MAJOR ARTICLE

Efficacy and Safety of Voriconazole in the Treatment of Acute Invasive Aspergillosis

David W. Denning,[1] Patricia Ribaud,[2] Noel Milpied,[3] Denis Caillot,[4] Raoul Herbrecht,[5] Eckhard Thiel,[7] Andrea Haas,[6] Markus Ruhnke,[8] and Hartmut Lode[9]

[1]North Manchester General Hospital, University of Manchester, United Kingdom; [2]Hospital Saint-Louis, Paris, [3]Hôtel Dieu, Nantes, [4]Hôpital du Bocage, Dijon, and [5]Hôpital de Hautepierre, Strasbourg, France; and [6]Klinikum Grosshadern, Munich, [7]Universitätsklinikum Benjamin Franklin, [8]Charite, Campus Virchow Klinikum, and [9]Krankenhaus Zehlendorf, Berlin, Germany

To evaluate the efficacy and safety of voriconazole in acute invasive aspergillosis (IA), an open, noncomparative multicenter study was conducted. Immunocompromised patients with IA were treated with intravenously administered voriconazole 6 mg/kg twice a day (b.i.d.) twice and then 3 mg/kg b.i.d. for 6–27 days, followed by 200 mg b.i.d. administered orally for up to 24 weeks. Response was assessed by clinical and radiographic change. A total of 116 patients were assessable. IA was proven in 48 (41%) and probable in 68 patients. Voriconazole was given as primary therapy in 60 (52%). Good responses were seen in 56 (48%); 16 (14%) showed complete response and 40 (34%) partial response. A stable response was seen in 24 patients (21%), and 36 (31%) of the infections failed to respond to therapy. Good responses were seen in 60% of those with pulmonary or tracheobronchial IA ($n = 84$), 16% with cerebral IA ($n = 19$), 58% with hematologic disorders ($n = 67$), and 26% of allogeneic stem cell transplant recipients ($n = 23$). Voriconazole is efficacious in treating acute IA.

Invasive aspergillosis (IA) is the most common life-threatening invasive mold infection worldwide. Acute IA is a complication of immunosuppression, including that due to allogeneic stem cell transplantation, lung and liver transplantation, the treatment of acute leukemia, late-stage AIDS, and a variety of other diseases treated with corticosteroids [1], and rarely are non-immunocompromised patients affected [2]. The incidence of IA was estimated from autopsy data to have risen 14-fold in the 12 years preceding 1992 and affect 4% of patients who die in modern hospitals [3].

Overall, the response rate to treatment with amphotericin B (AmB) is ~35% [1, 4, 5], but only 10%–15% for allogeneic bone marrow transplant recipients [4, 6]. Treatment with AmB desoxycholate is limited by poor toleration and nephrotoxicity [7, 8]. Lipid-associated AmB preparations are associated with less nephrotoxicity, but none has been proven to be more efficacious than AmB deoxycholate [5], despite other encouraging reports [9–11]. The lack of an intravenous formulation of itraconazole at the time this study was started and the drug's unpredictable oral bioavailability (capsules) made this an unsuitable alternative.

Voriconazole (UK-109,496) is a novel wide-spectrum triazole antifungal agent active in vitro against *Aspergillus* species for which the geometric mean MIC is 0.4 mg/L, which compares favorably with that of AmB [12–15]. The drug is fungicidal in vitro for a majority of isolates [12]. Voriconazole is efficacious in animal models (regardless of immune status), usually sterilizing tissues in experimental systemic and pulmonary aspergillosis [15–18]. The drug can also be given orally and intravenously, making switch therapy easier. The objective of this study was to evaluate the clinical efficacy and safety of voriconazole in the treatment of

Received 12 April 2001; revised 24 July 2001; electronically published 22 January 2002.

Financial support: Pfizer Central Research, Sanwich, Kent, United Kingdom.

Reprints or correspondence: Dr. David W. Denning, Research and Teaching Block, Wythenshawe Hospital, Southmoor Rd., Manchester M23 9LT, United Kingdom (ddenning@man.ac.uk).

Clinical Infectious Diseases 2002; 34:563–71

1058-4838/2002/3405-0001$03.00

acute IA in neutropenic and other immunocompromised patients.

PATIENTS AND METHODS

Protocol 150-304 was an open, noncomparative multicenter study of IA in patients aged ⩾14 years and conducted between 1994–1996. Each institution's ethical committee approved the protocol, and each patient gave informed consent by signing a consent form.

Inclusion and exclusion criteria. Definite (e.g., proven) IA required histopathologic evidence of tissue invasion with hyphae morphologically consistent with *Aspergillus* species or a positive culture of *Aspergillus* from a sterile site obtained by an invasive procedure [19, 20]. Probable IA required radiologic evidence suggestive of acute IA [20]. Recovery of *Aspergillus* species from respiratory fluids or other sites in highly immunocompromised patients with characteristic radiology were classified as probable cases [20]. In patients with hematologic disease and profound neutropenia ($<500 \times 10^6$ cells/L) or an allogeneic hematopoietic stem cell transplant (HSCT) a "halo" or "air crescent" sign on CT scan was sufficient for enrollment as probable IA with or without culture confirmation. In the context of profound neutropenia, typical radiologic shadows and clinical features were sufficient for enrollment without culture confirmation. Patients with characteristic features of cerebral aspergillosis on scans or multiple site disease and documentation of disease in one site were classified as probable cerebral or disseminated cases, respectively.

Patients previously treated with >10 mg/kg total dose of AmB, >40 mg/kg total dose of a lipid formulation of AmB, or ⩾400 mg daily itraconazole for ⩾10 days for an episode of definite IA could be given voriconazole as salvage treatment when previous treatment was considered ineffective or toxic. Patients with either probable or definite IA who received previous empirical antifungal therapy at lower doses or for a shorter duration of therapy were given voriconazole as primary therapy, as were those who received the drug for the first time.

Patients were excluded from the study if transaminases were >3 times the upper limit of normal (ULN), if bilirubin and alkaline phosphatase were >2 times ULN or if the serum creatinine was >3 times ULN, if the patients were pregnant or lactating, or if they were allergic to azole drugs.

Treatment. The doses used in the study were based on volunteer data. The protocol defined initial therapy as intravenous for 6–27 days, starting with 2 loading doses of 6 mg/kg at 12-h intervals, followed by 3 mg/kg at 12-h intervals, then orally administered therapy (200 mg b.i.d.) for 4–24 weeks. Patients were followed up for 30 days after discontinuation of voriconazole. Plasma samples for determination of voriconazole concentration by HPLC were collected at various times during the dosing interval more or less randomly. The dose of voriconazole could be escalated initially to 250 mg and then to 300 mg twice daily after a week's interval, when the clinical response was considered inadequate or if random plasma concentrations were lower than an arbitrary 1000 ng/mL. Investigators assessed their patients' clinical response, collected samples for fungal culture during therapy, and determined whether there was any radiographic improvement or deterioration.

Safety evaluation. All adverse events and laboratory abnormalities that arose during treatment and follow-up were recorded and their relationship to voriconazole determined by the investigator. Treatment could be discontinued if the investigator judged this necessary because of an adverse event. Abnormal liver function tests (>5 times ULN transaminases, >3 times ULN bilirubin, or >3 times ULN alkaline phosphatase) necessitated discontinuation.

Assessment of response. All patients who received voriconazole were evaluated in a systematic fashion by one of us (D.W.D.). Each patient was assessed on the basis of the case report form, copies of imaging investigations (x-ray, CT scan and MRI scans, if available) and bronchoscopy results. The original histologic slides were reviewed in 2 patients because of uncertainty about the diagnosis. Classification of probable or definite IA and site of infection was based on all the data available for the patient, including autopsy if one was performed. Cases for which the criteria for probable IA were not met were downgraded to possible or indeterminate IA. Patients with inactive or chronic disease were also excluded. The primary site of infection was determined and stratified by cerebral, disseminated (noncerebral), pulmonary, sinus, and other by use of this hierarchy. Clinical, radiologic, and mycologic outcomes were evaluated separately, and then a global assessment of outcome was made. Response categorization of complete, partial, and stable response and treatment failure was as used in the Mycoses Study Group study of itraconazole [20].

Complete response indicates resolution of all clinical signs and symptoms attributable to IA and complete or very nearly complete radiographic resolution (figure 1). Partial response indicates major improvement or resolution of the attributable clinical signs and symptoms and at least a 50% improvement in radiologic findings. A stable response encompasses intermediate responses (some improvement but <50% radiologic improvement), short courses of therapy with little assessment of response other than that the patients is alive or death due to another documented cause, and some indication that IA was improving, but not enough to reach a partial response. Failure encompasses progression and death due to IA. In uncertain cases, conservative assessments were used. The term "good response" is used to denote both complete and partial responses. Patient deaths were classified as being "due to," "with," or

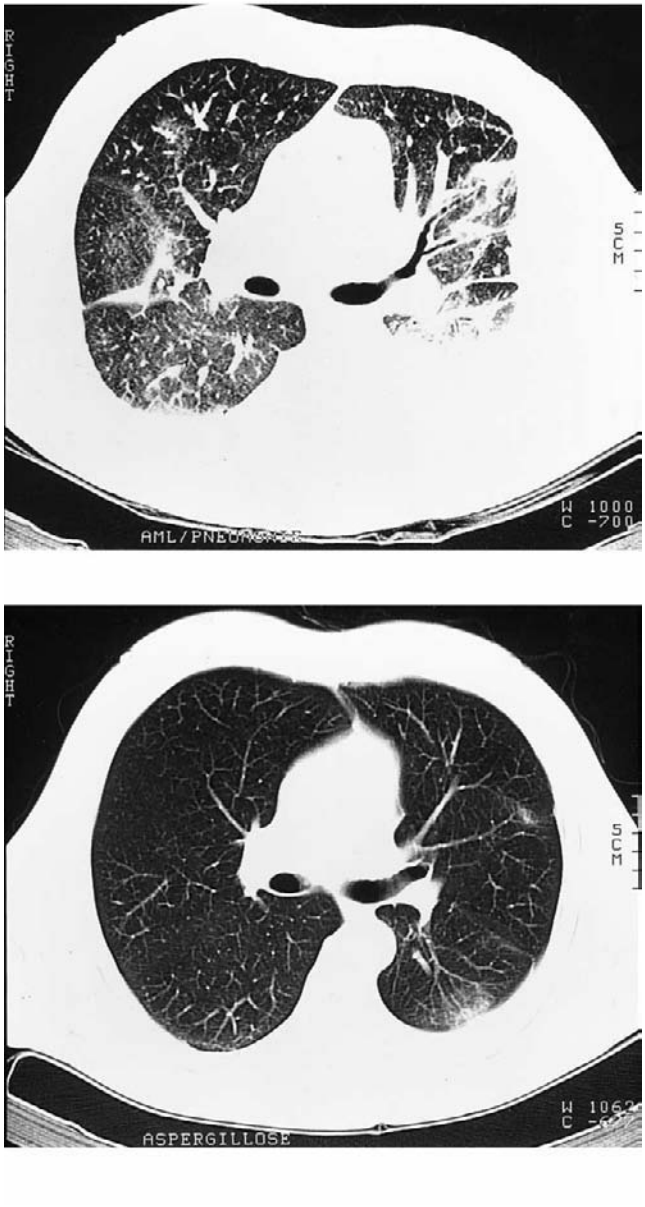

Figure 1. *Top,* CT scan of the thorax, just below the carina, showing extensive infiltrates on the left with a loculated pleural infusion and some infiltrates in the right lung. The patient was a 47-year-old man, first diagnosed with acute myeloid leukemia (M3) in February 1993, with a relapse in August 1994. He received reinduction chemotherapy and was back in remission by October 1994. He was receiving consolidation chemotherapy and developed a cough and progressive shortness of breath. He received itraconazole (600 mg daily) for 17 days before enrollment in this study. His symptoms and radiologic appearances worsened while receiving itraconazole, even though his neutropenia resolved (7400×10^6 cells/L at enrollment). A percutaneous biopsy aspiration revealed hyphal elements in pleural tissue (definite aspergillosis) (patient 304-111-162). *Bottom,* Follow-up scan of the thorax after 12 weeks of voriconazole therapy. At this time, his leukemia was back in remission and his cough had resolved, but he had mild shortness of breath (which later resolved). The results of his CT scan are much improved, with essentially complete resolution of all abnormalities, save 2 minor areas of probable scarring. He is classified as a complete responder.

"without" IA. If the cause of death was uncertain, death as a result of IA was assumed.

Statistical analysis. Comparisons of response rate according to the underlying disease, site of infection, certainty of diagnosis, and whether primary or salvage therapy were carried out by the χ^2 test. Survival times for those given primary treatment were compared with those given salvage treatment by the log rank test, and a Kaplan-Meier plot was generated.

RESULTS

A total of 141 patients were enrolled in the study from 1994–1996. Four received no treatment, and data from these patients are not included in any analyses. Of the 137 patients given the drug, 24 patients were not eligible. Eight patients did not have IA (2 *Scedosporium,* 2 *Pseudomonas,* 1 *Fusarium,* 1 *Pneumocystis,* 1 *Mucorales* infection, and 1 unspecified bacterial pneumonia). Three patients probably did not have IA (classified as "indeterminate"), 2 had inactive (treated) aspergillosis, 1 had chronic invasive sinus aspergillosis, and the response of 1 patient to therapy was not assessable; he was withdrawn from the study after receiving 3 doses of voriconazole because of abnormal liver function tests performed at study entry. All 19 of these patients were excluded from analyses of efficacy. Six other patients were categorized as having possible aspergillosis and were also excluded from further efficacy analyses (3 had complete responses to therapy, 2 had partial responses to therapy, and 1 patient's infection failed to respond to therapy). Thus, 116 patients were considered assessable for efficacy and 137 for safety.

Patient demographics. Fifty of the patients were women and 66 (57%) were men. The patients' ages ranged from 18 to 79 years (median, 52 years). The primary underlying disease for each patient is shown in table 1. At baseline, neutropenia ($<500 \times 10^6$ cells/L) was present in 28 patients (11 patients, $<100 \times 10^6$/L; 17 patients, $100–500 \times 10^6$/L). At least 16 (70%) of 23 patients with allogeneic HSCT had moderate to severe graft versus host disease and were receiving large doses of corticosteroids, as were many other patients. Several patients had multiple predisposing factors.

Clinical features and sites of IA. The most common site of disease was the lungs (table 2). Among 115 patients for whom data are available, 74 (64%) had a pyrexia at enrollment, with an equal frequency in primary and salvage cases. Fever was more frequent in neutropenic patients than in nonneutropenic patients (79% vs. 49%).

Positive cultures were obtained in 71 patients (61%), and microscopy was positive but culture negative in 6 patients (5%). *A. fumigatus* was cultured from 50 patients, *A. flavus* from 8, *A. nidulans* from 3, and *A. niger* and *A. terreus* from 2 each. Six *Aspergillus* isolates were not speciated. Appropriate samples

Table 1. Underlying disease/condition of 116 patients, categorized by the factor perceived to be most important for the development of invasive aspergillosis.

Underlying disease/condition	No. (%) of patients
Hematological disorder	67 (58)
Acute myeloid leukemia	41 (35)
Other hematological malignancy	15
Lymphoma	6
Other	5
Allogeneic HSCT	23 (20)
Solid-organ transplantation	6 (5)
Liver	3
Lung	1
Heart	1
Kidney	1
AIDS	5 (4)
Diabetes mellitus	4 (3)
Solid tumor	4 (3)
Carcinoma of lung	2
Testicular cancer	2
Other[a]	7 (6)

NOTE. HSCT, hematopoietic stem cell transplant.

[a] One each of aspergilloma with local invasion, corticosteroid therapy, systemic lupus erythematosus, chronic pulmonary disease, polyarteritis with pancytopenia, polyneuropathy with an empyema, and trauma.

were obtained but were culture negative in 19 patients, and no appropriate samples were obtained in 20 patients.

Of the 81 patients with pulmonary aspergillosis, 20 (25%) had definite (proven) IA diagnosed and 61 had probable IA diagnosed (table 2). All 61 patients had developed a new area of consolidation or nodule, as assessed by a chest radiograph or a CT scan of the thorax. Only 21 (34%) of these 61 patients had a CT scan of the thorax at enrollment into the study. A halo sign was found in 12 patients (all with hematologic disorders and current or previous neutropenia), and either cavitation or evidence of an air crescent sign was seen in 11. *Aspergillus* species was seen or cultured in 33 of 61 probable IA cases. In 18 patients with hematologic disorders, all of whom were or had been neutropenic, typical clinical and radiologic features were not confirmed by direct culture evidence of *Aspergillus.* In 14 (74%) of 19 patients with cerebral disease, the diagnosis was confirmed by surgery (aspiration or biopsy) or at autopsy and in 5 was presumed on the basis of a characteristic clinical course, radiologic findings, and documented disease at another site.

Nature of therapy. Voriconazole was given as primary therapy to 60 (52%) of 116 patients. Of these, 31 (27%) had received no other treatment, and 29 (25%) had received some AmB ($n = 21$), itraconazole ($n = 6$), AmBisome (Gilead Sciences; $n = 2$), Abelcet (The Liposome Company; $n = 2$), or flucytosine ($n = 1$) in low (subtherapeutic) doses for a short duration (e.g., <7 days) or for prophylaxis. Fifty-six patients (48%) received voriconazole as salvage therapy. The specific reason for switching from standard therapy to voriconazole was not captured in the case record form, but clinical failure of the previous regimen was substantially more common than elevated serum creatinine levels. Infections had failed to respond to many different regimens, including AmB ($n = 51$ patients), itraconazole ($n = 19$), AmBisome ($n = 12$), Abelcet ($n = 3$), and Amphocil (AstraZeneca; $n = 1$).

Clinical outcome of treatment. Of the 116 assessable patients, 16 patients (14%) had a complete, 40 (34%) a partial, and 24 (21%) a stable response to voriconazole; the infections of 36 patients (31%) failed to respond to therapy (table 3). An example of a complete response is shown in figure 1. Three patients (all with acute myeloid leukemia [AML] and probable IA who achieved remission of their underlying disease) had a complete response with 8 weeks of therapy; the other 13 patients received at least 13 weeks of therapy for a complete response to occur. Relapse occurred in only 2 patients at 77 and 112 days after 153 and 172 days, respectively, of voriconazole therapy; both of these patients died as a result of IA.

Of the 116 assessable patients, 67 (58%) died, 48 (41%) within 90 days of enrollment, 5 (4%) while receiving treatment after 90 days' therapy, and 14 (12%) >30 days after discontinuing therapy that lasted ⩾90 days. Of the 48 patients who died within 90 days of enrollment, 31 (65%) had infections that failed to respond to voriconazole therapy, 10 patients (21%) were stable, and the infections of 7 patients (15%) partially responded. In those who died while receiving treatment or within 30 days of the end of therapy ($n = 53$), the time to death ranged 1–225 days (median and mean, 30 days). Of these, 31 (59%) died as a result of IA, 21 (40%) as the result of another cause with IA, and 1 without IA (autopsy negative). In the 14 patients who died at least 30 days after the end of treatment, the time to death ranged 38–284 days after enroll-

Table 2. Site (or type) and probability of invasive aspergillosis.

Site of type of disease	Probability of invasive aspergillosis		
	Definite	Probable	Total
Cerebral	14 (74)	5 (26)	19 (16)
Disseminated	5 (83)	1 (17)	6 (5)
Pulmonary	20 (25)	61 (75)	81 (70)
Sinus	4 (80)	1 (20)	5 (4)
Tracheobronchial	3	0	3 (3)
Osteomyelitis	1	0	1 (1)
Hepatosplenic	1	0	1 (1)
Total	48 (41)	68 (59)	116 (100)

NOTE. Data are no. (%) of patients.

Table 3. Response at end of therapy, by site or type of disease or by prior treatment.

Site or type	Response to treatment, no. (%)				Total
	Complete	Partial	Stable	Failure	
Pulmonary and TBR	15 (18)	35 (42)	16 (19)	18 (21)	84
Cerebral	0	3 (16)	5 (26)	11 (58)	19
Disseminated	1 (17)	2 (33)	0	3 (50)	6
Sinus	0	0	2 (40)	3 (60)	5
Other[a]	0	0	1 (50)	1 (50)	2
Previous therapy					
Primary	10 (17)	25 (42)	11 (18)	14 (23)	60 (52)
Salvage	6 (11)	15 (27)	13 (23)	22 (39)	56 (48)
Total	16 (14)	40 (34)	24 (21)	36 (31)	116 (100)

NOTE. TBR, tracheobronchial.

[a] Hepatosplenic aspergillosis (failure) and *Aspergillus* osteomyelitis (stable).

ment (median, 95 days). Among these 14 patients, 3 died of IA and 9 with active IA of another cause, one of reinfection (different pulmonary site) and of relapse of IA. Among those 16 patients with a complete response, only 2 (13%) patients died, one with chronic lymphatic leukemia of pneumonia on day 225 on voriconazole and one with AML of IA relapse 53 days after completing 77 days' treatment with voriconazole. Among the 40 partial responders, 7 died within the first 90 days of enrollment, 4 while receiving therapy ⩾90 days after starting itraconazole, and 5 at least 90 days after treatment, a total of 16 (40%). This compares with 32 deaths among the 36 patients (89%) whose infections failed to respond to therapy; 31 of these deaths occurred within 90 days of enrollment.

Duration of therapy. Intravenous voriconazole was given for periods ranging 1–40 days (mean, 11.5 days) in the 116 patients with IA. Twenty-two patients received ⩽7 days' therapy; in 20 of these patients, the short duration of therapy was a result of their deaths after entry into the study. Orally administered voriconazole was subsequently given to 91 patients (78%) for a mean of 77 days (range, 2–219 days). Patients who had a complete response ($n = 16$) were treated for 54–250 days (median, 133 days). In contrast, patients whose infections failed to respond to therapy received 1–112 days' therapy (median, 20.5 days), 9 received ⩽5 days' therapy, and 12 received ⩽7 days' therapy. The doses of 12 patients were escalated because patients had random plasma concentrations <1000 ng/mL and inadequate clinical response. An improved response was seen in only one patient (with cerebral disease) after the dose was escalated.

Factors that influenced outcome. In terms of underlying disease, patients with hematologic disorders fared best (table 4). Good responses were seen in 58% of the 67 patients with hematologic disorders, compared with 20%–50% response in other groups ($P = .01$). Complete responses were seen exclusively in patients with hematologic disorders, excluding allogeneic HSCT. Precise durations of neutropenia were not recorded. Doses of corticosteroids were not collected.

Patients with pulmonary and tracheobronchial aspergillosis responded better than those with other sites of disease (table 3) ($P < .001$). There were 3 responders with cerebral aspergillosis (16%), and 3 of 6 patients with disseminated disease responded. One of the cerebral cases has been reported elsewhere [21]. Patients with sinus disease responded poorly (40% stable response), but only 5 patients with sinus disease were enrolled in the study.

Those patients with a definite diagnosis fared less well overall: 18 (38%) had a good response, compared with 38 (58%) of those with probable IA ($P = .05$). Patients who died and had an autopsy that showed IA were classified as definite cases, and it is therefore unsurprising that a much higher proportion of definite infections failed to respond to therapy.

Patients treated with voriconazole as salvage therapy did not respond as well as those in whom voriconazole was given as primary therapy (table 3). If good responses are compared between the primary and salvage groups, a statistical difference emerges in favor of primary therapy ($P = .02$). Comparison of survival time by log rank for the 116 assessable patients shows slightly better survival of those initially treated with voriconazole compared with salvage therapy ($P = .12$) (figure 2).

Plasma concentrations of voriconazole were obtained from 122 patients. Trough voriconazole concentrations ranged <100–9700 ng/mL in different patients. Some adverse events were probably attributable to high drug concentrations (see below, "adverse events" section). Five patients (4%) had mean plasma concentrations of voriconazole consistently <250 ng/mL. Three of these 5 patients' infections failed to respond to therapy; 1 patient had a stable response; and 1 patient deteriorated but improved when the dose was escalated, finally

Table 4. Response at the end of therapy, by patient group.

Patient group	Global response, no. (%)				Total
	Complete	Partial	Stable	Failure	
Hematological disorders	16 (24)	23 (34)	10 (15)	18 (27)	67
Allogeneic HSCT	0	6 (26)	8 (35)	9 (39)	23
Solid-organ transplantation	0	3 (50)	2 (33)	1 (17)	6
AIDS	0	1 (20)	0	4 (80)	5
Other	0	7 (47)	4 (27)	4 (27)	15
Total	16 (14)	40 (34)	24 (21)	36 (31)	116 (100)

NOTE. HSCT, hematopoietic stem cell transplant.

achieving a partial response. Six patients had mean concentrations >250 and <500 ng/mL, one due to a marked reduction in voriconazole concentration after therapy with carbamazepine was started on day 7. Responses in these 6 patients were as follows: complete response, 1 patient; partial response, 2 patients; and stable, 2 patients; and 1 patient's infection failed to respond to therapy. These responses are consistent with the whole study population.

Adverse events. As expected in this immunocompromised patient population, the number of adverse events reported was large. Of the 137 patients enrolled in the protocol who received at least 1 dose of drug, 9546 patient-days of exposure to voriconazole were recorded. A total of 623 adverse events (91%) were reported in 125 patients. Of these, only 95 adverse events (15%) were attributed by the investigator to voriconazole. There were 203 serious adverse events in 135 patients, 5 of which were attributed to the drug (hypoglycemia and pneumonitis, abnormal liver function, rashes [$n = 2$], and worsening of psoriasis). The most common adverse events were rash, visual disturbance, and elevated liver function. Four of 12 patients who developed skin rashes discontinued therapy. Twenty patients who developed abnormal liver function (>3 or 5 times the upper limit of normal) were obliged to discontinue therapy by the protocol. Usually this occurred in the first month of therapy, often within the first 10 days. In some, raised transaminase levels were seen; in others, raised alkaline phosphatase levels were seen; and some patients displayed both. Eleven of these patients were patients with allogeneic HSCT, and in 5, the investigator attributed the abnormality to another disease process. Usually the increase was in alkaline phosphatase, but some patients developed hyperbilirubinemia, increased transaminases, or both. γ-glutamyltransferase was not measured.

Six of the 22 patients with plasma concentrations >6000 ng/mL developed abnormal liver function or liver failure. Fifteen (11%) of 137 patients developed abnormal vision, variously described as blurring vision, or as seeing wavy or zigzag lines. These symptoms occurred shortly after dosing and lasted a few minutes. These visual symptoms typically faded with continued dosing, and no patient discontinued therapy for this reason. No permanent visual problems were recorded. Other events possibly attributable to voriconazole were infrequent, and none was severe; these events included nausea ($n = 3$), headache ($n = 2$), dry mouth ($n = 3$), hypercholesteremia ($n = 3$), abnormal taste ($n = 2$), and asthenia ($n = 2$).

One patient with sinus and orbital aspergillosis developed bilateral pneumonitis and hypoglycemia on day 5 of therapy, which required artificial ventilation and from which he did not recover. His plasma concentrations before and after his last dose of voriconazole on day 5 were very high (9700 [trough] to 13,900 ng/mL [peak]), and it is possible that this unexpected event was directly attributable to voriconazole. He had alcoholic cirrhosis, which was diagnosed after death (which occurred 34 days later due to hemorrhage from a liver biopsy). There were 6 other patients with voriconazole concentrations of >10,000 ng/mL (range, 10,102–13,900 ng/mL, recorded on days 4–16 of therapy). Five developed adverse events requiring discontinuation from the study, and 4 died of pulmonary or hepatic causes not attributed to voriconazole.

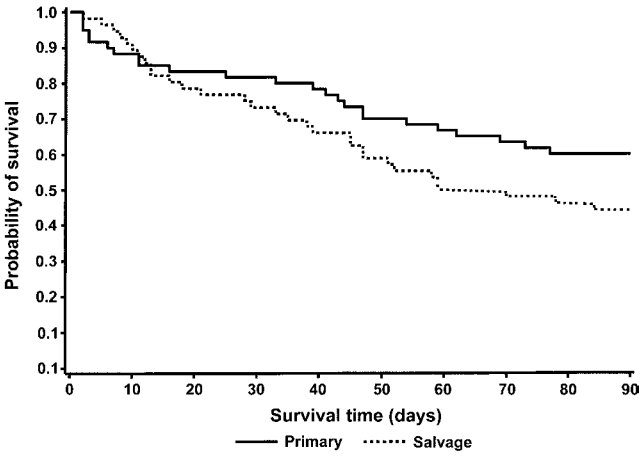

Figure 2. Kaplan-Meier plot of survival to 90 days after enrollment for the 116 assessable patients, according to whether they received voriconazole as primary therapy *(solid line)* or salvage therapy *(dashed line).*

DISCUSSION

Very few prospective therapeutic studies of IA have been performed [5, 8, 20, 22]. To our knowledge, this study is the largest prospective study of an azole in this disease and the first to use an intravenous azole. Overall, the infections of 48% of patients responded, and 31% failed to respond to therapy.

More than 75% of the assessable patients had a hematologic cause for their immunosuppression, including 20% who had had an allogeneic HSCT. Among hematology patients who had not had a HSCT, the response rate was 58% and the failure rate 27%. These data compare favorably with data for treatment with AmB [4, 5, 8, 23] (response rate, 35%) and lipid-associated AmB [9–11, 22]. The 26% partial response rate and 35% failure rate of infections in patients with allogeneic HSCT are a good result compared with AmB therapy, in which a failure rate (and mortality) of 85% is typical [4, 24]. In this study, 35% of the allogeneic HSCT recipients were alive 12 weeks after discontinuation of voriconazole, which is very encouraging.

A response rate of 50% in the 6 solid-organ transplant recipients appears less favorable than with itraconazole [20, 25], but in the present study, 3 of the patients had received liver transplants and 2 had cerebral aspergillosis , both poor prognostic factors [4, 26]. A 20% response rate in the 5 patients with AIDS is consistent with previous experience with itraconazole, AmB, or both [4, 23, 27]. The 47% response rate in the 15 patients in the "other" category in this study appears similar to that seen with itraconazole therapy [25], although the patients in the 2 studies were not matched.

Particularly notable are the 16% response rate with cerebral IA and the 50% response rate with disseminated aspergillosis. These favorable responses are superior to historical data with AmB therapy [4, 26] and consistent with data for itraconazole therapy [23, 26, 28]. The relatively poor responses in patients with sinus disease (60% of their infections failed to respond to therapy) are also consistent with previous data for itraconazole [23, 25] and inferior to AmB therapy (67% response rate in leukemic patients) [4, 11]. Overall, the nature of the patients recruited into the study, with many having difficult-to-treat IA (e.g., 19 with cerebral aspergillosis and 23 with allogeneic HSCT), emphasizes that there was little selection bias in recruitment.

In common with all previous prospective treatment studies, not all the patients had proven (definite) disease. Patients with positive histological results but negative cultures were included as definite cases, following previously established Mycoses Study Group criteria for disease [20]. In Europe, the frequency of non-*Aspergillus* hyaline mold infections is probably substantially less than in the United States [29], and 3 such cases were identified and removed from the analysis of this series. Overall, 71 (61%) of the patients had a positive culture of *Aspergillus.* Of those with pulmonary aspergillosis, 25% had a proven (definite) diagnosis and 75% a probable diagnosis. A halo sign, cavitation, or an air crescent sign [31–36] was found in 23 patients with probable IA. In the 18 patients with hematologic disorders without direct culture evidence of *Aspergillus,* 60% of infections had good responses and 22% failed to respond to therapy, which mirrors results for all 81 patients with pulmonary IA.

In this study, 38% patients with definite cases had a complete or partial response, compared with 33% at 12 weeks and 39% at the end of therapy in the Mycoses Study Group study of itraconazole [20]. In the earlier study, 84% of the patients were definite when identical enrollment criteria for definite cases were used [20]. In the current study, response rates were 20% better in the patients with probable disease than those with definite disease. However, those enrolled in the probable category who later died and had a confirmatory autopsy are assessed as definite cases, in accordance with work elsewhere [20]. In addition, 11 (58%) of 19 of the cerebral cases and 4 (80%) of 5 of the sinus cases were definite at enrollment. Patients in both these categories of infection fared less well than patients with pulmonary infection, 18% of whom were definite at enrollment and 5 of whom were confirmed later (2 at autopsy). Thus, there is a bias toward poorer outcomes in those with definite disease. In addition, late diagnosis carries a poorer outcome [36, 37]. Because it takes time to arrange, undertake, and receive the results of a biopsy, patients enrolled with a definite diagnosis will, on balance, be treated later than those enrolled on CT scan appearances or microbiologic results.

Just over half the patients received voriconazole as primary therapy. Among these patients, 58% of infections responded and 23% failed to respond to treatment. This is clearly a good outcome—and one that is substantially better than any published data for AmB in this disease, given the patient population [4]. It could be argued that the recent data in patients with acute leukemia that uses a comprehensive diagnostic approach [30] has materially contributed to the good results seen in these patients. Although it is true that some of the centers involved in this study used more aggressive diagnostic approaches, only a minority did.

Voriconazole is rapidly absorbed after oral administration [38] and exhibits nonlinear kinetics with disproportionate rises in plasma concentrations with increasing doses. Voriconazole accumulates up to 8-fold after multiple dosing as a result of saturation of its own metabolism. Voriconazole is extensively metabolized by the liver, with <2% of the dose excreted in urine as unchanged form. In vitro studies that used human liver microsomes show that voriconazole is a substrate and an inhibitor of CYP2C9 and CYP2C19 isozymes. Data from volunteer studies have indicated that CYP2C19 makes a large, and CYP3A4 a small, contribution to the metabolism of voriconazole. CYP2C19 exhibits genetic polymorphism, with 3%–5%

of the white population and ~20% of the Asian population proving to be poor metabolizers for CYP2C19 substrates [39] and will have predictably higher plasma levels of voriconazole than those who metabolize these substrates normally. The interpatient variability in this study was ~100-fold, but the intrapatient variability was much less. The terminal phase half-life of voriconazole varies; it is typically at the lower end of 6–24 h after a dose of 200 mg is administered.

The data presented here are consistent with a threshold for response in IA of plasma voriconazole of >250 ng/mL. Three patients, 2 with cerebral disease (stable response) and a patient with AIDS whose infection failed to respond to therapy, received other potentially interacting drugs (carbamazepine, rifampicin, and both rifampicin and phenytoin). Voriconazole metabolism is markedly induced by rifampicin. Even though these drugs were prohibited in the protocol and probably contributed to treatment failure by reducing voriconazole concentrations, they have been included in the analysis of outcome. Four such patients were included in the analysis of response to itraconazole [20] in which similar interaction problems occur [40, 41].

Treatment with voriconazole does carry some risk of toxicity. In most patients, this was trivial or nonexistent. Temporary visual disturbances, skin rash, and abnormal liver function were most frequent but were usually of little consequence. One episode of prolonged hypoglycemia with severe pneumonitis was unexpected and possibly attributable to voriconazole because very high concentrations were documented and no other cause was evident. In volunteers, plasma voriconazole concentrations of >6000 ng/mL were associated with occasional liver function abnormalities (Pfizer Central Research, personal communication). This was also apparent in this study. Given the relative unpredictability of plasma concentrations in patients, measurement of plasma concentrations to identify those with levels at either extreme is appropriate. Guidelines about dose modification for patients with very low or high plasma concentrations need to be developed and validated.

Voriconazole is a potent new antifungal compound that is efficacious in a significant proportion of patients with IA. It is most efficacious as primary therapy. Randomized trials, which are ongoing, will directly address its efficacy relative to AmB. Even earlier diagnosis may improve these results further.

Acknowledgments

We thank our colleagues who enrolled patients and collected data. Peter Donnelly (Nijmegen, the Netherlands), David Hawkins (London), Danika Milatovic (Munich), David Norfolk (Leeds, UK), Jacques Troncy (Lyon, France), Catherine Cordonnier (Creteil, France), Henning Breithaupt (Geissen, Germany), Beryl Oppenheim (Manchester, UK), Wilfried Boehning (Bad Lippspringe, Germany), Dieter Huhn and Stephan Schwarz (Berlin), Roland Mertelsmann (Freiburg, Germany), Matthias Schrappe (Cologne, Germany), Steven Schey (London), Christian Witt (Berlin), Albano del Favaro (Perugia, Italy), Michel Aoun (Brussels), Giuseppe Leone (Rome), San Miguel (Santamarta de Tormes, Spain), Hernandez Navarro (Madrid), Johannes Wandt (Nürnberg, Germany), David Barnard (Birmingham, UK), Claudio Viscoli (Genoa, Italy), J. Diaz Mediavilla (Madrid), Daniele Scevola (Pavia, Italy), E. Rocha (Pamplona, Spain), and Werner Langer (Essen, Germany). We wish to acknowledge contributions from several other personnel at Pfizer who made important contributions to the protocol and study. Contributions to data analysis were made by Fiona Perry, Jane Evans, and David Hanlon and to statistics by Dr. Andrew Vail. The manuscript was prepared by Hilary Gough. In particular, we thank the patients who participated. We dedicate this article to them.

References

1. Denning DW. Invasive aspergillosis. Clin Infect Dis **1998**; 26:781–805.
2. Saraceno JL, Phelps DT, Ferro TJ, Futerfas R, Schwartz DB. Chronic necrotisong pulmonary aspergillosis: approach to management. Chest **1997**; 112:541–8.
3. Groll AH, Shah PM, Mentzel C, et al. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J Infect **1996**; 33:23–32.
4. Denning DW. Therapeutic outcome of invasive aspergillosis. Clin Infect Dis **1996**; 23:608–15.
5. Bowden R, Chandrasekar P, White M, et al. A double-blind randomised controlled trial of Amphocil (ABCD) versus amphotericin B (AmB) for treatment of invasive aspergillosis in immunocompromised patients [abstract 091]. In: Program and abstracts of the International Immunocompromised Host Society Meeting (Davos, Switzerland). Dacula, Georgia: International Immunocompromised Host Society, **1998**.
6. Ribaud P, Denning DW. Allogeneic bone marrow transplantation. Updated June 1998; available at: http://www.aspergillus.man.ac.uk/secure/treatment_methods/alloHSCT.htm.
7. Gallis HA, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience. Rev Infect Dis **1990**; 12:308–29.
8. Verweij PE, Donnelly JP, Kullberg BJ, Meis JFGM, de Pauw BE. Amphotericin B versus amphotericin B plus 5-flucytosine: poor results in the treatment of proven systemic mycoses in neutropenic patients. Infection **1994**; 22:81–5.
9. 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.
10. Mills W, Chopra R, Linch DC, et al. Liposomal amphotericin B in the treatment of fungal infections in neutropenic patients: a single-centre experience of 133 episodes in 116 patients. Br J Haematol **1994**; 86: 754–60.
11. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis **1998**; 26:1383–96.
12. Oakley KL, Moore CB, Denning DW. In vitro activity of voriconazole against *Aspergillus* spp. and comparison with itraconazole and amphotericin B. J Antimicrob Chemother **1998**; 42:91–4.
13. Verweij PE, Mensink M, Rijs AJMM, Donnelly JP, Meis JFGM, Denning DW. In vitro activities of amphotericin B, itraconazole, and voriconazole against 150 clinical and environmental *Aspergillus fumigatus* isolates. J Antimicrob Chemother;**1998**; 42:389–92.

14. Cuenca-Estrella M, Rodriguez-Tudela J-L, Mellado E, Martinez-Suarez JV, Monzon A. Comparison of the in vitro activity of voriconazole (UK-109,496), itraconazole and amphotericin B against clinical isolates of *Aspergillus fumigatus.* J Antimicrob Chemother **1998**; 42:531–3.
15. Murphy M, Bernard EM, Ishimaru T, Armstrong D. Activity of voriconazole (UK-109,496) against clinical isolates of *Aspergillus* species and its effectiveness in an experimental model of invasive aspergillosis. Antimicrob Agents Chemother **1997**; 41:696–8.
16. Martin MV, Yates J, Hitchcock CA. Comparison of voriconazole (UK-109,496) and itraconazole in prevention and treatment of *Aspergillus fumigatus* endocarditis in guinea pigs. Antimicrob Agent Chemother **1997**; 41:13–6.
17. George D, Miniter P, Andriole VT. Efficacy of UK-109,496, a new azole antifungal agent, in an experimental model of invasive aspergillosis. Antimicrob Agents Chemother **1996**; 40:86–91.
18. Kirkpatrick WR, McAtee RK, Fothergill AW, Rinaldi MG, Patterson TF. Efficacy of voriconazole in a guinea pig model of disseminated invasive aspergillosis. Antimicrob Agents Chemother **2000**; 44:2865–8.
19. Denning DW, Marinus A, Cohen J, et al., and the EORTC Invasive Fungal Infections Cooperative Group. An EORTC multicentre prospective survey of invasive aspergillosis in cancer patients: diagnosis and therapeutic outcome. J Infect **1998**; 37:173–80.
20. Denning DW, Lee JY, Hostetler JS, et al. NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy of invasive aspergillosis. Am J Med **1994**; 97:135–44.
21. Schwartz S, Milatovic D, Thiel E. Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukaemia. Br J Haematol **1997**; 97:663–5.
22. Ellis M, Spence D, de Pauw B, et al. An EORTC international multicenter randomised trial (EORTC number 19923) comparing two dosages of liposomal amphotericin B for treatment of invasive aspergillosis. Clin Infect Dis **1998**; 27:1406–12.
23. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2121 published cases. Rev Infect Dis **1990**; 12:1147–201.
24. Ribaud P, Chastang C, Latge JP, et al. Outcome and prognostic factors of invasive aspergillosis after allogeneic bone marrow transplantation. Clin Infect Dis **1999**; 28:322–30.
25. Stevens DA, Lee JY. Analysis of compassionate use itraconazole therapy for invasive aspergillosis by NIAID mycoses study group criteria. Arch Intern Med **1997**; 157:1857–62.
26. Pagano L, Ricci P, Montillo M, et al. Localization of aspergillosis to the central nervous system among patients with acute leukemia: report of 14 cases. Gruppo Italiano Malattie Ematologiche dell'Adulto Infection Program. Clin Infect Dis **1996**; 23:628–30.
27. Holding KJ, Dworkin MS, Wan PT, et al. Aspergillosis among people infected with human immunodeficiency virus: incidence and survival. Clin Infect Dis **2000**; 31:1253–7.
28. Sanchez C, Mauri E, Dalmau D, Quintana S, Aparicio A, Garau J. Treatment of cerebral aspergillosis with itraconazole. Do high doses improve the prognosis? Clin Infect Dis **1995**; 21:1485–7.
29. Pagano L, Ricci P, Nosari A, et al. Gimema Infection Program (Gruppo Italiano Malattie Ematologiche dell'Adulto). Fatal haemoptysis in pulmonary filamentous mycosis: an underevaluated cause of death in patients with acute leukaemia in haematological complete remission. A retrospective study and review of the literature. Br J Haematol **1995**; 89:500–5.
30. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. J Clin Oncol **1997**; 15:139–47.
31. Moro M, Galvin JR, Barloon TJ, Gingrich RD, Stanford W. Fungal pulmonary infections after bone marrow transplantation: evaluation with radiography and CT. Radiology **1991**; 178:721–6.
32. 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.
33. Blum U, Windfuhr M, Buitrago-Tellez C, Sigmund G, Herbst EW, Langer M. Invasive pulmonary aspergillosis: MRI, CT, and plain radiographic findings and their contribution for early diagnosis. Chest **1994**; 106:1156–67.
34. Primack SL, Hartman TE, Lee KS, Müller KS. Pulmonary nodules and the CT halo sign. Radiology **1994**; 190:513–5.
35. Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high resolution computed tomography. J Clin Oncol **1999**; 17:796–805.
36. Aisner J, Wiernik PH, Schimpff SC. Treatment of invasive aspergillosis: relation of early diagnosis and treatment to response. Ann Intern Med **1977**; 5:539–43.
37. von Eiff M, Zuhlsdorf M, Roos N, Hesse M, Schulten R, van de Loo J. Pulmonary fungal infections in patients with hematological malignancies—diagnostic approaches. Ann Hematol **1995**; 70:135–41.
38. Patterson BE, Coates PE. UK-109,496, a novel, wide-spectrum triazole derivative for the treatment of fungal infections: pharmacokinetics in man [abstract F78]. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **1995**:126.
39. Balian JD, Sukhova N, Harris JW, et al. The hydroxylation of omeprazole correlates with S-mephenytoin metabolism: a population study. Clin Pharmacol Ther **1995**; 57:662–9.
40. Tucker RM, Hanson LH, Denning DW, et al. The interaction of azoles with rifampin, phenytoin and carbamazepine: in vitro and clinical observations. Clin Infect Dis **1992**; 14:165–74.
41. Kramer MR, Marshall SE, Denning DW, et al. Drug interaction between cyclosporin and itraconazole in heart and heart-lung and lung transplant recipients with fungal disease. Ann Intern Med **1990**; 113:327–9.