluconazole for long-term prophylaxis of invasive fungal infections after allogeneic hematopoietic stem-cell transplantation. Except for gastrointestinal side effects, itraconazole is well tolerated.

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**F**ungal infections have become an increasing cause of morbidity and death after allogeneic hematopoietic stem-cell transplantation. Indeed, with better prevention of cytomegalovirus disease, invasive fungal infections are now the leading cause of death from infection at many transplantation centers (1,2). Consequently, antifungal agents are often used for prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. An amphotericin B formulation or fluconazole has been most commonly used (3–11). Each of these agents, however, has substantial limitations for prophylaxis. The amphotericin B formulations are limited by toxicity, and the lipid preparations of amphotericin B can be expensive. Furthermore, the prophylactic efficacy of standard amphotericin B and the newer lipid formulations of amphotericin has not been consistently demonstrated in randomized, controlled trials (1, 5–11). Routine use of fluconazole for prophylaxis has been associated with the emergence of fluconazole-resistant *Candida*

infections (12–14). Fluconazole also lacks reliable activity against *Aspergillus* species, which have now become the primary cause of invasive fungal infection at many transplantation centers (15, 16).

Itraconazole is an azole antifungal agent that may overcome some of the limitations of fluconazole and the amphotericin B formulations as prophylactic agents in allogeneic hematopoietic stem-cell transplant recipients. Itraconazole has excellent in vitro activity against many opportunistic fungi that are resistant to fluconazole, including *Aspergillus* and some *Candida* species (17, 18). Itraconazole is less toxic than the amphotericin B formulations. It is now available in an oral hydroxypropyl- $\beta$ -cyclodextrin solution as well as an intravenous formulation. Compared with itraconazole capsules, itraconazole oral solution is much better absorbed and has been used successfully for antifungal prophylaxis in neutropenic patients who had not received an allogeneic hematopoietic stem-cell trans-

**Context**

Fungal infections after allogeneic hematopoietic stem-cell transplantation are a serious problem. Current prophylactic regimens are limited by toxicity and the emergence of resistant infections.

**Contribution**

This open-label randomized trial of 140 patients undergoing stem-cell transplantation found that prophylaxis with itraconazole for 100 days after transplantation prevented more invasive fungal infections than did prophylaxis with fluconazole (absolute difference,  $-16$  percentage points [95% CI,  $-29$  to  $-5$  percentage points]). More fungal pathogens were resistant to fluconazole. Nausea, vomiting, diarrhea, and abdominal pain were more common in patients receiving itraconazole.

**Implications**

Itraconazole is better than fluconazole for preventing invasive fungal infections in allogeneic stem-cell transplant recipients but causes more gastrointestinal side effects.

—The Editors

plant (19–21). Intravenous itraconazole is the only azole approved for empirical antifungal therapy in febrile neutropenic patients (22). We performed a randomized trial to compare intravenous and oral itraconazole with intravenous and oral fluconazole for prevention of fungal infections in allogeneic hematopoietic stem-cell transplant recipients.

**METHODS****Patients**

Patients of either sex who were 13 years of age or older and undergoing allogeneic hematopoietic stem-cell transplantation were eligible for the study if they had no history of an invasive yeast or mold infection within 8 weeks before initiation of therapy with the study drug. Because of the paucity of efficacy and safety data on the use of intravenous and oral itraconazole in children at the time this study was initiated, patients younger than 13 years of age were excluded. Patients with liver enzyme values greater than five times the upper limit of normal, a bilirubin level greater than  $85.5 \mu\text{mol/L}$  ( $5.0 \text{ mg/dL}$ ), an allergy to imidazoles or azoles, or a body temperature greater than  $38.0^\circ\text{C}$  within 48 hours of starting therapy with the study drug were also excluded. Similarly, patients who had received a previous bone marrow or peripheral stem-cell transplant and patients requiring concomitant therapy with drugs (rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, midazolam, triazolam, cisapride, terfenadine, or astemizole) having potential interactions with azole antifungal agents were not eligible for the study. Women were required to have a negative result on a pregnancy test.

Informed consent was obtained from each patient or appropriate relative in a manner approved by the institutional review board at each study center.

**Study Drugs and Design**

Eligible patients were randomly assigned to receive prophylaxis with either itraconazole or fluconazole. We used blocked randomization, which was done in a 1:1 ratio and stratified by study center. The randomization process was performed by the pharmacy department at each study site. The study design was open label because blinding of intravenous and oral itraconazole against intravenous and oral fluconazole was technologically impossible at the time the study was conducted.

Prophylaxis with each study medication was started on the first day after transplantation. Because a previous trial had shown both a reduction in fungal infections and improved survival when prophylactic fluconazole was used for 75 days after transplantation (4), use of the study drug was continued until day 100 after transplantation. Patients randomly assigned to receive itraconazole were initially given intravenous itraconazole at a loading dose of 200 mg every 12 hours for 2 days, followed by 200 mg every 24 hours for 12 days. Patients were then switched to oral itraconazole solution at a dose of 200 mg every 12 hours until day 100 after transplantation. Similarly, patients randomly assigned to receive fluconazole were initially given intravenous fluconazole at a dose of 400 mg once daily for 14 days and were then switched to oral fluconazole tablets at a dose of 400 mg once daily until day 100 after transplantation. If patients could not take or tolerate oral medications, they resumed prophylaxis with the intravenous form of the study drug. The dose of itraconazole was not adjusted in patients with renal failure. However, if the serum creatinine level increased to greater than  $354 \mu\text{mol/L}$  ( $4.0 \text{ mg/dL}$ ) during treatment with intravenous itraconazole, patients were changed to itraconazole oral solution because of the prolonged elimination rate of intravenous hydroxypropyl- $\beta$ -cyclodextrin with severe renal impairment. The daily dose of fluconazole was decreased by 50% for a creatinine clearance of 0.33 to  $0.84 \text{ mL/s}$  (20 to  $50 \text{ mL/min}$ ) and by 75% for a creatinine clearance of less than  $0.33 \text{ mL/s}$  ( $20 \text{ mL/min}$ ).

After transplantation, prophylaxis with the study drug was discontinued if an invasive fungal infection was documented, a serious adverse event definitely related to the study drug occurred, or the patient died. Patients with a documented superficial fungal infection could be treated with a topical antifungal agent while continuing prophylaxis with the study drug. Use of the study drug was temporarily discontinued when empirical therapy with amphotericin B was administered for suspected but undocumented fungal infection. After the empirical amphotericin B therapy was stopped, prophylaxis with the study drug was resumed.

## Transplantation Regimen

Investigators at each study center were allowed to use the preparative regimens of chemoradiation therapy and the immunosuppressive agents for prophylaxis and treatment of graft-versus-host disease that were considered standard practice at their institutions. Similarly, each study center used its own standard agents to prevent and treat bacterial and viral infections. The criteria used to diagnose and grade graft-versus-host disease have been previously published (23, 24).

## Laboratory Procedures

We obtained complete blood counts with differential leukocyte count and platelet count, blood urea nitrogen levels, serum creatinine and electrolyte determinations, urinalyses, and liver function studies (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin levels) at study entry, at least once weekly during the study, and within 3 days of completion of prophylaxis with the study drug. Serum cyclosporine levels, measured by using high-pressure liquid chromatography, were also monitored during the study (25). In patients receiving itraconazole, trough plasma levels of itraconazole and its active metabolite, hydroxy-itraconazole, were measured by using high-performance liquid chromatography on days 3 and 7 of the study and then once every 1 or 2 weeks thereafter (26).

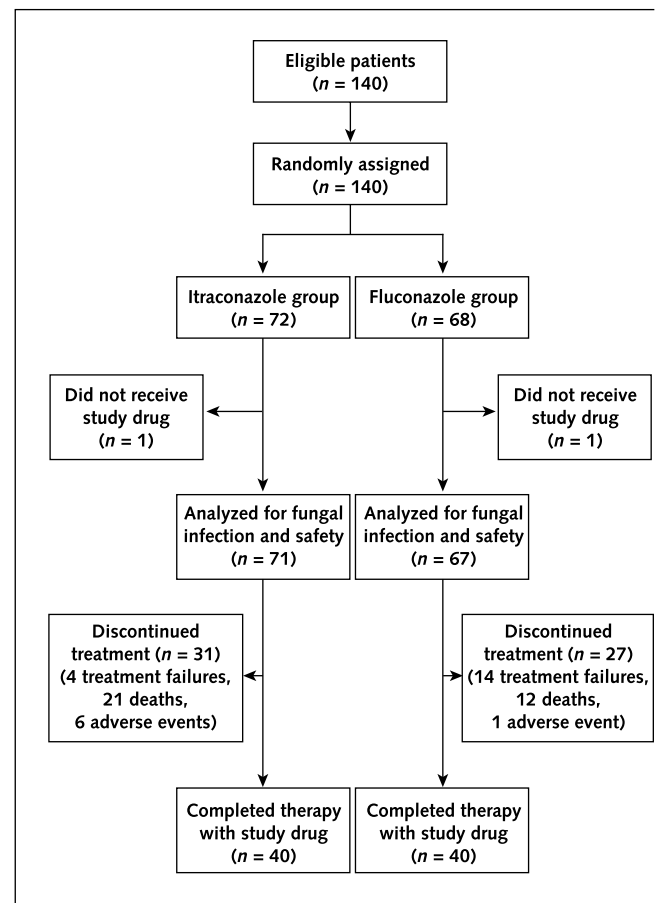
We obtained cultures of the blood and other suspected sites of fungal infection whenever a patient's clinical condition suggested the possibility of infection. Chest radiography, computed tomography, bronchoscopy, and biopsies were also done when clinically indicated to diagnose fungal infection.

We determined minimum inhibitory concentrations (MICs) of itraconazole and fluconazole for yeast and filamentous fungi isolated from patients with documented fungal infections to evaluate the possible emergence of resistant organisms. Antifungal susceptibility testing was performed by a central reference laboratory according to guidelines of the National Committee for Clinical Laboratory Standards (27, 28).

## Definitions of Fungal Infection

Superficial fungal infections were diagnosed by the isolation of a fungus from the skin, oropharynx, gastrointestinal tract, or vagina in association with signs of inflammation, ulcerations, plaques, exudates, or other manifestations of infection not explainable by other pathogens. Invasive fungal infections were diagnosed by using criteria published by the National Institutes of Health Mycoses Study Group and the European Organization for Research and Treatment of Cancer (29). The diagnosis of invasive fungal infection required the presence of fungus in the blood, pulmonary tissues or secretions, sinuses, soft tissues, or other organ structures in association with symptoms and signs of infection not explainable by other pathogens.

Figure 1. Profile of patients in the study.



## Statistical Analysis

All statistical tests were two tailed. Differences in proportions between treatment groups were compared by using the Fisher exact test (30). We determined 95% CIs for differences by using the normal approximation. Comparisons of time to specific events in the treatment groups were performed by using the Kaplan–Meier method and log-rank test (31). A propensity score method and a stratified analysis with the Mantel–Haenszel test were used to analyze multiple factors that might influence the development of invasive fungal infection (32). *P* values of 0.05 or less were considered to be statistically significant.

The primary end point of the study was the incidence of invasive fungal infection. Other end points were the incidence of superficial fungal infection, adverse events related to the study drug, mortality from fungal infection, and overall survival rates. All patients who received at least one dose of study drug were included in both the efficacy and safety analysis (modified intention-to-treat analysis). Patients were followed until day 180 after transplantation or time of death. For this study, the incidence of invasive fungal infection in patients receiving prophylactic fluconazole was assumed to be 10%; therefore, itraconazole was

Table 1. Patient Characteristics

Characteristic	Itraconazole Group (n = 71)	Fluconazole Group (n = 67)
Median age (range), y	41 (14–63)	38 (17–61)
Sex, n (%)		
Male	44 (62)	39 (58)
Female	27 (38)	28 (42)
Underlying disease, n (%)		
Acute leukemia	22 (31)	23 (34)
Chronic myelogenous leukemia	24 (34)	25 (37)
Myelodysplastic syndrome	7 (10)	9 (13)
Lymphoma	8 (11)	5 (8)
Aplastic anemia	8 (11)	2 (3)
Multiple myeloma	1 (1.5)	2 (3)
Chronic lymphocytic leukemia	1 (1.5)	1 (2)
Donor type, n (%)		
Related	54 (76)	35 (52)
Unrelated	17 (24)	32 (48)*
HLA matching, n (%)		
Matched	65 (92)	58 (87)
Mismatched	6 (8)	9 (13)
Stem-cell source, n (%)		
Bone marrow	57 (80)	59 (88)
Peripheral blood	14 (20)	8 (12)
Conditioning regimen, n (%)		
Chemotherapy alone	19 (27)	12 (18)
Radiation and chemotherapy	52 (73)	55 (82)
Fungal colonization at baseline, n (%)	21 (30)	29 (43)†
Graft-versus-host disease prophylaxis, n (%)		
Cyclosporine	21 (29)	18 (27)
Cyclosporine and methotrexate	2 (3)	2 (3)
Cyclosporine and corticosteroids	30 (42)	39 (45)
Cyclosporine, corticosteroids, and methotrexate	16 (23)	15 (22)
Antithymocyte globulin and corticosteroids	2 (3)	2 (3)
Mean duration of neutropenia (neutrophil count <500 cells × 10 <sup>6</sup> /L [ $<500$ cells/ $\mu$ L] range), d	19 (7–97)	19 (9–42)
Corticosteroids for prevention or treatment of graft-versus-host disease, n (%)	59 (83)	58 (87)
Acute graft-versus-host disease, n (%)		
None (grades 0–1)	55 (77)	36 (54)
Yes (grades 2–4)	16 (23)	31 (46)‡
Chronic graft-versus-host disease, n (%)		
None	65 (92)	52 (78)
Yes	6 (8)	15 (22)§
Cytomegalovirus disease	1 (1.5)	3 (4)

\*  $P = 0.001$  (difference, 24 percentage points [CI, 8.3 to 39.4 percentage points]).

†  $P = 0.112$  (difference, 13 percentage points [CI, –2.2 to 29.6 percentage points]).

‡  $P = 0.004$  (difference, 23 percentage points [CI, 8.4 to 39.2 percentage points]).

§  $P = 0.032$  (difference, 14 percentage points [CI, 2.0 to 25.8 percentage points]).

considered to be noninferior to fluconazole if the difference in the incidence of invasive fungal infection with itraconazole was not more than 15 percentage points higher than the incidence with fluconazole. A sample size of 65 patients per study group would be sufficient to show noninferiority with 82% power at an  $\alpha$  level of 0.05 (33).

### Role of the Funding Source

The study design was developed jointly by the study sponsor (Janssen Research Foundation, Titusville, New

Jersey) and the investigators. The Foundation also provided clinical research associates for review of data and comparison with source documentation and established a contract with PRA International, Charlottesville, Virginia, for analysis and statistical evaluation of the data. Interpretation of the study results and decisions about publication of the manuscript were made by the investigators.

## RESULTS

### Patient Characteristics

From October 1996 to November 1998, 140 patients were eligible for study. One patient requiring continuation of phenytoin therapy for a seizure disorder was excluded from the study because this drug interacts with azoles. The 140 eligible patients were randomly assigned to receive either itraconazole or fluconazole (Figure 1). Two randomly assigned patients (1 in the itraconazole group and 1 in the fluconazole group) were subsequently withdrawn from the study before they had received any study drug and were excluded from all analyses. Table 1 summarizes the characteristics of the other 138 patients. Seventy-one patients received itraconazole, and 67 were given fluconazole. The two groups of patients had similar demographic characteristics, except that more patients given fluconazole received stem cells from unrelated donors. The incidence of acute and chronic graft-versus-host disease was also higher in the patients given fluconazole. Approximately 85% of the patients in both study groups were given systemic corticosteroids for preventing or treating graft-versus-host disease. The mean duration of corticosteroid use was 56 days (range, 2 to 161 days) in the itraconazole group and 67 days (range, 2 to 180 days) in the fluconazole group ( $P = 0.12$ ).

### Study Drug Administration

The mean duration of intravenous administration of study drug was 26 days (range, 1 to 95 days) in the itraconazole group and 22 days (range, 3 to 65 days) in the fluconazole group. The mean duration of oral administration of study drug was 52 days (range, 1 to 94 days) in the itraconazole group and 63 days (range, 2 to 91 days) in the fluconazole group. Thirteen patients given itraconazole and 13 given fluconazole received intravenous study drug for more than 30 days.

### Fungal Infection

Table 2 summarizes the incidence of proven fungal infection within 180 days after transplantation. Fungal infection was confirmed in 9 of 71 patients given itraconazole (13%) and in 19 of 67 patients given fluconazole (28%) (difference, –15 percentage points [CI, –29.0 to –2.4 percentage points];  $P = 0.03$ ). Invasive fungal infections of the blood, lungs, or other organs were especially less frequent in patients receiving prophylactic itraconazole. Six of 71 patients given itraconazole (9%) compared with 17 of 67 patients given fluconazole (25%) had an

invasive fungal infection (difference,  $-16$  percentage points [CI,  $-29.2$  to  $-4.7$  percentage points];  $P = 0.01$ ). This difference fulfills the protocol-defined criteria for noninferiority of itraconazole, since the upper bound ( $-4.7$  percentage points) of the CI falls within the pre-defined lower bound of  $+15$  percentage points. Kaplan–Meier estimates of the percentage of patients in each group who had a proven invasive fungal infection also showed that itraconazole was more effective than fluconazole in preventing invasive fungal infections ( $P = 0.01$ ) (Figure 2). Similarly, among patients with acute graft-versus-host disease (grades 2 to 4), who are usually considered at increased risk for serious fungal infections, Kaplan–Meier estimates of the percentage of patients in each study group who had a proven invasive fungal infection demonstrated a trend of a lower probability of developing invasive fungal infection within the first 180 days after transplantation in patients given prophylactic itraconazole ( $P = 0.08$ ) (Figure 3).

Table 3 presents the types of organisms that cause invasive fungal infections. Fewer infections were caused by either yeasts or molds in the patients given itraconazole. *Candida glabrata* and *C. krusei* were the most common yeasts causing invasive infection. Of note, no cases of invasive fungal infection due to *C. albicans* occurred in either study group. *Aspergillus* was the most common mold causing invasive fungal infection. Three of 71 patients given itraconazole (4%) and 8 of 67 patients given fluconazole (12%) had *Aspergillus* infections (difference,  $-8$  percentage points [CI,  $-16.8$  to  $1.4$  percentage points]), but this difference was not statistically significant ( $P = 0.12$ ). Eight isolates of *Candida* and 2 isolates of *Aspergillus* that caused invasive fungal infection were available for in vitro susceptibility testing. Of these 10 isolates, 8 were resistant to fluconazole (MIC  $\geq 64$   $\mu\text{g/mL}$ ) but only 1 was resistant to itraconazole (MIC  $\geq 1.0$   $\mu\text{g/mL}$ ) ( $P = 0.005$ ).

### Multivariable Analyses

We used a propensity score method to adjust for factors that might simultaneously influence the incidence of invasive fungal infections and the results of antifungal prophylaxis. Propensity scores were generated by using a logistic regression model, with study drug (itraconazole or fluconazole) as the dependent variable. The logistic regression model included the following factors: age, sex, underlying disease, type of transplantation (related or unrelated donor), conditioning regimen, baseline fungal colonization, acute graft-versus-host disease, chronic graft-versus-host disease, systemic corticosteroids, and graft failure. A stratified analysis using the Mantel–Haenszel test, controlling for propensity scores, showed that prophylaxis with itraconazole was still associated with fewer invasive fungal infections than prophylaxis with fluconazole (odds ratio, 0.300 [CI, 0.111 to 0.814];  $P = 0.02$ ).

### Plasma Itraconazole Concentrations

Table 4 summarizes mean trough plasma concentrations of itraconazole and its active metabolite, hydroxy-

**Table 2. Incidence of Proven Fungal Infections within 180 Days after Transplantation**

Variable	Itraconazole Group (n = 71)	Fluconazole Group (n = 67)
	n (%)	
Patients with proven fungal infection	9 (13)	19 (28)*
Invasive infection of blood, lungs, brain, liver, or multiple organs	6 (9)	17 (25)†
Superficial infection of oral cavity, skin, or gastrointestinal tract	3 (4)	2 (3)

\*  $P = 0.03$  (difference, 15 percentage points [CI,  $-29.0$  to  $-2.4$  percentage points]).

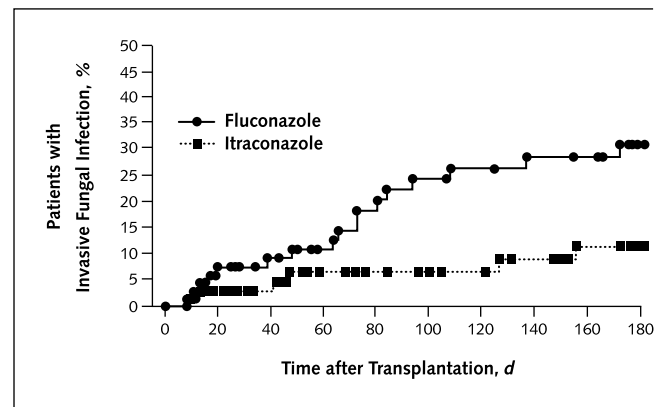
†  $P = 0.01$  (difference, 16 percentage points [CI,  $-29.2$  to  $-4.7$  percentage points]).

itraconazole. The mean trough plasma concentration of itraconazole was 627 ng/mL after 3 days of treatment with intravenous itraconazole. Mean trough plasma concentrations of greater than 600 ng/mL were subsequently maintained throughout the administration of intravenous itraconazole. When patients were changed to oral itraconazole solution, the mean trough plasma concentrations of itraconazole increased further and were all greater than 750 ng/mL during each week of the study.

### Side Effects

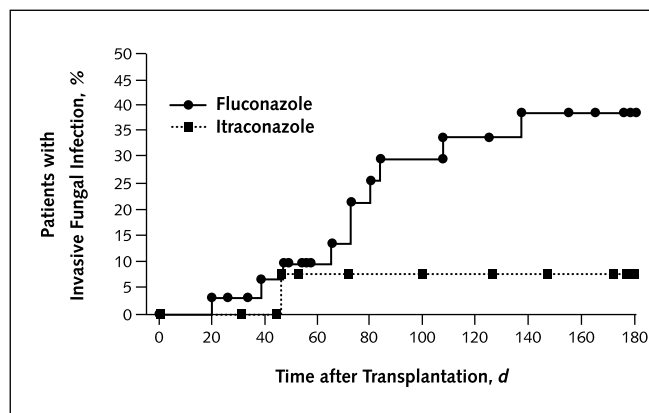
Adverse clinical events or laboratory abnormalities possibly or probably related to study drug occurred in 33 of 71 patients given itraconazole (46%) and in 14 of 67 patients given fluconazole (21%) (difference, 25 percentage points [CI, 10.4 to 40.7 percentage points];  $P < 0.001$ ). Gastrointestinal side effects (nausea, vomiting, diarrhea, or abdominal pain) were the only side effects that occurred significantly more often in patients who received itraconazole (17 of 71 itraconazole recipients [24%] vs. 6 of 67

**Figure 2. Time to development of proven invasive fungal infection in all patients.**



Survival distributions of time to development of proven invasive fungal infection in itraconazole and fluconazole recipients were derived by using Kaplan–Meier product-limit estimates. For the difference in time of onset of proven invasive fungal infection between itraconazole and fluconazole recipients,  $P = 0.01$ .

**Figure 3. Time to development of proven invasive fungal infection in patients with acute graft-versus-host disease (grades 2 to 4).**



Survival distributions of time to development of proven invasive fungal infection in itraconazole and fluconazole recipients were derived by using Kaplan-Meier product-limit estimates. For the difference in time of onset of proven invasive fungal infection between itraconazole and fluconazole recipients,  $P = 0.08$ .

fluconazole recipients [9%]) (difference, 15 percentage points [CI, 2.9 to 27.0 percentage points];  $P = 0.02$ ). Serum bilirubin or hepatic enzyme levels were elevated, possibly as a result of the study drug, in 11 patients given itraconazole and 7 given fluconazole. Skin rash, possibly associated with the study drug, occurred in 3 itraconazole recipients and in 4 fluconazole recipients. The incidences of neurologic symptoms (headaches, dizziness, or tremors), renal dysfunction (elevated serum creatinine level), cardiovascular events (hypertension, hypotension, or electrocardiogram changes), and respiratory complications (dyspnea or hypoxemia), possibly or probably related to the study drug, were low (<3%) and similar in each study group. Six patients who were given itraconazole (8.5%) (3 with nausea and vomiting, 2 with hepatic dysfunction, and 1 with hypotension) and 1 patient who was given fluconazole (1.5%) and developed hepatic dysfunction were withdrawn from the study (difference, 7 percentage points [CI, -0.1 to 14.0 percentage points];  $P = 0.12$ ). The respective me-

**Table 3. Types of Organisms Causing Invasive Fungal Infection**

Organism	n	
	Itraconazole Group	Fluconazole Group
Patients with yeast infection		
<i>Candida glabrata</i>	0	4
<i>C. krusei</i>	0	3
<i>C. glabrata</i> and <i>C. krusei</i>	1	0
<i>C. tropicalis</i>	0	1
<i>C. guilliermondii</i>	1	0
Patients with mold infection		
<i>Aspergillus</i> species	3	8
<i>Fusarium</i> species	0	1
<i>Rhizopus</i> species	1	0
Total	6	17

dian trough serum cyclosporine levels for itraconazole and fluconazole recipients were 366 ng/mL and 311 ng/mL at week 1 (difference, 55 ng/mL [CI, -32.0 to 82.0 ng/mL];  $P > 0.2$ ); 364 ng/mL and 304 ng/mL at week 2 (difference, 60 ng/mL [CI, 0.0 to 77.0 ng/mL];  $P = 0.05$ ); 349 ng/mL and 313 ng/mL at week 4 (difference, 36 ng/mL [CI, -23.0 to 95.0 ng/mL];  $P > 0.2$ ); 338 ng/mL and 316 ng/mL at week 6 (difference, 22 ng/mL [CI, -64.0 to 98.0 ng/mL];  $P > 0.2$ ); 244 ng/mL and 324 ng/mL at week 8 (difference, -80 ng/mL [CI, -127.0 to 67.0 ng/mL];  $P > 0.2$ ); 324 ng/mL and 269 ng/mL at week 10 (difference, 55 ng/mL [CI, -43.0 to 99.0 ng/mL];  $P > 0.2$ ); and 286 ng/mL and 263 ng/mL at week 12 (difference, 23 ng/mL [CI, -46.0 to 156.0 ng/mL];  $P > 0.2$ ) after transplantation.

### Survival

Thirty-two patients given itraconazole (45%) and 28 patients given fluconazole (42%) died within 180 days after transplantation (difference, 3 percentage points [CI, -13.2 to 19.8 percentage points];  $P > 0.2$ ). Fewer patients given itraconazole died of fungal infection: 6 of 71 itraconazole recipients (9%) compared with 12 of 67 fluconazole recipients (18%) (difference, -9 percentage points [CI, -20.6 to 1.8 percentage points]), but this difference was not statistically significant ( $P = 0.13$ ). Other causes of death were bacterial or viral infection (5 itraconazole recipients and 4 fluconazole recipients), toxicity due to chemotherapy and radiation (6 itraconazole recipients and 6 fluconazole recipients), graft-versus-host disease (3 itraconazole recipients and 3 fluconazole recipients), relapsed leukemia (4 itraconazole recipients and 2 fluconazole recipients), idiopathic interstitial pneumonia (3 itraconazole recipients and 1 fluconazole recipient), hemorrhage (3 itraconazole recipients), thrombotic thrombocytopenia purpura (1 itraconazole recipient), and myocardial infarction (1 itraconazole recipient).

### DISCUSSION

In our study, itraconazole was more effective than fluconazole in preventing invasive fungal infection after allogeneic hematopoietic stem-cell transplantation (Table 2, Figure 2). Patients receiving prophylactic itraconazole had fewer invasive fungal infections caused by *C. glabrata*, *C. krusei*, and *Aspergillus* species (Table 3). This reduction in infection is consistent with itraconazole's greater in vitro activity for *Aspergillus* and some fluconazole-resistant *Candida* species (17, 18). Of note, of the 10 fungal isolates causing invasive infection that were available for in vitro susceptibility testing, 8 were resistant to fluconazole and only 1 was resistant to itraconazole. A study of neutropenic patients also showed that oral itraconazole solution provided greater protection than fluconazole against fatal aspergillosis (20).

The 25% incidence of proven invasive fungal infections among patients given fluconazole in this study is rel-

atively high. In two previous trials of prophylactic fluconazole in the early 1990s, the incidence of serious fungal infections in hematopoietic stem-cell transplant recipients receiving prophylactic fluconazole was approximately 10% (3, 4). In our study, patients given itraconazole had a higher incidence of acute and chronic graft-versus-host disease than patients given fluconazole. Earlier studies have identified graft-versus-host disease as a risk factor for fungal infection (1, 34–37). However, the difference in the incidence of invasive fungal infections between patients with or without graft-versus-host disease in our study was not statistically significant (23% vs. 13%) (difference, –10 percentage points [CI, –24.2 to 3.7 percentage points];  $P = 0.15$ ). On the other hand, approximately 85% of the patients in both the itraconazole and fluconazole groups in our study received systemic corticosteroids for the prevention or treatment of graft-versus-host disease. Corticosteroids, independent of the occurrence of graft-versus-host disease, have been strongly associated with an increased risk for fungal infections in previous studies (1, 6, 15, 36, 38). Thus, the overwhelming use of corticosteroids in our study probably contributed to the high incidence of serious fungal infections. Finally, the earlier studies of prophylactic fluconazole were performed 10 years ago. Over the past decade, invasive fungal infections have increased notably at many transplantation centers as a result of more intensive transplantation procedures in higher-risk patients (1, 15, 16). The 32% to 40% incidence of all fungal infections at autopsy (39, 40) and the 12% to 13% incidence of *Aspergillus* infections (15, 16) in hematopoietic stem-cell transplant recipients recently reported by other transplantation centers are similar to the incidences of fungal infection among patients in the fluconazole group in our study.

Our study may be limited by the lack of blinding to treatment assignment. Consequently, despite well-defined prestudy criteria for evaluating efficacy and adverse events, evaluation of the treatment response and causes of adverse events could have been somewhat biased. In addition, randomization was not stratified by donor type, and the number of patients with unrelated donors in the study groups was not balanced. More patients given fluconazole than patients given itraconazole received stem cells from unrelated donors, which may have contributed to the higher incidence of acute and chronic graft-versus-host disease in the fluconazole group (Table 1). However, in a multivariable analysis of possible risk factors for invasive fungal infection (including graft-versus-host disease), prophylaxis with itraconazole was still associated with fewer fungal infections. Furthermore, patients taking prophylactic itraconazole had a lower probability of developing an invasive fungal infection in a separate analysis of only patients with acute graft-versus-host disease (Figure 3). Of note, in the only other clinical trial evaluating long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients, prophylactic fluconazole was more effective than placebo in decreasing *Candida* infections and gas-

**Table 4. Mean Trough Plasma Concentrations of Itraconazole and Its Metabolite, Hydroxy-Itraconazole**

Treatment Day	Patients <i>n</i>	Mean Plasma Concentration ± SD	
		Itraconazole	Hydroxy-Itraconazole
		<i>ng/mL</i>	
Intravenous administration			
Day 3	45	627 ± 595	617 ± 299
Week 1	40	657 ± 443	787 ± 396
Week 2	21	656 ± 379	861 ± 487
Oral administration			
Week 3	10	785 ± 485	1136 ± 520
Week 4	18	1033 ± 700	1297 ± 757
Week 6	17	1181 ± 895	1369 ± 888
Week 8	12	943 ± 900	1200 ± 1055
Week 10	15	993 ± 953	1374 ± 1078
Week 12	11	1178 ± 1145	1539 ± 1285
Week 14	12	1052 ± 1129	1572 ± 1431

trointestinal graft-versus-host disease (41). Those investigators postulated that effective antifungal prophylaxis may decrease graft-versus-host disease by reducing microbial antigenic stimulation of donor T cells involved in the graft-versus-host disease process (41).

A previous concern about the use of itraconazole for prophylaxis in transplant recipients was the erratic bioavailability of the capsule formulation of itraconazole. The oral itraconazole solution used in our study contains hydroxypropyl- $\beta$ -cyclodextrin, which greatly increases the bioavailability of itraconazole and eliminates the need for food or gastric acidity for optimal absorption (18). Furthermore, the availability of the intravenous formulation of itraconazole allowed the continuation of effective prophylaxis in patients unable to take any medication by mouth. Consequently, mean trough plasma concentrations of itraconazole were greater than 500 ng/mL throughout the study. Although it is difficult to define the most ideal plasma itraconazole concentration needed for efficacy, a plasma concentration of greater than 500 ng/mL has recently been correlated with effective prophylaxis in neutropenic patients (42).

Both itraconazole and fluconazole were generally well tolerated. The oral itraconazole solution was associated with more gastrointestinal side effects. The hydroxypropyl- $\beta$ -cyclodextrin in oral itraconazole solution has an osmotic effect, which may cause diarrhea and other gastrointestinal side effects (18–20). In our study, intravenous itraconazole was usually substituted for the oral itraconazole solution in patients experiencing frequent gastrointestinal side effects. The intravenous formulation was used safely for more than 30 days in 13 patients who had difficulty taking oral medications. Itraconazole also has drug interactions that may limit its use in certain patients. In transplant recipients, itraconazole may increase serum levels of cyclosporine by inhibiting the cytochrome P-450 enzyme system (43). Pharmacokinetic studies of the interactions between itraconazole and cyclosporine suggest that patients taking ei-

ther the intravenous or oral formulation of itraconazole require a dose reduction of cyclosporine to maintain safe therapeutic levels of cyclosporine (44, 45).

Several new second-generation triazoles have recently become available and are being evaluated in clinical trials. Agents of this class include voriconazole, posaconazole, and ravuconazole (17). They have greater activity against fluconazole-resistant *Candida* species (including *C. glabrata* and *C. krusei*) as well as *Aspergillus* species and certain other molds. Whether these drugs can provide improved prophylactic efficacy over itraconazole requires additional investigation in randomized, controlled trials. The favorable results achieved with itraconazole in our study provide a framework for future trials of long-term antifungal prophylaxis in hematopoietic stem-cell transplant recipients.

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