The following full text is a publisher’s version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/185528

Please be advised that this information was generated on 2019-07-24 and may be subject to change.
VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS


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.)

Copyright © 2002 Massachusetts Medical Society.

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. 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. Amphotericin B is associated with multiple side effects, which may be ameliorated with the use of lipid formulations.

Voriconazole is a new broad-spectrum triazole that is active in vitro against various yeasts and molds, including aspergillus species. A noncomparative study demonstrated a response rate of 48 percent among patients with acute invasive aspergillosis. 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, and from 5 percent to more than 20 percent in high-risk groups.

From the Hôpital de Hautepierre, Strasbourg, France (R.H.); the University of Manchester, Manchester, United Kingdom (D.W.D.); the University of Texas Health Science Center, San Antonio (T.E.P.); the National Institute of Allergy and Infectious Diseases, Bethesda, Md. (J.E.B.); Massachusetts General Hospital, Boston (R.E.G.); Châtel, Campus Vochow-Klinikum, Berlin, Germany (J.-W.O.); Medizinische Universitätshse, Freiburg, Germany (W.V.K.); Fred Hutchinson Cancer Research Center, Seattle (K.A.M.); Hôpital Saint-Louis, Paris (P.R.); Institut Pasteur, Paris (O.L.); the European Organisation for Research and Treatment of Cancer, Brussels, Belgium (R.S.); Brigham and Women’s Hospital, Boston (R.H.R.); the University of Florida College of Medicine, Gainesville (J.R.W.); the University of California at San Diego, San Diego (P.S.); Hôpital du Bocage, Dijon, France (C.D., D.C.); University Hospital Benjamin Franklin, Berlin, Germany (E.T.); Wayne State University School of Medicine, Detroit (P.F.T.); Pfizer Global Research and Development, New York (M.R.H., H.T.S.); and Sandwich, United Kingdom (P.F.T.); and University Medical Center, Nijmegen, the Netherlands (B.P.). Address reprint requests to Dr. Herbrecht at the Département d’Hématologie et d’Oncologie, Hôpital de Hautepierre, Ave. Molière, 67098 Strasbourg CEDEX, France, or at raoul.herbrecht@chu-strasbourg.fr.

*Other members of the study are listed in the Appendix.

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-crecent sign on a computed tomographic (CT) scan of the lung 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; 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.

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-
erect 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 study: 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>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>VORICONAZOLE GROUP (N=144)</th>
<th>AMPHOTERICIN B GROUP (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>48.5</td>
<td>50.5</td>
</tr>
<tr>
<td>Male</td>
<td>98 (68.1)</td>
<td>89 (66.9)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (31.9)</td>
<td>44 (33.1)</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>70.4</td>
<td>71.0</td>
</tr>
<tr>
<td>Underlying condition — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>58 (40.3)</td>
<td>60 (45.1)</td>
</tr>
<tr>
<td>Other hematologic cancer</td>
<td>17 (11.8)</td>
<td>18 (13.5)</td>
</tr>
<tr>
<td>Solid-organ transplantation</td>
<td>9 (6.2)</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>9 (6.2)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>65 (45.1)</td>
<td>60 (45.1)</td>
</tr>
<tr>
<td>No</td>
<td>79 (54.9)</td>
<td>73 (54.9)</td>
</tr>
</tbody>
</table>

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

---

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

<table>
<thead>
<tr>
<th>TYPE OF EVENT</th>
<th>VORICONAZOLE GROUP (N=194)</th>
<th>AMPHOTERICIN B GROUP (N=185)</th>
<th>P VALUE†</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>2</td>
<td>19</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>1</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>Other metabolic event (hypoglycemia, hypoalbuminemia, worsening of adrenal insufficiency, or metabolic acidosis)</td>
<td>4</td>
<td>2</td>
<td>0.69</td>
</tr>
<tr>
<td>Hepatic abnormalities</td>
<td>7</td>
<td>4</td>
<td>0.54</td>
</tr>
<tr>
<td>Systemic event (fever, chills, anaphylaxis, asthenia, or myalgia)</td>
<td>1</td>
<td>7</td>
<td>0.03</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>4</td>
<td>0.06</td>
</tr>
<tr>
<td>Digestive tract event (nausea, vomiting, dysesthesia, abdominal pain, or pancreatitis)</td>
<td>4</td>
<td>1</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>0</td>
<td>0.54</td>
</tr>
<tr>
<td>Hematologic event (thrombocytopenia, cosinophilia, or exacerbation of paroxysmal nocturnal hemoglobinuria)</td>
<td>2</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Neurologic event (progressive encephalopathy, hallucinations, or Guillain–Barré syndrome)</td>
<td>2</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Visual events</td>
<td>2</td>
<td>0</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*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.
patients receiving voriconazole, they were transient and generally mild or moderate, and they seldom re-
sulted 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 am-
photericin B as initial therapy for invasive aspergillosis,
in terms of response rate, survival rate, and safety.

Supported by grants from Pfizer.

Presented in part at the 41st International Conference on Antimicrobial

Drs. Herbrecht, Patterson, Bennett, Marr, de Pauw, Rubin, and Wingard
have served as consultants for Pfizer. Drs. Hodges, Schlamm, and Troke
are employees of Pfizer.

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. Aur (Düsseldorf, Germany), M. Björkholm (Stockholm, Swe-
den), K.L. Blanchard (Sheerwater, 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, Germa-
y), J.Y. Cahn (Besançon, France), A. Calmaggi (La Plata, Argentina), J.M.
Cisneros (Sevilla, Spain), C. Cordonnier (Créteil, France), J. Daly (Worce-
ter, Mass.), C.A. Da Cunha (Curitiba, Brazil), R. De Rock (Antwerp, Bel-
gium), A. Del Favero (Perugia, Italy), J. Diaz Mediavilla (Madrid), M.C.
Dignani (Buenos Aires, Argentina), C. Doyen (Voor, Belgium), J.S. Dum-
mer (Nashville), B. Dupont (Paris), M. Egedy (Kaposvar, Hungary), D.
Engelhard (Jerusalem, Israel), G. Fatkenheuer (Cologne, Germany), R.
Feld (Toronto), D. Fure (Lyons, France), G. Furiotoni (Pescara, Italy), P.
Garber (Ottawa, Ont.), Z. Gazsymy (Gyor, Hungary), K. Godder (Co-
lumbia, S.C.), D. Graham (Springfield, Ill.), A. Gratwohl (Basel, Switzer-
land), R. Greenberg (Lexington, Ky.), K. High (Winston-Salem, N.C.), F.
Jacobs (Brussels, Belgium), V. Kremery (Bratislava, Slovakia), P. Kornar
(Washington, D.C.), W. Langer (Essen, Germany), M. Laverdière (Mon-
tréal), P. Ljungman (Huddinge, Sweden), H. Lode (Berlin, Germany), A.
Louie (Albany, NY), D. Maki (Madison, Wis.), J. Marie (Paris), D.E.
Marriott (Sydney, Australia), D.S. McKinsey (Kansas City, Mo.), R.
Mer-
telmann (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. Perfact
(Durham, N.C.), J. Pottage (Chicago), V. Ranza (New Delhi, India), J. Rein-
hardt (Newark, Del.), S. Richardson (Toronto), L. Rickman (San Diego,
Calif.), M. Ruhnke (Berlin, Germany), I. Salit (Toronto), W.M. Scheld
(Chattanooga, Va.), S. Schuler (Dresden, Germany), M. Schuster (Phil-
adelphia), R. Schwertzfeiger (Wiesbaden, Germany), S.D. Shafar (Edmon-
ton, Alta.), B. Simmons (Memphis, Tenn.), M. Slavin (Parkville, Australia),
M. Sokol-Anderson (St. Louis), P. Tebas (St. Louis), C. Tsoukas (Montre-
al), A. Ullmann (Mainz, Germany), J. Van Burik (Minneapolis), J.W. Van't
Wouw (Leiden, the Netherlands), E.C. Vinaya Kumar (Hyderabad, India),
P. Volkow-Fernandez (Mexico City, Mexico), C. Wallrauch (Munich, Ger-
many), 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. Ostmann, T.F. Patterson, P. Ribaud, R.H. Rubin, P.
Stark, J.R. Wingard.

Data and Safety Monitoring Boards: D.G. Altman (Oxford, United King-
dom), J. Cohen (London), R.J. Duma (Daytona Beach, Fla.), F. Meunier
(Brussels, Belgium), R.B. Pollard (Galveston, Tex.), A.S. Sugar (Boston),
J. Verter (Rockville, Md.), J. Witter (Washington, D.C.); Voriconazole team

REFERENCES

disease spectrum, treatment practices, and outcomes. Medicine (Baltimore)
icity in patients treated with amphotericin B for suspected or proven as-
formulations: pharmacologic characteristics, clinical efficacy, and tolerabil-
7. Espinel-Ingroff A. In vitro fungicidal activities of voriconazole, itraco-
zole, and amphotericin B against opportunistic monilial and dema-
8. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of vori-
conazole in the treatment of acute invasive aspergillosis. Clin Infect Dis
9. Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary as-
pergillosis in acute leukemia: characteristic findings on CT, the CT halo
10. Freedman LS, White SJ. On the use of Pocock and Simon’s method
for balancing treatment numbers over prognostic factors in the controlled
11. Ellis M, Spence D, de Pauw B, et al. An EORTC international multi-
center randomized trial (EORTC number 19923) comparing two dosages
of liposomal amphotericin B for treatment of invasive aspergillosis. Clin In-
solution vs. amphotericin B as therapy for invasive aspergillosis. Clin Infect
Dis 1997;24:635-42.
liposomal amphotericin B for empirical antifungal therapy in patients with

Copyright © 2002 Massachusetts Medical Society.