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Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

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ABSTRACT

BACKGROUND

Invasive fungal infections are an important cause of morbidity and mortality after allogeneic hematopoietic stem-cell transplantation.

METHODS

In an international, randomized, double-blind trial, we compared oral posaconazole with oral fluconazole for prophylaxis against invasive fungal infections in patients with graft-versus-host disease (GVHD) who were receiving immunosuppressive therapy. The primary end point was the incidence of proven or probable invasive fungal infections from randomization to day 112 of the fixed treatment period of the study.

RESULTS

Of a total of 600 patients, 301 were assigned to posaconazole and 299 to fluconazole. At the end of the fixed 112-day treatment period, posaconazole was found to be as effective as fluconazole in preventing all invasive fungal infections (incidence, 5.3% and 9.0%, respectively; odds ratio, 0.56; 95 percent confidence interval [CI], 0.30 to 1.07; P=0.07) and was superior to fluconazole in preventing proven or probable invasive aspergillosis (2.3% vs. 7.0%; odds ratio, 0.31; 95% CI, 0.13 to 0.75; P=0.006). While patients were receiving study medications (exposure period), in the posaconazole group, as compared with the fluconazole group, there were fewer breakthrough invasive fungal infections (2.4% vs. 7.6%, P=0.004), particularly invasive aspergillosis (1.0% vs. 5.9%, P=0.001). Overall mortality was similar in the two groups, but the number of deaths from invasive fungal infections was lower in the posaconazole group (1%, vs. 4% in the fluconazole group; P=0.046). The incidence of treatment-related adverse events was similar in the two groups (36% in the posaconazole group and 38% in the fluconazole group), and the rates of treatment-related serious adverse events were 13% and 10%, respectively.

CONCLUSIONS

Posaconazole was similar to fluconazole for prophylaxis against fungal infections among patients with GVHD. It was superior in preventing invasive aspergillosis and reducing the rate of deaths related to fungal infections. (ClinicalTrials.gov number, NCT00034645.)

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Invasive fungal infections remain one of the leading causes of death among recipients of hematopoietic stem-cell transplants.[1-3] In these patients, factors associated with complications resulting from transplantation, such as prolonged neutropenia, graft failure, immunosuppression, and graft-versus-host disease (GVHD), increase the risk of an invasive fungal infection.[4-6]

Randomized, controlled trials have shown the superiority of fluconazole over placebo for the prevention of fungal infections, primarily those caused by candida species, after hematopoietic stem-cell transplantation. Fluconazole prophylaxis reduces both fungal-infection–related and overall mortality[7,8] and has become a standard of care for antifungal prophylaxis after the first 100 days of the post-transplantation period in recipients of hematopoietic stem-cell transplants.[7-9]

The incidence of infections caused by aspergillus species among recipients of hematopoietic stem-cell transplants ranges from 3 to 14%,[1,10-14] with the peak occurrence after hematopoietic recovery associated with GVHD and immunosuppressive therapy.[1,4,10-15] So far, no prophylactic strategies for the prevention of mold infections during this period of risk have been validated in randomized, controlled trials. The lack of established prophylactic measures for these patients underscores the need for options for broad-spectrum, well-tolerated antifungal prophylaxis for this population.

Posaconazole is an extended-spectrum triazole with in vitro activity against a broad spectrum of fungi[16-18] and clinical activity against various fungal pathogens, including aspergillus species, candida species, zygomycetes, and fusarium species.[19-21] On the basis of this broad spectrum of antifungal activity, we compared posaconazole with fluconazole for efficacy, safety, and tolerability in the prevention of invasive fungal infections among recipients of allogeneic hematopoietic stem-cell transplants with GVHD who were receiving immunosuppressive therapy.

METHODS

STUDY DESIGN

The study was a phase 3, randomized, multicenter, double-blind and double-dummy, parallel-group, multinational trial comparing posaconazole with fluconazole for prophylaxis against invasive fungal infections in high-risk patients with GVHD after allogeneic hematopoietic stem-cell transplantation. The trial was conducted from March 1999 through February 2003. The study protocol and informed-consent form were reviewed and approved by an independent ethics committee or institutional review board at each study site. Written informed consent was obtained from all participants before the initiation of any study-related activities. An independent data review committee of eight physicians with expertise in opportunistic infections in transplant recipients reviewed all suspected and documented fungal infections in a blinded fashion and classified the infections according to consensus criteria.[22]

The study was designed in part by the academic authors and in part by a clinical team of employees of the sponsor. All authors, except those employed by the sponsor, gathered the clinical data. The sponsor was responsible for the analysis of the data. All authors contributed to the writing of the manuscript. All authors also had full access to the primary data and to the analysis, and all vouch for the accuracy and completeness of the reported data.

PATIENTS

Male and female patients 13 years of age or older and weighing more than 34 kg (75 lb) who had undergone allogeneic hematopoietic stem-cell transplantation were eligible to participate in the study if they had either acute GVHD, grade II to IV, or chronic extensive GVHD,[23,24] or if they were being treated with intensive immunosuppressive therapy consisting of either high-dose corticosteroids (≥1 mg per kilogram of body weight per day for patients with acute GVHD or ≥0.8 mg per kilogram every other day for patients with chronic GVHD), antithymocyte globulin, or a combination of two or more immunosuppressive agents or types of treatment. Patients were excluded if they had a history of proven or probable mold infections or a suspected invasive fungal infection at baseline, clinically significant hepatic dysfunction as indicated by elevated alanine aminotransferase or aspartate aminotransferase levels or both (>10 times the upper limit of the normal range), or renal dysfunction. Patients were also excluded if they required medications known to interact with azoles.[25] For a detailed description of the inclusion and exclusion criteria, see the Supplementary Appendix (available with the full text of this article at www.nejm.org).

STRATIFICATION AND RANDOMIZATION

Patients were stratified according to GVHD status at baseline and were randomly assigned to receive posaconazole oral suspension (Noxafil, Schering-Plough), at a dose of 200 mg three times daily plus placebo capsules once daily, or fluconazole capsules (Diflucan, Pfizer), at a dose of one 400-mg encapsulated tablet orally once daily plus placebo oral suspension three times daily, for the expected 112-day fixed treatment period of the study. After randomization, patients were treated for up to 112 days or until a protocol-specified end point (a breakthrough invasive fungal infection, an adverse event requiring discontinuation of the study medication, or death) was reached. Patients who discontinued treatment for reasons other than death were followed for the full 112 days. The period from the first dose of the study drug to 7 days after receipt of the last dose was defined as the exposure period. Patients or physicians could interrupt the study medication for up to 5 consecutive days.

EFFICACY END POINTS

The primary efficacy end point was the incidence of proven or probable invasive fungal infections,[22] as adjudicated by the data review committee in a blinded fashion, during the period from randomization to day 112 (the treatment period) in the intention-to-treat population (patients who had given informed consent and undergone randomization). For the primary end point, failure of prophylaxis was defined as the development of an invasive fungal infection during the fixed treatment period.

Other end points were based on cases adjudicated by the data review committee and included the following: the incidence of proven or probable aspergillosis during the treatment period in the intention-to-treat population, the incidence of breakthrough proven or probable invasive fungal infections during the exposure period, the time to the occurrence of an invasive fungal infection, the overall mortality in the intention-to-treat population, and mortality attributable to fungal infection in the intention-to-treat population. Deaths occurring at any time during the study were included in the mortality analysis. The cause of death was assessed by the investigators and was attributed to intercurrent illness, drug-related adverse events, GVHD progression, complications of an invasive fungal infection, or other causes that could not be categorized. If a patient was unable to continue taking the assigned study medication or had a probable or proven invasive fungal infection,[22] treatment with the study drug was discontinued, and the patient was treated according to the local standard of care for antifungal therapy.

Laboratory evaluations for susceptibility to fungal isolates and testing for colonization were performed every 2 weeks by a designated laboratory.[26,27] Immunoassays for the detection of aspergillus galactomannan antigen in serum (Platelia Aspergillus EIA, Bio-Rad Laboratories) were performed at the central laboratory.[28] Fungal colonization at baseline and colonization at the end of therapy were compared. An increase of more than 4 times the minimum inhibitory concentration was considered a clinically significant change in susceptibility. Plasma concentrations of posaconazole were determined with the use of a validated method of liquid chromatography–tandem mass spectrometry.[29]

SAFETY ASSESSMENT

The safety and tolerability of the study drugs were assessed in all patients who underwent randomization. The assessment was based on paired electrocardiographic and laboratory evaluations and evaluation for changes in clinical signs and symptoms. Patients were monitored for 16 weeks (the fixed 112-day treatment period) and were followed for an additional 8 weeks; the total of 24 weeks was considered the observation period. Adverse events were characterized according to the National Cancer Institute's Common Toxicity Criteria (version 2.0, revised March 23, 1998). Reasons for early discontinuation of the study treatment were recorded.

STATISTICAL ANALYSIS

At the time of the initiation of the study, the incidence of invasive fungal infections among patients with GVHD who were receiving fluconazole was not known. The study was designed with 90% power at a significance level of 0.05 to detect a risk ratio of 2 or more, assuming an overall incidence of invasive fungal infection of 15%. The design required 93 invasive fungal infections and a total of approximately 600 patients.

The primary analysis was a comparison of the incidence rates of proven or probable invasive fungal infections during the period from random-

Table 1. Demographic and Baseline Clinical Characteristics of the Patients and Risk Factors for Invasive Fungal Infections.*

Characteristic	Fixed Treatment Period		
	Posaconazole Group (N=301)	Fluconazole Group (N=299)	P Value†
Age			
Mean — yr	42.2	40.4	0.07
Range — yr	13–72	13–70	
13 to <18 yr — no. (%)	4 (1)	8 (3)	
18 to <65 yr — no. (%)	292 (97)	286 (96)	
≥65 yr — no. (%)	5 (2)	5 (2)	
Male sex — no. (%)	203 (67)	187 (63)	0.23
Primary underlying diagnosis — no. (%)‡			
Chronic myelogenous leukemia	98 (33)	104 (35)	0.60
Acute myeloid leukemia	81 (27)	66 (22)	0.18
Non-Hodgkin's lymphoma	40 (13)	35 (12)	0.62
Acute lymphoblastic leukemia	25 (8)	36 (12)	0.14
Myelodysplastic disorder	19 (6)	13 (4)	0.36
Chronic lymphoblastic leukemia	10 (3)	11 (4)	0.83
Multiple myeloma	10 (3)	12 (4)	0.67
Aplastic anemia	8 (3)	7 (2)	1.0
Hodgkin's lymphoma	2 (1)	7 (2)	0.11
Other	12 (4)	9 (3)	0.66
None	0	1 (<1)	
GVHD class — no. (%)			
Acute			
Grade I	3 (1)	1 (<1)	0.62
Grade II	135 (45)	136 (45)	0.94
Grade III	52 (17)	54 (18)	0.83
Grade IV	12 (4)	6 (2)	0.23
Chronic limited	2 (1)	1 (<1)	1.0
Chronic extensive	96 (32)	99 (33)	0.79
Missing data	1 (<1)	2 (1)	

ization to day 112 in the two treatment groups. As stated in the protocol, the evaluation of efficacy occurred in two stages. First, the noninferiority of posaconazole to fluconazole was assessed. If noninferiority was demonstrated, then the superiority of posaconazole to fluconazole was assessed. This two-stage process allowed for control of the type I error rate. Furthermore, adjustment for the two prespecified, unequally spaced interim analyses resulted in 95.01% confidence intervals (CIs, hereafter called 95% CI) in the final analysis.

Posaconazole was considered to be noninferior to fluconazole, with respect to the primary efficacy end point, on the basis of evaluations of all patients if the upper limit of the 95% CI for the adjusted odds ratio did not exceed a maximum value corresponding to a relative difference of 15 percentage points from the observed incidence rates in the fluconazole group. The 95% CI of Mantel–Haenszel odds ratios, adjusted for the stratification factor (acute vs. chronic GVHD), were computed for the effect of treatment on the incidence of proven or probable invasive fungal infections.

The incidence of proven or probable aspergillosis during the fixed treatment period in the intention-to-treat population and the incidence of

Table 1. (Continued.)

Characteristic	Fixed Treatment Period		
	Posaconazole Group (N=301)	Fluconazole Group (N=299)	P Value†
Days from transplantation to baseline			
<30 — no. (%)	45 (15)	37 (12)	
30–60 — no. (%)	98 (33)	103 (34)	
61–100 — no. (%)	32 (11)	37 (12)	
≥101 — no. (%)	124 (41)	121 (40)	
Missing data — no. (%)	2 (1)	1 (<1)	
Mean — no.	156.1±222.2	171.6±262.3	0.46
Median — no.	63	64	
Range — no.	0–1858	0–1692	
Aspergillus galactomannan antigen index — no. (%)			
Positive (≥0.5)	21 (7)	30 (10)	0.19
Negative	259 (86)	243 (81)	
Missing data	21 (7)	26 (9)	
Corticosteroids — no. (%)§			
≥2.0 mg/kg/day	41 (14)	32 (11)	0.32
<2.0 but ≥1.0 mg/kg/day	107 (36)	129 (43)	0.07
<1.0 mg/kg/day	142 (47)	127 (42)	0.25
Missing data	10 (3)	10 (3)	
None	1 (<1)	1 (<1)	
No. of immunosuppressive agents used — no. (%)			
1	64 (21)	48 (16)	0.12
2	151 (50)	168 (56)	0.14
≥3	85 (28)	82 (27)	0.86
None	1 (<1)	1 (<1)	
Days of prior antifungal therapy before first dose			
Mean	26.4±39	35.3±82	0.09
Median	16	19	
Range	0–254	0–1002	

* Plus–minus values are means ±SD. For information on the baseline characteristics of the patients during the exposure period, see the Supplementary Appendix (available with the full text of this article at www.nejm.org).
† P values for continuous variables were calculated with Student's t-test; P values for categorical variables were calculated with Fisher's exact test.
‡ Some patients had multiple primary diagnoses.
§ The corticosteroids used were methylprednisolone or equivalents.

breakthrough proven or probable invasive fungal infections during the exposure period were evaluated in a similar manner, with the use of the Mantel–Haenszel method. The time to invasive fungal infection, the time to death, and the time to death related to invasive fungal infection were evaluated with the use of the Kaplan–Meier method, and between-group comparisons were performed with the use of the log-rank test.

RESULTS

STUDY POPULATION

Patients were enrolled during the 4-year study period at 90 centers worldwide. A total of 600 patients underwent randomization (301 patients assigned to posaconazole, and 299 to fluconazole) and were included in the intention-to-treat population. Approximately 40% of the patients under-

went randomization in the United States. Of the 600 patients, 291 received at least one dose of posaconazole, and 288 received at least one dose of fluconazole. The duration of treatment was similar in the two groups. Patients in the posaconazole group were treated for a mean of 80 days (median, 111; range, 1 to 138), and those in the fluconazole group were treated for a mean of 77 days (median, 108; range, 1 to 130).

The demographic characteristics and the selected risk factors for invasive fungal infections were similar in the two groups (Table 1). The majority of patients had two or more known risk factors for invasive fungal infections; the two groups appeared to be balanced with respect to these risk factors. Few patients (≤5%) had a history of invasive yeast or mold infection, and none were considered to have evidence of proven or probable invasive fungal infections at baseline or were receiving secondary prophylaxis.

EFFICACY

A total of 175 cases of suggestive invasive fungal infections were submitted to the independent data review committee for adjudication. Of these 175 cases, 62 were judged to be proven or probable infections occurring during the 24-week observation period (overall incidence, 10%); 43 of the cases occurred during the treatment period from randomization to day 112, and 19 occurred after day 112.

The incidence of invasive fungal infections during the fixed treatment period (the primary end point) was 5.3% in the posaconazole group and 9.0% in the fluconazole group (odds ratio for invasive fungal infection in the posaconazole group, 0.56; 95% CI, 0.30 to 1.07). Given the total number of events, ruling out a 15% relative difference between the two groups resulted in an odds ratio of 1.16. Since the upper limit of the CI (1.07) was less than 1.16, the noninferiority of posaconazole, as compared with fluconazole,

Table 2. Proven or Probable Invasive Fungal Infections during the Fixed Treatment Period and the Exposure Period, According to Pathogen, among Patients Assigned to a Study Drug.

Pathogen or Pathogen Group	Posaconazole Group (N=301)	Fluconazole Group (N=299)	Odds Ratio (95% CI)	P Value
	no. (%)			
Fixed treatment period				
All proven and probable invasive fungal infections*	16 (5.3)	27 (9.0)	0.56 (0.30–1.07)	0.07
All invasive aspergillosis	7 (2.3)	21 (7.0)	0.31 (0.13–0.75)	0.006
Aspergillus (not otherwise specified)	0	5		
Aspergillus galactomannan antigen index	5	6		
A. fumigatus	2	5		
A. flavus	0	3		
A. niger	0	1		
A. terreus	0	1		
All candida species	4	4		
C. krusei	1	1		
C. albicans	0	1		
C. glabrata	2	1		
C. parapsilosis	0	1		
Candida (not otherwise specified)	1	0		
Other fungi	5	2		
Pseudallescheria boydii	1	0		
Rhizomucor miehei	0	1		
Trichosporon beigelii	1	0		
Scedosporium prolificans	1	0		
Mold (not otherwise specified)	2	1		

was established; superiority was not demonstrated (P=0.07).

The majority of the invasive fungal infections occurring during the fixed treatment period were invasive aspergillosis (Table 2). In other analyses, posaconazole was superior to fluconazole in reducing the incidence of proven or probable aspergillosis (odds ratio, 0.31; 95% CI, 0.13 to 0.75; P=0.006) during the treatment period and was superior to fluconazole in reducing the incidence of breakthrough proven or probable invasive fungal infections (odds ratio, 0.30; 95% CI, 0.12 to 0.71; P=0.004) and invasive aspergillosis during the exposure period (odds ratio, 0.17; 95% CI, 0.05 to 0.57; P=0.001). Rates of invasive fungal infections in the two groups during the fixed treatment period, according to selected risk factors considered to be predictive of such infections, are shown in Table 3. In general, the results of this subgroup analysis were consistent with the overall results.

Among patients for whom the results of pharmacokinetic testing were available, the mean concentration of posaconazole was 1470 ng per milliliter (coefficient of variation, 57%) in the 82 patients with chronic GVHD and 958 ng per milliliter (coefficient of variation, 68%) in the 158 patients with acute GVHD. Analysis of the time to invasive fungal infection by the Kaplan–Meier method showed a delay in the onset of infections

Table 2. (Continued.)

Pathogen or Pathogen Group	Posaconazole Group (N=291)	Fluconazole Group (N=288)	Odds Ratio (95% CI)	P Value
	no. (%)			
Exposure period†				
All proven and probable invasive fungal infections*	7 (2.4)	22 (7.6)	0.30 (0.12–0.71)	0.004
All invasive aspergillosis	3 (1.0)	17 (5.9)	0.17 (0.05–0.57)	0.001
Aspergillus (not otherwise specified)	0	4		
Aspergillus galactomannan antigen index	3	4		
A. fumigatus	0	6‡		
A. flavus	0	2		
A. niger	0	0		
A. terreus	0	1		
All candida species	1	3		
C. krusei	0	1		
C. albicans	0	1		
C. glabrata	1	1		
C. parapsilosis	0	0		
Candida (not otherwise specified)	0	0		
Other fungi	3	2		
P. boydii	1	0		
R. miehei	0	1		
T. beigelii	1	0		
S. prolificans	0	0		
Mold (not otherwise specified)	1	1		

* Cases of probable invasive aspergillosis confirmed on aspergillus galactomannan immunossay (Platelia Aspergillus EIA, Bio-Rad Laboratories) were included in this category.

† The total numbers of patients for the analysis of invasive fungal infections during the exposure period were 291 in the posaconazole group and 288 in the fluconazole group.

‡ An invasive fungal infection that developed in one patient on day 113 (while the patient was receiving the study drug) was not counted as occurring during the fixed treatment period (the interval beginning on the date of randomization and ending on day 112).

Table 3. Incidence of Invasive Fungal Infections during the Fixed Treatment Period, According to Selected Risk Factors.*

Risk Factor	Posaconazole Group (N=301)		Fluconazole Group (N=299)	
	no.	*no. with invasive fungal infections (%)*	*no.*	*no. with invasive fungal infections (%)*
GVHD class				
Acute				
Grade I	3	0	1	0
Grade II	135	6 (4)	136	11 (8)
Grade III	52	5 (10)	54	10 (19)
Grade IV	12	0	6	0
Chronic limited	2	0	1	0
Chronic extensive	96	5 (5)	99	6 (6)
Aspergillus galactomannan antigen index at baseline				
Positive (≥0.5)	21	2 (10)	30	7 (23)
Negative	259	12 (5)	243	20 (8)
Missing data	21	2 (10)	26	0
Baseline use of corticosteroids (mg/kg/day)†				
≥2.0	41	4 (10)	32	5 (16)
<2.0 but ≥1.0	107	6 (6)	129	13 (10)
<1.0 but ≥0.4	108	4 (4)	100	7 (7)
<0.4 but ≥0	34	0	27	1 (4)
None	1	0	1	0
Dose unknown	10	2 (20)	10	1 (10)
Cytomegalovirus status‡				
Positive	96	7 (7)	78	11 (14)
Negative	205	9 (4)	221	16 (7)
No. of immunosuppressive agents used at baseline				
1	64	5 (8)	48	3 (6)
2	151	6 (4)	168	16 (10)
≥3	85	5 (6)	82	8 (10)
None	1	0	1	0
Region				
United States	117	10 (9)	121	14 (12)
Not United States	184	6 (3)	178	13 (7)

* Additional data on the exposure period are available in the Supplementary Appendix.
† The corticosteroids used were methylprednisolone or equivalents.
‡ Cytomegalovirus status was determined by a test for pp65 antigen or by a polymerase-chain-reaction assay.

in the posaconazole group, as compared with the fluconazole group, during the fixed treatment period (P=0.048) (Fig. 1). Fewer deaths occurred in the posaconazole group than in the fluconazole group; deaths caused by invasive fungal infections were significantly fewer (P=0.046) in the posaconazole group (Table 4).

COLONIZATION

In both the posaconazole group and the fluconazole group, the principal pathogens were *Candida albicans* and *C. glabrata*. *C. krusei* was detected in only four patients treated with fluconazole. The development of resistance to the study drug occurred more frequently among patients taking

fluconazole (17%, 4 of 24 patients) than among those taking posaconazole (5%, 1 of 21 patients).

SAFETY EVALUATION

The safety evaluation included all 600 patients. The majority of the adverse events were considered by the investigators to be unrelated to the study treatment. The incidence of adverse events judged to be related to the study drugs was similar in the two groups (36% in the posaconazole group and 38% in the fluconazole group) (Table 4).

The frequency of discontinuation of a study drug because of an adverse event was similar in the two groups (103 patients [34%] in the posaconazole group and 114 patients [38%] in the fluconazole group). For detailed information on discontinuation of a study drug prematurely, see the Supplementary Appendix. The most common treatment-related adverse events that led to discontinuation of the study drug were those associated with gastrointestinal disorders. Overall, the frequency of treatment-related serious adverse events was similar in the two groups (Table 4). No single serious, treatment-related adverse event occurred at a rate higher than 2% in either group. A high rate of treatment discontinuation occurred in this study because of the severity of the underlying disease; only 46% of the patients in the posaconazole group and 41% of those in the fluconazole group completed the full 16 weeks of treatment.

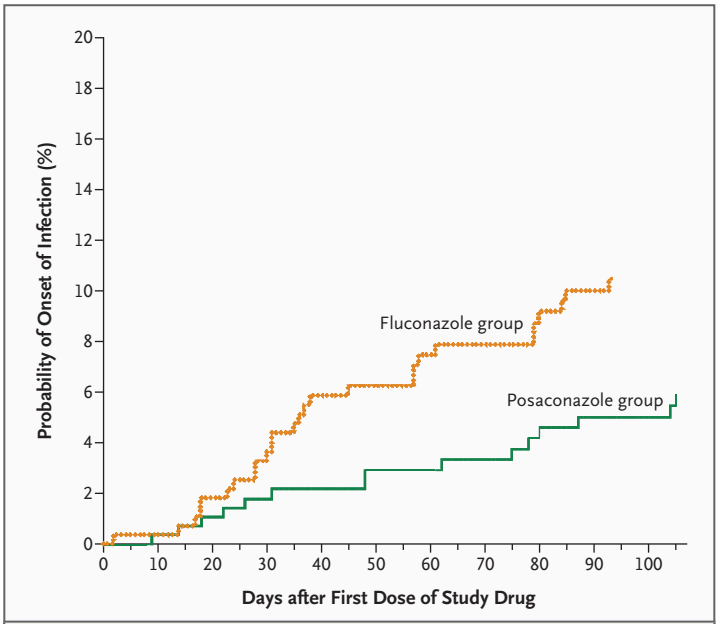

Figure 1. Time to Proven or Probable Invasive Fungal Infection.
All events not related to invasive fungal infections were considered censored; data on all patients were censored as of the end of the treatment period (day 112). The mean day of the onset of invasive fungal infection was day 102 in the posaconazole group and day 88 in the fluconazole group (P=0.048).

DISCUSSION

This large, randomized, multicenter, double-blind trial showed that posaconazole was as effective as fluconazole in preventing all invasive fungal diseases in recipients of hematopoietic stem-cell transplants with severe GVHD who were receiving immunosuppressive agents during a 16-week period. Posaconazole was superior to fluconazole in the prevention of invasive aspergillosis. Rates of invasive fungal infections among patients with chronic GVHD are reported to be as high as 39%.[30] Previous trials of prophylaxis focused on the efficacy of primary prophylaxis only during the early period (up to day 100) after hematopoietic stem-cell transplantation.[7,8,31-34] The advantage of our study design is that the patients enrolled were at high risk for invasive fungal infections as well as at increased risk for disorders related to the underlying disease. Therefore, any potential shortcoming in safety would be readily identified in this population with complicated conditions.

Although a previous study of itraconazole prophylaxis followed patients for up to 180 days, itraconazole was associated with greater toxic effects and poorer tolerability than fluconazole, thus limiting its success.[35] In contrast, in our study, the discontinuation rates in the two groups were similar. Fluconazole was considered in the past to be a benchmark for safe antifungal prophylaxis acceptable to patients in the setting of hematopoietic stem-cell transplantation. In our study, posaconazole was shown to be as safe and as acceptable as fluconazole. This finding confirms the results of previous studies involving patients with neutropenia.[36] The high incidence of gastrointestinal abnormalities in both treatment groups was expected, and most of these events were considered to be related to GVHD.

As in other trials, efficacy was analyzed in the group of patients who had received at least one dose of the study medication.[7,35,37] Not all patients continued taking the study drug for the planned duration of 112 days; however, posaconazole was significantly more effective in preventing invasive fungal infections during the exposure period than

Table 4. Treatment-Related Adverse Events and All-Cause Mortality during the Observation Period.*

Event	Posaconazole Group (N=301)	Fluconazole Group (N=299)
	no. (%)	
Adverse events		
Total	107 (36)	115 (38)
Headache	3 (1)	8 (3)
Gastrointestinal disorders		
Diarrhea	8 (3)	12 (4)
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
Liver and biliary disorders		
Bilirubinemia	8 (3)	5 (2)
Increased γ-glutamyltransferase	9 (3)	7 (2)
Increased hepatic enzymes	8 (3)	7 (2)
Increased aspartate aminotransferase	8 (3)	3 (1)
Increased alanine aminotransferase	9 (3)	4 (1)
Serious adverse events		
Total	40 (13)	29 (10)
Increased hepatic enzymes	6 (2)	1 (<1)
Increased γ-glutamyltransferase	5 (2)	3 (1)
Hepatocellular damage	4 (1)	0
Bilirubinemia	3 (1)	3 (1)
Abnormal hepatic function	0	3 (1)
Vomiting	4 (1)	1 (<1)
Nausea	4 (1)	0

was fluconazole. How long prophylaxis is required at this stage of disease is not established. Although previous studies used longer periods of prophylaxis, the prophylactic regimen was initiated earlier in the disease in these studies than it was in our study.[7,8,31,33]

The study was powered under the assumption that there would be 93 invasive fungal infections. However, only 43 cases were observed at the time of the final analysis, making it difficult to show significant differences. Given this outcome, the finding of noninferiority can be considered strengthened. The overall incidence of invasive fungal infections in the study was lower than incidences reported in other studies.[3,30] This low incidence may be explained, in part, by the relatively short duration of prophylaxis and by the fact that all study patients received prophylaxis. Many patients with GVHD remain at risk for much longer periods, depending on the extent of the GVHD and the duration of immunosuppressive therapy needed. After the onset of GVHD, invasive fungal infections developed later among patients receiving posaconazole at any time after transplantation than among those receiving fluconazole, underscoring the prophylactic effect of this agent. The superiority of posaconazole in preventing invasive aspergillosis reflects the lack of activity of fluconazole against filamentous fungi, which are the major fungal pathogens affecting patients with GVHD.[1,3,4] The demographic and clinical characteristics of the patients, including baseline risk factors for infection, did not differ significantly between the two groups; the results were therefore not influenced by differences in the baseline risk of infection.

The effects of factors such as the environment or compliance with other strategies for fungal prevention could have played an additional role in the incidence of invasive fungal infections in

Table 4. (Continued.)

Event	Posaconazole Group (N=301)	Fluconazole Group (N=299)
	no. (%)	
Deaths		
All causes		
During the observation period	76 (25)	84 (28)
During the fixed treatment period	58 (19)	59 (20)
During the exposure period†	22 (8)	24 (8)
Cause of death		
Adverse event	39 (13)§	37 (12)
Invasive fungal infection		
Complications of infection‡	4 (1)	12 (4)
Proven or probable infection§	2 (1)	11 (4)
Possible infection	2 (1)	1 (<1)
Progression of underlying disease or GVHD	31 (10)	33 (11)
Other	2 (1)	2 (1)

* Treatment-related adverse events were those that occurred at a frequency of at least 3% in either of the two groups. Treatment-related serious adverse events were those that occurred in at least three patients. Actual totals are also shown. (For further details on treatment-related serious events, see the Supplementary Appendix.) Deaths from all causes were those that occurred during the 24-week observation period. Invasive fungal infections were adjudicated by the data review committee in a blinded fashion. The cause of death was assessed by an investigator as one of the following: an invasive fungal infection, a cause other than an invasive fungal infection but in the presence of an invasive fungal infection, or a cause other than an invasive fungal infection (without evidence on autopsy of invasive fungal infection or with clinical evidence of the resolution of an invasive fungal infection).

† Data are for 291 patients in the posaconazole group and 288 in the fluconazole group. Only one adverse event was considered by an investigator to be related to the study drug. Ninety days after posaconazole was discontinued, only a single death from multiple-organ failure occurred after cyclosporine-associated thrombotic thrombocytopenic purpura–like syndrome developed; the death was considered by the investigator to be possibly related to treatment with posaconazole.

‡ $P=0.046$ by the log-rank test.

§ $P=0.01$ by the chi-square test.

our study. In addition, patients discontinuing participation in the study for any reason were evaluated for the efficacy of treatment; however, these patients usually received fluconazole during the observation period, a fact that explains the similarity between the two groups in the intention-to-treat population. It would have been unethical to withhold prophylaxis as standard care.

Although posaconazole provided no advantage over fluconazole with respect to overall mortality, a difference in mortality due to invasive fungal infections was observed, and this finding has been reported in only a few trials conducted in different settings.[7,8,32] Some suggest that survival free of invasive fungal infections should be included as a primary end point in a prophylaxis trial,[35,38] but our trial was not powered to demonstrate differences in mortality.

In the majority of the patients in our study, plasma levels of posaconazole were above the minimum inhibitory concentration for most fungal pathogens.[16,18] The low number of breakthrough invasive fungal infections in the posaconazole group confirms the bioavailability of oral posaconazole in this patient population. Though the emergence of fungi with reduced susceptibility to posaconazole was not detected during the study period, the development of resistance remains a concern with prophylaxis and warrants further investigation.

Our study showed that although posaconazole was as effective as fluconazole in preventing all invasive fungal infections, it was superior in preventing invasive aspergillosis in a high-risk population of patients who had undergone hematopoietic stem-cell transplantation and in reducing the rate of death attributable to invasive fungal infections. Posaconazole should be considered an option for prophylaxis in patients with severe GVHD.

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APPENDIX

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REFERENCES

1. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of Aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis 1997;175:1459-66.

2. Ribaud P, Chastang C, Latge JP, et al. Survival and prognostic factors of invasive aspergillosis after allogeneic bone marrow transplantation. Clin Infect Dis 1999;28:322-30.

3. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002;34:909-17.

4. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002;100:4358-66.

5. Thursky K, Byrnes G, Grigg A, Szer J, Slavin M. Risk factors for post-engraftment invasive aspergillosis in allogeneic stem cell transplantation. Bone Marrow Transplant 2004;34:115-21.

6. Martino R, Subira M, Rovira M, et al. Invasive fungal infections after allogeneic peripheral blood stem cell transplantation: incidence and risk factors in 395 patients. Br J Haematol 2002;116:475-82.

7. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation — a prospective, randomized, double-blind study. J Infect Dis 1995; 171:1545-52.
8. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 1992;326:845-51.
9. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 2000;49:RR-10:1-7. [Erratum, MMWR Recomm Rep 2004;53:396.]
10. Saugier-Veber P, Devergie A, Sulahian A, et al. Epidemiology and diagnosis of invasive pulmonary aspergillosis in bone marrow transplant patients: results of a 5 year retrospective study. Bone Marrow Transplant 1993;12:121-4.
11. Wingard JR, Beals SU, Santos GW, Merz WG, Saral R. Aspergillus infections in bone marrow transplant recipients. Bone Marrow Transplant 1987;2:175-81.
12. Meyers JD. Fungal infections in bone marrow transplant patients. Semin Oncol 1990;17:Suppl 6:10-3.
13. Morrison VA, Haake RJ, Weisdorf DJ. Non-Candida fungal infections after bone marrow transplantation: risk factors and outcome. Am J Med 1994;96:497-503.
14. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood 2003; 102:827-33.
15. Grow WB, Moreb JS, Roque D, et al. Late onset of invasive aspergillus infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant 2002;29:15-9.
16. Sabatelli F, Patel R, Mann PA, et al. In vitro activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. Antimicrob Agents Chemother 2006;50:2009-15.
17. Espinel-Ingroff A. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol 1998;36:2950-6.
18. Pfaller MA, Messer SA, Hollis RJ, Jones RN. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. Antimicrob Agents Chemother 2002;46:1032-7.
19. Raad II, Hachem RY, Herbrecht R, et al. Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. Clin Infect Dis 2006;42:1398-403.
20. van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis 2006;42:e61-e65. [Erratum, Clin Infect Dis 2006;43:1376.]
21. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007;44:2-12.
22. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7-14.
23. Ferrara JL, Deeg HJ. Graft-versus-host disease. N Engl J Med 1991;324:667-74.
24. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995;15:825-8.
25. Albengres E, Le Louet H, Tillement JP. Systemic antifungal agents: drug interactions of clinical significance. Drug Saf 1998;18:83-97.
26. Barry AL, Pfaller MA, Brown SD, et al. Quality control limits for broth microdilution susceptibility tests of ten antifungal agents. J Clin Microbiol 2000;38:3457-9.
27. Espinel-Ingroff A, Bartlett M, Chaturvedi V, et al. Optimal susceptibility testing conditions for detection of azole resistance in Aspergillus spp.: NCCLS collaborative evaluation. Antimicrob Agents Chemother 2001;45:1828-35.
28. de Repentigny L, Boushira M, Ste-Marie L, Bosisio G. Detection of galactomannan antigenemia by enzyme immunoassay in experimental invasive aspergillosis. J Clin Microbiol 1987;25:863-7.
29. Shen JX, Krishna G, Hayes RN. A sensitive liquid chromatography and mass spectrometry method for the determination of posaconazole in human plasma. J Pharm Biomed Anal 2007;43:228-36.
30. Jantunen E, Ruutu P, Niskanen L, et al. Incidence and risk factors for invasive fungal infections in allogeneic BMT recipients. Bone Marrow Transplant 1997;19:801-8.
31. Morgenstern GR, Prentice AG, Prentice HG, Ropner JE, Schey SA, Warnock DW. A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies. Br J Haematol 1999;105:901-11.
32. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood 2000;96:2055-61.
33. Winston DJ, Maziarz RT, Chandrasekar PH, et al. 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. Ann Intern Med 2003;138:705-13.
34. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004; 39:1407-16.
35. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood 2004;103:1527-33.
36. Ullmann AJ, Cornely OA, Burchardt A, et al. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. Antimicrob Agents Chemother 2006;50:658-66.
37. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-15.
38. Marr KA. Issues in the design of the fluconazole prophylaxis trials in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004;39:Suppl 4:S170-S175.

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CORRECTION

Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease . The second sentence of the third paragraph under Efficacy (page 341) should have read ``In other analyses, posaconazole was superior to fluconazole in reducing the incidence of proven or probable aspergillosis (odds ratio, 0.31; 95% CI, 0.13 to 0.75; P=0.006) during the treatment period and was superior to fluconazole in reducing the incidence of breakthrough proven or probable invasive fungal infections (odds ratio, 0.30; 95% CI, 0.12 to 0.71; P=0.004) and invasive aspergillosis during the exposure period (odds ratio, 0.17; 95% CI, 0.05 to 0.57; P=0.001)´´ rather than ``invasive aspergillosis during the treatment period.´´ The text has been corrected on the *Journal*'s Web site at www.nejm.org.