VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS

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ABSTRACT

Background   Voriconazole is a broad-spectrum triazole that is active against aspergillus species. We conducted a randomized trial to compare voriconazole with amphotericin B for primary therapy of invasive aspergillosis.

Methods   In this randomized, unblinded trial, patients received either intravenous voriconazole (two doses of 6 mg per kilogram of body weight on day 1, then 4 mg per kilogram twice daily for at least seven days) followed by 200 mg orally twice daily or intravenous amphotericin B deoxycholate (1 to 1.5 mg per kilogram per day). Other licensed antifungal treatments were allowed if the initial therapy failed or if the patient had an intolerance to the first drug used. A complete or partial response was considered to be a successful outcome.

Results   A total of 144 patients in the voriconazole group and 133 patients in the amphotericin B group with definite or probable aspergillosis received at least one dose of treatment. In most of the patients, the underlying condition was allogeneic hematopoietic-cell transplantation, acute leukemia, or other hematologic diseases. At week 12, there were successful outcomes in 52.8 percent of the patients in the voriconazole group (complete responses in 20.8 percent and partial responses in 31.9 percent) and 31.6 percent of those in the amphotericin B group (complete responses in 16.5 percent and partial responses in 15.0 percent; absolute difference, 21.2 percentage points; 95 percent confidence interval, 10.4 to 32.9). The survival rate at 12 weeks was 70.8 percent in the voriconazole group and 57.9 percent in the amphotericin B group (hazard ratio, 0.59; 95 percent confidence interval, 0.40 to 0.88). Voriconazole-treated patients had significantly fewer severe drug-related adverse events, but transient visual disturbances were common with voriconazole (occurring in 44.8 percent of patients).

Conclusions   In patients with invasive aspergillosis, initial therapy with voriconazole led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B. (N Engl J Med 2002;347: 408-15.)

INVASIVE aspergillosis is a major infectious complication in patients with prolonged neutropenia and in transplant recipients. Its incidence ranges from 5 percent to more than 20 percent in high-risk groups.[1] For decades, amphotericin B deoxycholate has been the standard therapy for invasive aspergillosis, although responses are suboptimal (less than 40 percent) in severely immunosuppressed patients.[1-3] Amphotericin B is associated with multiple side effects, which may be ameliorated with the use of lipid formulations.[4-6]

Voriconazole is a new broad-spectrum triazole that is active in vitro against various yeasts and molds, including aspergillus species.[7] A noncomparative study demonstrated a response rate of 48 percent among patients with acute invasive aspergillosis.[8] We undertook an open, randomized trial comparing the efficacy, safety, and tolerability of voriconazole with those of amphotericin B for the primary therapy of acute invasive aspergillosis in immunocompromised patients; both types of therapy were followed by other licensed antifungal therapy when toxic effects or insufficient response dictated.

METHODS

Conduct of the Study

Two identical protocols (protocol 150-307 in Europe, Israel, and Australia and protocol 150-602 in the United States, Canada,

Mexico, Brazil, and India) were designed under the aegis of an international steering committee that included the Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer (EORTC). The protocols were approved by the appropriate institutional review boards, and written informed consent was obtained from all patients or their parents or guardians. The studies were assessed by an independent data review committee consisting of eight clinicians and four radiologists and were monitored by two data and safety monitoring boards. Statistical analysis was conducted by the EORTC Data Center. The study's sponsor, Pfizer, allowed the investigators independence in study design and analysis. The data were held at the EORTC Data Center in Brussels, Belgium, and at Pfizer.

Study Patients

Eligible patients were those with definite or probable invasive aspergillosis who were 12 years of age or older and were immunocompromised because of one of the following: allogeneic hematopoietic-cell transplantation; autologous hematopoietic-cell transplantation, hematologic cancer, aplastic anemia, or myelodysplastic syndrome; or other immunocompromising conditions, including the acquired immunodeficiency syndrome (AIDS), receipt of corticosteroid therapy, and solid-organ transplantation.

Definite invasive aspergillosis was defined as a clinically compatible illness plus one or more of the following: isolation of aspergillus species from a normally sterile site; hyphae consistent with the presence of aspergillus in a biopsy specimen or aspirate, plus culture of aspergillus from the same organ; radiologic evidence of pulmonary lesions that were not attributable to other factors and a culture of bronchoalveolar-lavage fluid that was positive for aspergillus in a patient who had undergone allogeneic hematopoietic-cell transplantation or who had a neutropenic hematologic condition; or tracheobronchial lesions confirmed by bronchoscopy, with a positive culture for aspergillus. Neutropenia was defined by a neutrophil count of less than 500 per cubic millimeter at some point during the previous two weeks.

Probable invasive aspergillosis was defined as a clinically compatible illness plus one or more of the following: hyphae consistent with the presence of aspergillus in a biopsy specimen or aspirate but without culture; the presence of a halo or an air-crescent sign on a computed tomographic (CT) scan of the lung[9] in a patient who had undergone allogeneic hematopoietic-cell transplantation or who had a neutropenic hematologic condition; radiologic evidence of new pulmonary lesions that were not attributable to other factors in a patient who had undergone allogeneic hematopoietic-cell transplantation or who had a neutropenic hematologic condition with either hyphae consistent with the presence of aspergillus in bronchoalveolar-lavage fluid or sputum or a sputum culture that was positive for aspergillus; clinical evidence of sinusitis, opacification of a sinus on CT or magnetic resonance imaging, and positive histopathological examination or culture of aspergillus from a lesion in the nose or paranasal sinus in a patient who had undergone allogeneic hematopoietic-cell transplantation or who had a neutropenic hematologic condition; radiologic evidence of new pulmonary lesions that were not attributable to other factors and bronchoalveolar-lavage fluid that was positive for aspergillus on a smear or culture in a patient with another immunocompromising condition (other than lung transplantation); or tracheobronchial lesions confirmed by bronchoscopy and a positive finding on histopathological or microscopic examination of a biopsy specimen or bronchoalveolar lavage fluid.

Patients were ineligible if they had chronic aspergillosis, aspergilloma, or allergic bronchopulmonary aspergillosis or had received systemic therapy for more than 96 hours with more than 0.5 mg of amphotericin B per kilogram of body weight per day (including lipid derivatives) or more than 200 mg of itraconazole per day during the preceding 14 days. Patients were also ineligible if they had received or were receiving interacting drugs (e.g., rifampin), were hypersensitive to azoles or amphotericin B, or had an aminotransferase, bilirubin, or alkaline phosphatase level higher than five times the upper limit of normal or a serum creatinine level higher than 2.5 mg per deciliter (221 μmol per liter). Patients who were receiving artificial ventilation, who had a life expectancy of less than 72 hours, or who were pregnant or lactating were also ineligible.

Study Design

With the use of central randomization according to the minimization technique,[10] patients were assigned to treatment groups, with stratification according to the center, the site of infection (pulmonary or other), the underlying condition (allogeneic hematopoietic-cell transplantation, hematologic condition, or other immunocompromising condition), and the base-line neutropenic status (neutropenic or nonneutropenic). Patients received primary therapy with either voriconazole (6 mg per kilogram intravenously twice a day on day 1, followed by 4 mg per kilogram intravenously twice daily for at least seven days, after which time patients could switch to oral voriconazole, 200 mg twice daily) or intravenous amphotericin B deoxycholate (1.0 to 1.5 mg per kilogram once daily). Patients with an intolerance or no response to the initial therapy could be switched to other licensed antifungal therapy and continue to be included in the analyses. The planned duration of therapy was 12 weeks. Administration of study drugs was discontinued in cases of severe adverse events, an increase in the serum creatinine level to double the base-line value or more than 3.0 mg per deciliter (265 μmol per liter) if the base-line value was higher than 1.5 mg per deciliter (133 μmol per liter), or an increase in aminotransferase levels to more than 5 times the upper limit of normal or 10 times the upper limit of normal if the base-line value was more than 2 times the upper limit of normal.

The data-review committee, which was blinded to the study-drug assignment and to adverse events and laboratory abnormalities whose presence would suggest the use of a particular study drug, assessed the certainty of the diagnosis at study entry and the response to treatment on the basis of predefined criteria. The committee assessed the global response at week 12 and at the end of the initial period of randomized therapy.

Digitized radiologic images were reviewed by the radiologists on the data-review committee. Lesions were evaluated visually for changes with the use of computerized planimetry for assistance in estimating the percentage change. Complete responses were defined by the resolution of all clinical signs and symptoms and more than 90 percent of the lesions due to invasive aspergillosis that were visible on radiology. Partial responses were defined by clinical improvement and greater than 50 percent improvement in findings on radiology. Stable responses were defined by the absence of change from base line or an improvement of less than 50 percent. Failure of therapy was defined by worsening disease. Complete and partial responses were classified as successful outcomes. Stable and indeterminate responses and failures of therapy were regarded as unsuccessful outcomes.

Statistical Analysis

Before the two studies began, we planned to combine the results of both in a predefined analysis. The intention-to-treat population consisted of all patients who underwent randomization. The modified intention-to-treat population consisted of those who received at least one dose of the medication they were initially assigned to receive and who had a base-line diagnosis of definite or probable invasive aspergillosis as confirmed by the data-review committee. The population included in the safety analysis consisted of all patients who received their initial study medication.

The primary objective of the studies was to demonstrate the noninferiority of voriconazole as compared with amphotericin B at week 12 in the modified intention-to-treat population. We estimated that the rate of successful outcomes with amphotericin B at week 12 would be 50 percent. Voriconazole would be consid-

ered not to be inferior to amphotericin B if the lower limit of the two-sided 95 percent confidence interval for the difference in voriconazole response rate minus the difference in amphotericin B response rate was above −20 percentage points.

One secondary objective was the demonstration of the superiority of the response to voriconazole at the end of the initial therapy in the modified intention-to-treat population — as indicated by a two-sided 95 percent confidence interval entirely above zero for the difference between the proportion with a complete or partial response in the voriconazole group and the proportion in the amphotericin B group. Other secondary objectives were to compare the safety of the two drugs and the duration of survival in the two groups up to week 12.

A sample size of 276 was required to assess the primary end point with at least 90 percent power. We compared the responses by calculating the estimated difference between the response rates, with stratification according to study protocol (150-307 or 150-602), and the corresponding approximate two-sided 95 percent confidence interval. The hazard ratio for death was estimated by the Cox proportional-hazards model, with stratification according to study. The numbers of adverse events were compared by Fisher's exact test. The mean numbers of adverse events were compared by the Wilcoxon rank-sum test. All tests were two-sided.

RESULTS

Enrollment and Base-Line Characteristics of the Patients

Between July 1997 and October 2000, a total of 391 patients recruited by 95 centers in 19 countries underwent randomization in the studies: 252 patients were recruited in the 150-307 protocol and 139 in the 150-602 protocol.

A total of 197 patients were assigned to the voriconazole group, and 194 patients were assigned to the amphotericin B group; these patients comprised the intention-to-treat population. Twelve patients (three in the voriconazole group and nine in the amphotericin B group) did not receive any treatment and were excluded from the safety analyses. A total of 102 patients (50 in the voriconazole group and 52 in the amphotericin B group) were excluded from the modified intention-to-treat population because they did not have a confirmed diagnosis of invasive aspergillosis at base line. The most common reason for the lack of confirmation was the inability of the data-review committee to confirm the presence of a halo or air-crescent sign at base line in patients with no supporting mycologic or pathological evidence (35 in the voriconazole group and 25 in the amphotericin B group). Other reasons included inadequate mycologic evidence (in 10 patients in the voriconazole group and 15 in the amphotericin B group), no radiologic evidence of pulmonary or sinus infection (in 1 patient in the voriconazole group and 4 in the amphotericin B group), and absence of documentation of neutropenia or immunocompromised condition before base line (in 4 patients in the voriconazole group and 8 in the amphotericin B group).

The demographic characteristics and underlying conditions of the patients in the modified intention-to-treat population are summarized in Table 1. The two groups were well matched, and there was no significant difference in these characteristics between the intention-to-treat population and the modified intention-to-treat population. Patients enrolled according to the 150-602 protocol were more likely than those enrolled according to the 150-307 protocol to have undergone allogeneic hematopoietic-cell transplantation (41 of 107 [38.3 percent] vs. 26 of 170 [15.3 percent], P<0.001), to have graft-versus-host disease (31 of 107 [29.0 percent] vs. 16 of 170 [9.4 percent], P<0.001), and to have received a definite diagnosis of invasive aspergillosis (51 of 107 [47.7 percent] vs. 57 of 170 [33.5 percent], P=0.02), and they were less likely to have neutropenia (28 of 107 [26.2 percent] vs. 95 of 170 [55.9 percent], P<0.001).

Base-Line Characteristics of the Infection

Characteristics of the patients in terms of the site of the infection, the level of certainty of the diagnosis, and the evidence supporting the diagnosis are summarized in Table 2. The only significant difference between groups was that the voriconazole group had a higher proportion of definite cases of invasive aspergillosis (P=0.01). In the 110 infections in which the species was identified at base line, the species was

TABLE 1. CHARACTERISTICS OF THE PATIENTS IN THE MODIFIED INTENTION-TO-TREAT POPULATION.

CHARACTERISTIC	VORICONAZOLE GROUP (N=144)	AMPHOTERICIN B GROUP (N=133)
Age — yr		
Mean	48.5	50.5
Range	13–79	12–75
Sex — no. (%)		
Male	98 (68.1)	89 (66.9)
Female	46 (31.9)	44 (33.1)
Weight — kg		
Mean	70.4	71.0
Range	39–123	28–118
Underlying condition — no. (%)		
Allogeneic hematopoietic-cell transplantation	37 (25.7)	30 (22.6)
Autologous hematopoietic-cell transplantation	6 (4.2)	6 (4.5)
Acute leukemia	58 (40.3)	60 (45.1)
Other hematologic cancer	17 (11.8)	18 (13.5)
Solid-organ transplantation	9 (6.2)	5 (3.8)
AIDS	6 (4.2)	7 (5.3)
Corticosteroid treatment	9 (6.2)	7 (5.3)
Other	2 (1.4)	0
Neutropenia — no. (%)*		
Yes	65 (45.1)	60 (45.1)
No	79 (54.9)	73 (54.9)

*Neutropenia was defined by a neutrophil count of less than 500 per cubic millimeter at base line or during the previous two weeks.

TABLE 2. SITE OF THE INFECTION, DEGREE OF CERTAINTY, AND EVIDENCE SUPPORTING BASE-LINE DIAGNOSIS IN THE MODIFIED INTENTION-TO-TREAT POPULATION.

VARIABLE	VORICONAZOLE GROUP (N=144)	AMPHOTERICIN B GROUP (N=133)
	no. (%)	
Site of the infection		
Lung only	123 (85.4)	117 (88.0)
Sinus	8 (5.6)	7 (5.3)
Cerebral*	5 (3.5)	5 (3.8)
Disseminated†	4 (2.8)	1 (0.8)
Other	4 (2.8)	3 (2.3)
Level of certainty of the diagnosis of aspergillosis		
Definite‡	67 (46.5)	41 (30.8)
Probable	77 (53.5)	92 (69.2)
Initial evidence of aspergillosis§		
Positive finding on microscopy	56 (38.9)	46 (34.6)
Positive culture	84 (58.3)	65 (48.9)
Positive histologic examination	35 (24.3)	22 (16.5)
Halo or air-crescent sign only	46 (31.9)	49 (36.8)

*Category includes those with other organ involvement.

†Category excludes those with cerebral involvement.

‡There were significantly more definite cases in the voriconazole group (P=0.01).

§Some patients had more than one type of biologic evidence.

Aspergillus fumigatus (in 85 patients), *A. niger* (in 9 patients), *A. flavus* (in 7 patients), *A. terreus* (in 6 patients), *A. glaucus* (in 1 patient), *A. nidulans* (in 1 patient), and *A. sydowii* (in 1 patient).

Course of Therapy in the Modified Intention-to-Treat Population

The median duration of voriconazole treatment was 77 days (range, 2 to 84), of which intravenous therapy accounted for a median of 10 days (range, 2 to 78). The mean daily doses were 7.87 mg per kilogram (range, 4.48 to 10.87) during the intravenous phase and 416 mg (range, 200 to 750) during the oral phase. Other licensed antifungal therapy was given to 52 patients in the voriconazole group. The first other licensed antifungal therapy was amphotericin B deoxycholate in 20 patients, a lipid formulation of amphotericin B in 14, itraconazole in 17, and a combination in 1.

The median duration of amphotericin B treatment was 10 days (range, 1 to 84), and the mean daily dose was 0.97 mg per kilogram (range, 0.27 to 1.50). During the first 14 days of therapy, administration of amphotericin B was suspended for more than 1 day in 13 patients. Other licensed antifungal therapy was given to 107 patients in the amphotericin B group. The first other licensed antifungal therapy was a lipid formulation of amphotericin B in 47 patients, itracona-

zole in 38, and another antifungal drug or a combination of drugs in 22.

Response

The outcome at week 12 in the modified intention-to-treat population was significantly better in patients receiving voriconazole, with a successful outcome in 76 of 144 patients (52.8 percent), as compared with 42 of 133 patients (31.6 percent) in the amphotericin B group (Table 3). The absolute difference was 21.2 percent, with a 95 percent confidence interval for the difference between groups stratified according to the study protocol of 10.4 to 32.9 percentage points. Since the lower 95 percent confidence limit for the difference between voriconazole and amphotericin B was above zero, voriconazole was considered not only not to be inferior to amphotericin B, but also to be superior to it.

Retrospective stratification according to the level of certainty of the diagnosis, the site of infection, the underlying condition, or the neutropenic status did not change the overall conclusions. Responses in patients receiving voriconazole appeared to be superior at week 12 in all the various subgroups (Fig. 1). Of 95 patients included with a diagnosis of probable aspergillosis that was based on the presence of a halo sign without microbiologic confirmation, 31 in the voriconazole group (67.4 percent) had a successful outcome, as compared with 21 (42.9 percent) in the amphotericin B group. The difference (24.5 percentage points in favor of voriconazole) was almost identical to that among all patients with probable aspergillosis — 22.7 percentage points in favor of voriconazole.

In the intention-to-treat population, a successful outcome at week 12 was observed in 49.7 percent of the patients in the voriconazole group and 27.8 per-

TABLE 3. RESPONSE RATE AT WEEK 12 IN THE MODIFIED INTENTION-TO-TREAT POPULATION.

RESPONSE	VORICONAZOLE GROUP (N=144)	AMPHOTERICIN B GROUP (N=133)
	no. (%)	
Successful outcome*	76 (52.8)	42 (31.6)
Complete response	30 (20.8)	22 (16.5)
Partial response	46 (31.9)	20 (15.0)
Unsuccessful outcome	68 (47.2)	91 (68.4)
Stable disease	8 (5.6)	8 (6.0)
Failure of therapy	55 (38.2)	78 (58.6)
Indeterminate	5 (3.5)	5 (3.8)

*The 95 percent confidence interval around the difference in successful outcomes (stratified according to study) was 10.4 to 32.9 percent.

	Successful Outcome (%)	
---	Voriconazole group	Amphotericin B group
Modified intention-to-treat population	52.8	31.6
Protocol 150-307	57.0	36.9
Protocol 150-602	46.6	22.5
Pulmonary infection only	54.5	34.2
Extrapulmonary infection	42.9	12.5
Allogeneic hematopoietic-cell transplantation	32.4	13.3
Neutropenic hematologic condition	63.0	38.1
Other immunocompromising condition	50.0	31.6
Neutropenia	50.8	31.7
No neutropenia	54.3	31.5
Definite aspergillosis	44.8	19.5
Probable aspergillosis	59.7	37.0
Overall intention-to-treat population	49.7	27.8

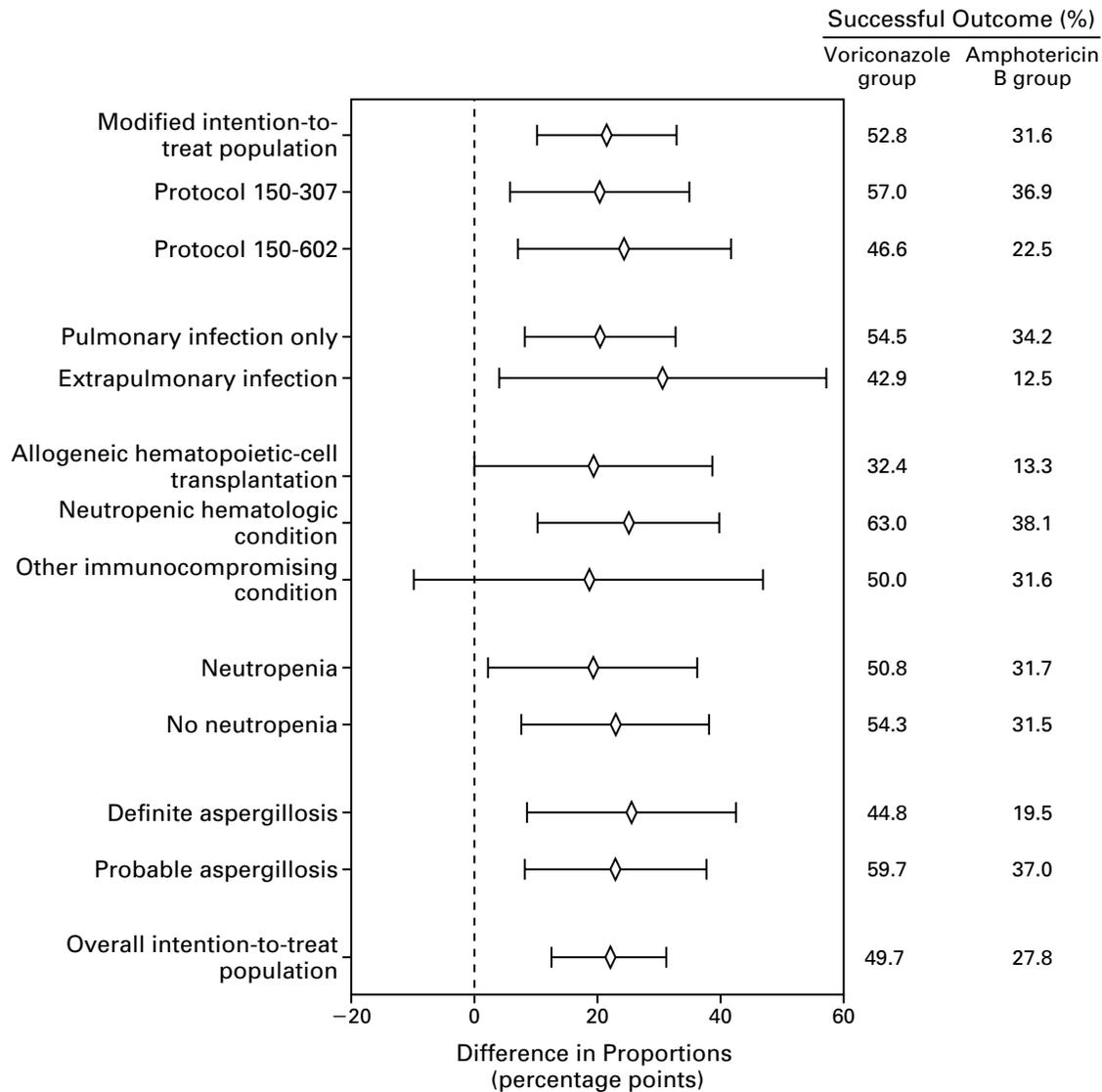Difference in Proportions (percentage points)

Figure 1. Response Rates in the Modified Intention-to-Treat Population, According to the Study Protocol, Site of Infection, Underlying Condition, Neutropenic Status, and Degree of Certainty of the Diagnosis, and in the Intention-to-Treat Population.
Results are expressed as the differences (with 95 percent confidence intervals) between the voriconazole group and the amphotericin B group in the rate of successful outcomes.

cent of those in the amphotericin B group (absolute difference, 21.9 percent; 95 percent confidence interval, 12.4 to 31.2).

At the end of the initial period of randomized therapy, 53.5 percent of the patients in the modified intention-to-treat population who were receiving voriconazole had a satisfactory response, as compared with 21.8 percent of the patients treated with amphotericin B (absolute difference, 31.7 percent; 95 per-

cent confidence interval, 21.1 to 42.6). There were similar results in the intention-to-treat population.

Survival

At week 12, the survival rate was 70.8 percent in the patients in the modified intention-to-treat population who were treated with voriconazole, as compared with 57.9 percent in the amphotericin B group (hazard ratio, 0.59; 95 percent confidence interval,

0.40 to 0.88) (Fig. 2). Similar results were observed in the intention-to-treat population.
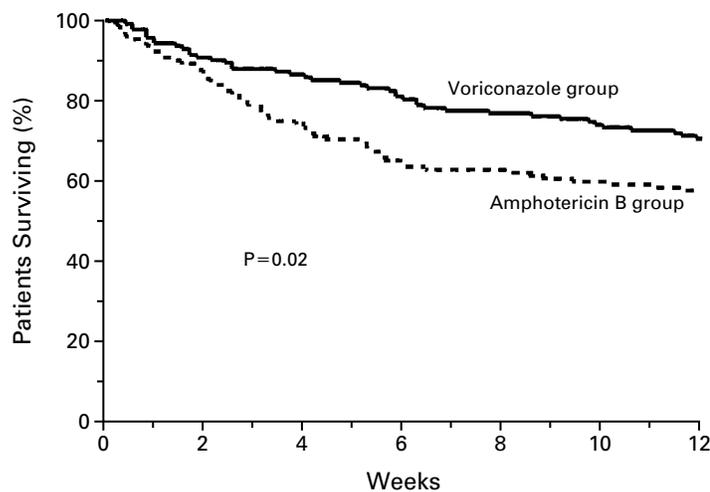
Safety

Significantly fewer adverse events that were regarded by the investigators as potentially related to treatment were observed during voriconazole therapy (343 events) than during amphotericin B therapy (421 events, P=0.02), even though the median duration of therapy was much longer in the voriconazole group. Visual disturbances were more common in patients receiving voriconazole, occurring in 87 patients (44.8 percent), as compared with 8 patients in the amphotericin B group (4.3 percent, P<0.001). The most frequent descriptions of such disturbances were blurred vision, altered visual perception, altered color perception, and photophobia. All visual events were transient and resolved without intervention. Thirteen patients receiving voriconazole had hallucinations or confusion that was considered to be possibly related to the study drug, as compared with five patients in the amphotericin B group (P=0.09). There was no evidence of a relation between the episodes of hallucination or confusion and visual disturbance (P=0.20). Chills, fever, or both that were potentially related to the study drugs were recorded in six patients receiving voriconazole (3.1 percent), as compared with 46 patients receiving amphotericin B

therapy (24.9 percent, P<0.001). Skin reactions (rash, pruritus, or photosensitivity) were observed in 16 patients in the voriconazole group (8.2 percent) and in 6 in the amphotericin B group (3.2 percent, P=0.05).

Fewer severe adverse events that were potentially related to the study drug occurred in the voriconazole group (26 patients [13.4 percent]) than in the amphotericin B group (45 patients [24.3 percent], P=0.008) (Table 4). The most frequent events were renal impairment (in 19 patients) in the amphotericin B group and liver-function abnormalities (in 7 patients) in the voriconazole group.

DISCUSSION

We conducted a large randomized, comparative study of the efficacy of two different drugs in the primary treatment of invasive aspergillosis. Previous studies either compared two doses of liposomal amphotericin B or used historical controls.[11,12] Definitions used in this study were determined by a consensus of international investigators and proved sufficiently clear for a blinded data-review committee to use for confirmation. The largest discrepancy between the diagnoses of investigators and the determinations of the data-review committee resulted not from misinterpretation of the diagnostic criteria but from the lack of confirmation by the radiologists on the data-

Figure 2. Survival Curves for the Modified Intention-to-Treat Population According to Treatment Group.
The P value was calculated by the log-rank test.

No. at Risk							
Voriconazole	144	131	125	117	111	107	102
Amphotericin B	133	117	99	87	84	80	77

TABLE 4. SEVERE ADVERSE EVENTS POTENTIALLY
RELATED TO INITIAL RANDOMIZED THERAPY.*

TYPE OF EVENT	VORICONAZOLE GROUP (N=194)	AMPHOTERICIN B GROUP (N=185)	P VALUE†
	no. of patients		
Renal impairment	2	19	<0.001
Hypokalemia	0	6	0.01
Other metabolic event (hypoglycemia, hypoalbuminemia, worsening of adrenal insufficiency, or metabolic acidosis)	4	2	0.69
Hepatic abnormalities	7	4	0.54
Systemic event (fever, chills, anaphylaxis, asthenia, or myalgia)	1	7	0.03
Dyspnea	0	4	0.06
Digestive tract event (nausea, vomiting, dysgeusia, abdominal pain, or pancreatitis)	4	1	0.37
Hypotension	1	0	
Hematologic event (thrombocytopenia, eosinophilia, or exacerbation of paroxysmal nocturnal hemoglobinuria)	2	1	
Rash	1	0	
Neurologic event (progressive encephalopathy, hallucinations, or Guillain–Barré syndrome)	2	1	
Visual events	2	0	

*The 12 patients (3 in the voriconazole group and 9 in the amphotericin B group) who did not receive any treatment were excluded from the analysis.

†P values are given for events for which there was sufficient frequency to permit a comparison between groups.

review committee of the presence of a halo or air-crescent sign on a CT scan of the lungs in 60 cases.

This open study compared two management strategies for invasive aspergillosis, one of which reflects the common clinical practice of treating patients with conventional amphotericin B and then changing drugs as dictated by the occurrence of toxic effects or a lack of response. Patients treated according to this strategy fared worse in terms of efficacy, toxic effects, and survival than those who instead began treatment with voriconazole.

The superiority of voriconazole in our study was not the result of excessive interruptions of therapy or insufficient doses in patients receiving amphotericin B. The duration of treatment is unlikely to be the only factor contributing to the better overall results with voriconazole. Acute invasive aspergillosis is a rapidly progressive infection, and its outcome is determined early in the course of therapy. In the highly immunosuppressed patients enrolled in this study, initial therapy with voriconazole proved superior to initial therapy with conventional amphotericin B. The presence of more definite cases of aspergillosis among patients in the voriconazole group did not bias the results, because the superiority of voriconazole was similar in both definite and probable cases. The dif-

ference in the rate of successful outcomes between the 150-602 and 150-307 studies can be explained by the fact that the group involved in the former study included more patients who either had a diagnosis of definite aspergillosis or had undergone allogeneic hematopoietic-cell transplantation.

The efficacy of voriconazole in invasive aspergillosis shown in this trial is consistent with the results of the recently published comparison of voriconazole with liposomal amphotericin B for empirical antifungal therapy in persistently febrile patients with neutropenia.[13] In that study, a secondary analysis found that among the 415 patients who received voriconazole, only 8 (1.9 percent) had breakthrough mycosis (4 of the cases involving aspergillus species), as compared with 21 (5.0 percent, 13 of the cases involving aspergillus species) among the 422 patients who received liposomal amphotericin B.

Voriconazole was better tolerated than amphotericin B, with fewer drug-related adverse events, severe adverse events, and discontinuations of therapy due to adverse events. Infusion-related adverse events and nephrotoxic effects are common in patients receiving amphotericin B but were not observed in patients receiving voriconazole.

Although visual adverse events were frequent in

patients receiving voriconazole, they were transient and generally mild or moderate, and they seldom resulted in discontinuation of treatment. Hallucination and episodes of confusion were more frequent with voriconazole than with amphotericin B, although it is unclear whether the antifungal drug was the cause of such episodes in these critically ill patients. This study shows the superiority of voriconazole over amphotericin B as initial therapy for invasive aspergillosis, in terms of response rate, survival rate, and safety.

APPENDIX

In addition to the authors, members of the study who recruited patients were as follows: R. Allen (Sacramento, Calif.), M. Aoun (Brussels, Belgium), C. Aul (Düsseldorf, Germany), M. Bjorkholm (Stockholm, Sweden), K.L. Blanchard (Shreveport, La.), M. Boogaerts (Leuven, Belgium), E. Bouza (Madrid), E.J. Bow (Winnipeg, Man.), H.R. Brodt (Frankfurt, Germany), J. Brown (Stanford, Calif.), D. Buchheidt (Mannheim, Germany), J.Y. Cahn (Besançon, France), A. Calmaggi (La Plata, Argentina), J.M. Cisneros (Seville, Spain), C. Cordonnier (Créteil, France), J. Daly (Worcester, Mass.), C.A. Da Cunha (Curitiba, Brazil), R. De Bock (Antwerp, Belgium), A. Del Favero (Perugia, Italy), J. Diaz Mediavilla (Madrid), M.C. Dignani (Buenos Aires, Argentina), C. Doyen (Yvoir, Belgium), J.S. Dummer (Nashville), B. Dupont (Paris), M. Egyed (Kaposvar, Hungary), D. Engelhard (Jerusalem, Israel), G. Fätkenheuer (Cologne, Germany), R. Feld (Toronto), D. Fière (Lyons, France), G. Fioritoni (Pescara, Italy), G. Garber (Ottawa, Ont.), Z. Gasztonyi (Gyor, Hungary), K. Godder (Columbia, S.C.), D. Graham (Springfield, Ill.), A. Gratwohl (Basel, Switzerland), R. Greenberg (Lexington, Ky.), K. High (Winston-Salem, N.C.), F. Jacobs (Brussels, Belgium), V. Krcmery (Bratislava, Slovakia), P. Kumar (Washington, D.C.), W. Langer (Essen, Germany), M. Laverdiere (Montreal), P. Ljungman (Huddinge, Sweden), H. Lode (Berlin, Germany), A. Louie (Albany, N.Y.), D. Maki (Madison, Wis.), J.P. Marie (Paris), D.J.E. Marriott (Sydney, Australia), D.S. McKinsey (Kansas City, Mo.), R. Mertelsmann (Freiburg, Germany), M.K. Nair (New Delhi, India), N. Milpied (Nantes, France), A. Nagler (Jerusalem, Israel), D. Niederwieser (Leipzig, Germany), L. Pagano (Rome), P. Pappas (Birmingham, Ala.), J. Perfect (Durham, N.C.), J. Pottage (Chicago), V. Raina (New Delhi, India), J. Reinhardt (Newark, Del.), S. Richardson (Toronto), L. Rickman (San Diego, Calif.), M. Ruhnke (Berlin, Germany), I. Salit (Toronto), W.M. Scheld (Charlottesville, Va.), S. Schuler (Dresden, Germany), M. Schuster (Philadelphia), R. Schwerdtfeger (Wiesbaden, Germany), S.D. Shafran (Edmonton, Alta.), B. Simmons (Memphis, Tenn.), M. Slavin (Parkville, Australia), M. Sokol-Anderson (St. Louis), P. Tebas (St. Louis), C. Tsoukas (Montreal), A. Ullmann (Mainz, Germany), J. Van Burik (Minneapolis), J.W. Van't Wout (Leiden, the Netherlands), E.C. Vinaya Kumar (Hyderabad, India), P. Volkow-Fernandez (Mexico City, Mexico), C. Wallrauch (Munich, Germany), H. Wandt (Nuremberg, Germany); *EORTC Data Center (Brussels, Belgium):* A. Marinus, C. Coens, R. Sylvester; *Data-Review Committee:* J.E. Bennett, D.W. Denning, C. Durand, R.E. Greene, R. Herbrecht, O. Lortholary, J.W. Oestmann, T.F. Patterson, P. Ribaud, R.H. Rubin, P. Stark, J.R. Wingard.

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REFERENCES

1. Denning DW. Invasive aspergillosis. Clin Infect Dis 1998;26:781-803.
2. Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for diseases caused by Aspergillus. Clin Infect Dis 2000;30:696-709.
3. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. Medicine (Baltimore) 2000;79:250-60.
4. Wingard JR, Kubilis P, Lee L, et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. Clin Infect Dis 1999;29:1402-7.
5. Bates DW, Su L, Yu DT, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis 2001;32:686-93.
6. Tiphine M, Letscher-Bru V, Herbrecht R. Amphotericin B and its new formulations: pharmacologic characteristics, clinical efficacy, and tolerability. Transpl Infect Dis 1999;1:273-83.
7. Espinel-Ingroff A. In vitro fungicidal activities of voriconazole, itraconazole, and amphotericin B against opportunistic moniliaceous and dematiaceous fungi. J Clin Microbiol 2001;39:954-8.
8. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infect Dis 2002;34:563-71.
9. Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 1985;157:611-4.
10. Freedman LS, White SJ. On the use of Pocock and Simon's method for balancing treatment numbers over prognostic factors in the controlled clinical trial. Biometrics 1976;32:691-4.
11. Ellis M, Spence D, de Pauw B, et al. An EORTC international multicenter randomized trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. Clin Infect Dis 1998;27:1406-12.
12. White MH, Anaissie EJ, Kusne S, et al. Amphotericin B colloidal dispersion vs. amphotericin B as therapy for invasive aspergillosis. Clin Infect Dis 1997;24:635-42.
13. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002;346:225-34.