Voriconazole for Invasive Bone Aspergillosis: A Worldwide Experience of 20 Cases

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Background. Bone aspergillosis remains a rare but potentially devastating fungal disease. Although voriconazole is effective for invasive pulmonary aspergillosis, evidence of its efficacy for aspergillosis located in bone is limited.

Methods. We report our experience with voriconazole in 4 cases of invasive bone aspergillosis. In addition, all cases of probable and definite bone aspergillosis from the Pfizer clinical database were reviewed and analyzed to determine the safety and efficacy of voriconazole treatment. Global response was evaluated at the end of therapy on the basis of a composite assessment of overall clinical, radiological, and mycological responses.

Results. Twenty patients are described, of whom 18 had definite bone involvement diagnosed (spondylodiskitis in 9, sternum/rib osteomyelitis in 6, and peripheral bone involvement in 5). Of 20 patients, 14 were immunocompromised. Oral or intravenous voriconazole was given as salvage therapy for 18 patients; 2 patients received voriconazole as first-line therapy. Median duration of voriconazole treatment was 83.5 days (range, 4–395 days). Global response at end of therapy was satisfactory in 11 (55%) of 20 patients, including complete responses in 4 patients and partial responses in 7 patients; there were no relapses of infection in the 4 patients with complete response to therapy with voriconazole. Treatment was generally well tolerated.

Conclusions. Long-term voriconazole treatment is a new therapeutic option for invasive aspergillosis with bone involvement.

Bone infections in patients with invasive aspergillosis are rare but often require prolonged antifungal treatment [1, 2]. The most frequent sites include vertebral osteomyelitis (spondylodiskitis) or diskitis alone and long-bone infections [2]. Although some cases may be cured by surgical intervention alone, systemic antifungal therapy is generally required. Until recently, amphotericin B remained the “gold standard” treatment for invasive aspergillosis [3], despite the suboptimal responses [4] and toxicity [5, 6] associated with this drug. Penetration of amphotericin B into bone tissues is also poor [3]. Itraconazole has been used to treat a limited number of cases of bone aspergillosis [7, 8], although the unpredictable bioavailability of the oral capsules [9] and the emergence of resistant strains [10] may limit the efficacy of this drug [11]. A combination of amphotericin B, caspofungin, and surgical intervention was used to treat a case of Aspergillus osteomyelitis and diskitis successfully [12].

Voriconazole is fungicidal against Aspergillus [13–15] and is effective as first-line and salvage therapy in patients with invasive aspergillosis [16–18]. Voriconazole has excellent tissue penetration, including penetration into the CNS [19], and although its penetration into bone tissue has not yet been described, case reports have described its successful use to treat bone infections due to Aspergillus species [20, 21] and Scedosporium species [22, 23]. We report 4 cases of bone aspergillosis treated with voriconazole and the results for 16 other patients with bone aspergillosis from the voriconazole clinical database.
**PATIENTS AND METHODS**

Data on patients with definite or probable invasive aspergillosis and bone involvement were selected retrospectively from a global database of information on patients treated with voriconazole during the period of January 1994 through June 1999. The certainty of diagnosis was reconfirmed by 2 infectious disease physicians (H.M. and O.L.) on the basis of European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria [24]. Given the retrospective nature of this analysis and the small number of cases, statistical analysis was limited to descriptive methods.

Definite diagnoses of bone aspergillosis were considered in patients with cultures of bone tissue or contiguous abscesses positive for *Aspergillus* species or histological evidence of bone aspergillosis. Probable diagnoses of bone aspergillosis were made for patients who had clinical and/or radiological evidence of involvement of any bone, together with histologically and/or mycologically confirmed invasive aspergillosis, with no alternative cause of bone infection.

Voriconazole was administered intravenously (loading dose of 6 mg/kg q12h on day 1, followed by 4 mg/kg q12h), with the option to switch to oral therapy (200 mg b.i.d.). When therapy was initiated with oral voriconazole, a loading dose of 400 mg b.i.d. was used on day 1, followed by 200 mg b.i.d. for patients who weighed ≥40 kg. In all patients, dose escalations and reductions were allowed in cases of insufficient clinical response or intolerance, respectively.

For each patient, response to therapy was assessed by local investigators at the end of therapy on the basis of clinical, radiological, and mycological responses. Global response (not based solely on the response of bone localizations of aspergillosis) was classified as “complete response,” “partial response,” “stable disease,” or “failure,” as described previously [17]. Complete or partial responses were categorized as “satisfactory” outcomes; stable disease or failures were “unsatisfactory.” All adverse events (AEs) and laboratory abnormalities that arose during treatment and follow-up were recorded, and their relationship to voriconazole was systematically determined.

**RESULTS**

**Patient demographic characteristics.** A total of 322 patients in the database had definite or probable invasive aspergillosis; 18 had bone involvement and were included in the present analyses. Two patients with data from other sources (one was treated in the compassionate program after database closure, and the other was treated after voriconazole was licensed) were included. Thus, a total of 20 patients were analyzed. Seventeen were male, and 3 were female; the median age was 43 years (range, 4–78 years). Some of these cases have been reported in part elsewhere [16, 17, 25]. The demographic characteristics and underlying conditions for patients are shown in Table 1, and more detailed case reports for the first 4 patients are presented below in Case Reports.

All but 6 patients had acquired or congenital immunodeficiency, and the most common underlying condition was chronic granulomatous disease (CGD; 5 patients). Ten cases occurred as a result of hematogenous spread, 4 were due to direct extension of infections from the lungs or sinuses, and 3 occurred after localized trauma or surgical intervention (2 cases of infected open fractures and 1 case of sternal infection after heart transplantation). In 3 cases, we were unable to identify the exact mechanism of spread of infection.

**Nature of infection.** Among the 18 patients with definite bone aspergillosis, 15 had positive results of cultures or histological tests of bone tissue specimens, and 3 had positive results for contiguous abscesses by culture. All cases were monomicrobial, and the species isolated included *Aspergillus fumigatus* (n = 15), *Aspergillus terreus* (n = 2), *Aspergillus versicolor* (n = 1), and *Aspergillus nidulans* (n = 1). In 1 case, the *Aspergillus* species was not identified.

The most common presentation was spondylodiskitis (9 patients), and 1 patient had disseminated aspergillosis with bone marrow involvement. Bone was the only site of infection in 10 patients. All cases were regarded as disseminated infections, because each patient presented with ≥2 noncontiguous lesions.

**Treatment.** Eighteen patients (90%) experienced treatment failure or did not tolerate antifungal therapy before receiving voriconazole treatment (Table 1). Twelve patients received initial therapy with intravenous voriconazole, and 7 were later switched to the oral formulation. Eight patients received oral voriconazole only (Table 1). Median duration of voriconazole therapy was 83.5 days (range, 4–395 days). Five patients received voriconazole therapy for <15 days; 3 of these patients died at the end of therapy (1 died of progression of aspergillosis, 1 died of myocardial infarction, and 1 died of pneumonia). Seven patients required surgical intervention.

**Response at end of therapy.** At the end of therapy, 11 (55%) of 20 patients had a satisfactory response to voriconazole (4 complete and 7 partial responses). Of 9 patients with unsatisfactory response at the end of therapy, 2 had stable disease, 2 discontinued treatment because of AEs, 1 experienced treatment failure, and 4 died (1 died of progression of cerebral aspergillosis, 2 died of bacterial pneumonia, and 1 died of sepsis and toxemia).

**Response by Underlying Condition**

Of 6 patients with normal immune function, 5 responded satisfactorily to voriconazole (3 had complete responses, and 2 had partial responses). Treatment failed for 1 patient, although this patient only received voriconazole for 4 days. In contrast, the 14 immunocompromised patients included 6 who had sat-
**Table 1. Patient demographics, infection sites, antifungal therapy, and global response at end of therapy.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Underlying condition or risk factor</th>
<th>Sex/age, years</th>
<th>Bone site</th>
<th>Radiological finding(s)</th>
<th>Other sites of infection</th>
<th>Aspergillus species</th>
<th>Prior therapy</th>
<th>Duration of voriconazole therapy, days (route)</th>
<th>EOT response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/76</td>
<td>Male/76</td>
<td>Spine</td>
<td>Spondylodiskitis with epiduritis</td>
<td>None</td>
<td>A. fumigatus</td>
<td>Itra, AmB</td>
<td>30 (iv), 356 (po)</td>
<td>Complete</td>
</tr>
<tr>
<td>2</td>
<td>M/46 $^{a}$</td>
<td>Male/46</td>
<td>Right wrist</td>
<td>Osteitis</td>
<td>None</td>
<td>A. terreus</td>
<td>None</td>
<td>93 (po)</td>
<td>Complete</td>
</tr>
<tr>
<td>3</td>
<td>M/43</td>
<td>Male/43</td>
<td>Femur and fibula</td>
<td>Osteitis</td>
<td>None</td>
<td>A. fumigatus</td>
<td>AmB and Itra</td>
<td>80 (po)</td>
<td>Partial</td>
</tr>
<tr>
<td>4</td>
<td>M/31</td>
<td>Male/31</td>
<td>Lungs, skin</td>
<td>Osteitis</td>
<td>Not known</td>
<td>A. fumigatus</td>
<td>AmB, Itra</td>
<td>83 (po)</td>
<td>Complete</td>
</tr>
<tr>
<td>5</td>
<td>M/55</td>
<td>Male/55</td>
<td>Ribs</td>
<td>None</td>
<td>None</td>
<td>A. fumigatus</td>
<td>Itra</td>
<td>72 (iv), 61 (po)</td>
<td>Complete</td>
</tr>
<tr>
<td>6</td>
<td>M/56 $^{b}$</td>
<td>Male/56</td>
<td>None (immunocompetence)</td>
<td>Spine (DS-D9)</td>
<td>Ribs, spine (DS-D9)</td>
<td>A. fumigatus</td>
<td>None</td>
<td>130 (iv), 166 (po)</td>
<td>Partial</td>
</tr>
<tr>
<td>7</td>
<td>M/55</td>
<td>Male/55</td>
<td>None (immunocompetence)</td>
<td>Sinus</td>
<td>None</td>
<td>A. fumigatus</td>
<td>None</td>
<td>7 (iv), 301 (po)</td>
<td>Complete</td>
</tr>
<tr>
<td>8</td>
<td>M/58</td>
<td>Male/58</td>
<td>Cervical and thoracic spine</td>
<td>Chronic spondylodiskitis with epiduritis</td>
<td>Lung, liver abscesses</td>
<td>A. fumigatus</td>
<td>Itra, FNC, lipid AmB</td>
<td>17 (po)</td>
<td>Partial</td>
</tr>
<tr>
<td>9</td>
<td>M/61</td>
<td>Male/61</td>
<td>Heart transplant</td>
<td>AML</td>
<td>None</td>
<td>A. fumigatus</td>
<td>Itra, AmB</td>
<td>47 (po)</td>
<td>Failure</td>
</tr>
<tr>
<td>10</td>
<td>M/35</td>
<td>Male/35</td>
<td>Mandibula</td>
<td>Osteomyelitis</td>
<td>None</td>
<td>A. fumigatus</td>
<td>Itra, AmB</td>
<td>127 (po)</td>
<td>Failure</td>
</tr>
<tr>
<td>11</td>
<td>M/40</td>
<td>Male/40</td>
<td>Spine (L3-L5)</td>
<td>Spondylodiskitis with epiduritis</td>
<td>Lung, liver abscesses</td>
<td>A. fumigatus</td>
<td>None</td>
<td>4 (iv)</td>
<td>Failure</td>
</tr>
<tr>
<td>12</td>
<td>M/47</td>
<td>Male/47</td>
<td>Diabetic mellitus</td>
<td>Osteomyelitis</td>
<td>None</td>
<td>A. fumigatus</td>
<td>Itra, AmB</td>
<td>11 (iv)</td>
<td>Failure</td>
</tr>
<tr>
<td>13</td>
<td>M/45</td>
<td>Male/45</td>
<td>Conception</td>
<td>Osteomyelitis</td>
<td>None</td>
<td>A. fumigatus</td>
<td>None</td>
<td>17 (po)</td>
<td>Failure</td>
</tr>
<tr>
<td>14</td>
<td>M/47</td>
<td>Male/47</td>
<td>Mandibula</td>
<td>Osteomyelitis</td>
<td>None</td>
<td>A. fumigatus</td>
<td>Itra, AmB</td>
<td>13 (iv)</td>
<td>Failure</td>
</tr>
<tr>
<td>15</td>
<td>M/45</td>
<td>Male/45</td>
<td>Spine (L3-L5)</td>
<td>Spondylodiskitis with epiduritis</td>
<td>Lung, liver abscesses</td>
<td>A. fumigatus</td>
<td>None</td>
<td>12 (iv)</td>
<td>Failure</td>
</tr>
<tr>
<td>16</td>
<td>M/47</td>
<td>Male/47</td>
<td>Diabetes melitus</td>
<td>Osteomyelitis</td>
<td>None</td>
<td>A. fumigatus</td>
<td>Itra, AmB</td>
<td>14 (iv)</td>
<td>Failure</td>
</tr>
</tbody>
</table>

**NOTE.**
- ALL: acute lymphocytic leukemia; AmB, amphotericin B; AML, acute myelogenous leukemia; CGD, chronic granulomatous disease; EOT, end of therapy; FNC, fluconazole; G-CSF, granulocyte colony-stimulating factor; Itra, itraconazole; lipid AmB, lipid-associated formulation of amphotericin B; Tero, terbinafine.
- $^{a}$ Patient described by Dupont et al. [26];
- $^{b}$ Patient described by Perfect et al. [17];
- $^{c}$ Patient described by Denning et al. [16].
isfactory responses (complete response for 1 and partial responses for 5) and 8 who had unsatisfactory responses (2 had stable disease, and 6 experienced treatment failure).

Response by Duration of Therapy
The 11 patients with satisfactory outcomes received voriconazole for a median duration of 180 days (range, 77–395 days). The 9 patients with unsatisfactory responses received voriconazole therapy for 14 days (range, 4–127 days).

Surgery and Response
Of 7 patients who required surgery in addition to voriconazole therapy, 4 (57%) had a satisfactory response at the end of therapy (3 had partial responses, and 1 had a complete response), and 3 (43%) experienced treatment failure. Of the 13 patients for whom surgical intervention was not required, outcomes were satisfactory for 7 patients (54%; including 3 who had complete responses and 4 who had partial responses), and there were 6 treatment failures (46%).

Safety
Twelve patients experienced ≥1 AE that was determined by the investigators to be related to voriconazole use, including increased liver function test values (5 patients), skin rash (5 patients), visual abnormalities (4 patients), and nausea (2 patients). Most AEs were mild to moderate in severity and resolved without discontinuation of therapy. Two patients (1 with increased liver function test values and 1 with skin rash) discontinued voriconazole because of AEs. Four patients died at the end of therapy, and 3 others died after the end of therapy (1 died of respiratory failure 62 days after completing 47 days of oral voriconazole therapy, 1 died of seizures 63 days after oral voriconazole therapy was discontinued because of increased liver function test values, and 1 died of end-stage AIDS).

CASE REPORTS

Patient 1. A 76-year-old immunocompetent man was hospitalized in April 2000 for weight loss (10 kg) associated with a fever of unknown origin and a high erythrocyte sedimentation rate. He had been treated for pulmonary tuberculosis in 1954.

Despite extensive investigations, a diagnosis of systemic inflammatory disease, neoplasia, or relapse of tuberculosis could not be made. Bronchoscopy and chest radiograph findings were normal, and the results of fungal cultures of bronchoalveolar lavage specimens were negative. The results of serological tests for Aspergillus—including hemagglutination, electrophoresis, and immunoelectrophoresis—were positive, and high concentrations of Aspergillus galactomannan (5.6 and 6.3 ng/mL; normal value, <1.5 ng/mL) were detected in 2 consecutive serum samples with a commercial assay (Platelia Aspergillus; Bio-Rad).

Itraconazole (400 mg q.d.) was added to presumptive antituberculosis treatment, with no apparent effect on clinical symptoms. One month later, the patient presented with tetraplegia related to a compression of the spinal cord secondary to spondylodiskitis involving C5 to T2. A vertebral biopsy was performed, revealing sepsate and dichotomously branched hyphae, and cultures of specimens grew A. fumigatus. Therapy was switched to amphotericin B deoxycholate, but after 3 weeks of treatment with no apparent response, this was discontinued (total dose, 1.2 g). The extent of cervical spondylodiskitis and epiduritis due to A. fumigatus at this time is indicated in figure 1A.
Intravenous voriconazole therapy was initiated, which was switched to the oral formulation after 1 month. Neurological signs improved after 1 month of voriconazole therapy, and 5 months later (in January 2001), _Aspergillus_ galactomannan was no longer detectable in serum samples, and the findings of MRIs were normal (figure 1B). Voriconazole therapy was well tolerated, except for mild hepatic events, which resolved after a dose reduction to 150 mg b.i.d. Voriconazole therapy was discontinued in August 2001, following a complete response to therapy. As of March 2004, the patient was alive, with no neurological sequelae; the results of tests for serum galactomannan remain negative.

**Patient 2.** A 46-year-old immunocompetent man was admitted to the intensive care unit in October 1994 after a motorcycle accident that resulted in wrist dislocation and an open fracture of the right metacarpus. Orthopedic treatment consisted of implantation of pins into the metacarpal bones and a screw in the scaphoid bone. Three days later, an infection developed at the operative site, with edema, skin necrosis, and intense pain. Treatment with broad-spectrum antibiotics was ineffective, and the patient underwent surgical debridement and removal of necrotic tissue. Histological examination of bone fragments revealed invading septate hyphae, and cultures grew _A. terreus_. The MICs of amphotericin B and itraconazole were 1 mg/L and 0.06 mg/L, respectively. _Aspergillus_ antibodies were not detected in the serum specimen, and there was no apparent dissemination of aspergillosis.

The patient was enrolled in a clinical trial involving invasive aspergillosis [26] and received oral voriconazole (200 mg b.i.d.) as primary antifungal therapy. Cultures of skin lesion specimens were positive for _Aspergillus_ species on day 7 of treatment, and 1 culture also had positive results on day 14; results of subsequent cultures were negative. A marked improvement in clinical symptoms was noticed after 14 days of voriconazole therapy. By day 38 of antifungal treatment, cultures and histological tests (of nail, tissue biopsy, and bone splinter specimens) were negative for fungi. Mild visual disturbances and an increase in the alkaline phosphatase level were reported, resulting in a reduction in the dosage of voriconazole to 150 mg b.i.d. These events resolved without sequelae within 3 months after the end of therapy, when the patient was determined to have had a complete response to voriconazole treatment. A final operation was performed, and the results of bacterial and fungal cultures were normal (figure 1B). Voriconazole therapy was switched to the oral formulation after 1 month. Neurological events resolved without sequelae within 3 months after the end of therapy, and histological findings were unremarkable. There has been no recurrence of the _Aspergillus_ infection during 9 years of follow-up.

**Patient 3.** A 43-year-old immunocompetent man was hospitalized in August 1991 for a right-side pneumothorax complicating aerosolized pentamidine isethionate prophylaxis for _Pneumocystis jiroveci_ (formerly “carinii”) pneumonia. The subject had received a diagnosis of HIV infection in 1986 and was severely immunocompromised (CD4+ cell count, 4 cells/mm³). Thoracic surgery was performed, and the results of bacterial and fungal cultures and the findings of histological examination of lung biopsy specimens were unremarkable. Fourteen days after the first surgical intervention, a new episode of bilateral pneumothorax occurred, again requiring surgery, and cultures of a fragment of the left lung grew _A. fumigatus_. No antifungal treatment was initiated at that time.

The patient remained asymptomatic until May 1992, when he became febrile and subcutaneous nodules developed on the thorax. Histological examination of surgical biopsy specimens of subcutaneous necrotic tissues, rib, and lung parenchyma fragments revealed septate hyphae, and cultures grew _A. fumigatus_. Antifungal therapy was initiated in June 1992 with amphotericin B (1 mg/kg once per day for 1 month, followed by 1 mg/kg 2–3 times per week for 6.5 months). Fluconazole was added to the regimen during the last month of amphotericin B treatment. In March 1993, fungal cultures of pus samples drawn from a subcutaneous abscess were positive for _A. fumigatus_, and therapy was switched to itraconazole (400 mg q.d.). After 3 months, despite appropriate serum levels of
itraconazole, the patient remained symptomatic, with positive fungal culture results and detectable serum galactomannan. Therapy with amphotericin B was resumed for 4 months, without clinical improvement.

The patient’s regimen was switched to oral voriconazole (200 mg b.i.d.) in November 1993 because of progression of the infection during the course of amphotericin B therapy. After 15 days of voriconazole therapy, the patient became afebrile for the first time, and bone pain resolved. After 1 month of voriconazole therapy, the patient’s subcutaneous abscess disappeared. After 2 months, the dosage was reduced to 100 mg b.i.d., following major weight loss attributed to disseminated Mycobacterium avium infection. In December 1993, pus samples tested positive for septate hyphae, but culture results remained negative. The patient died of end-stage AIDS in February 1994.

**DISCUSSION**

To our knowledge, this report represents the largest study of cases of bone aspergillosis treated with the same antifungal agent. Patients, most of whom were experiencing treatment failure or did not tolerate other antifungals, had a global response rate to voriconazole of 55%. This evaluation reflected response not only of the bone localizations, but also at other sites of infection.

Aspergillus infections of the bones are extremely rare. In a review of the literature, only 38 (1.8%) of 2121 cases of invasive aspergillosis had bone involvement [4]. However, in patients with CGD, osteomyelitis is not uncommon, and Aspergillus species are the second most common causative pathogens, causing 22% of cases [27]. Our analysis of the voriconazole clinical database revealed that the frequency of bone infections among patients with definite or probable invasive aspergillosis was 5.6% (18 of 322 patients), and CGD was the most common underlying condition.

The data from this analysis suggest that a number of factors influence patient outcome. As with aspergillosis at other sites, immunological status or underlying disease appear to influence outcomes of bone infection. Six patients without significant immunosuppression were included in this study, and all but 1 had satisfactory responses to voriconazole. This response rate (83%) was higher than that for patients with underlying immunosuppression (6 [43%] of 14 patients). However, this response rate (and the 20% mortality rate) among immunocompromised patients with bone aspergillosis compares favorably with historical data and the rate seen in the voriconazole clinical program in general [4, 16, 19, 28].

The length of therapy also influenced outcome. Because the optimum duration of antifungal treatment for bone aspergillosis has not been identified [1] (in contrast with Candida bone infection, for which a 6–12-month course of antifungal therapy has been advocated [29]), the length of therapy was selected by the physicians on the basis of the patients’ clinical and radiological responses. The 11 patients with satisfactory responses received a median duration of voriconazole therapy of 180 days, compared with just 14 days for the 9 patients with unsatisfactory responses. This suggests that factors such as underlying illnesses and comorbidities may influence response.

Previously, it has been indicated that surgery is an important factor in the cure of spinal aspergillosis [3, 4, 20]. The importance of surgery when amphotericin B is used as initial therapy has been highlighted: cure rates were 14% when amphotericin B was used alone, compared with 75% when combined with surgery [20]. In the present analysis, there was no apparent difference in response between patients who underwent surgery in addition to antifungal therapy and those who did not. However, these data were obtained retrospectively, and it is possible that patients with poor prognoses (those with underlying diseases likely to cause death within a few days) would not have been referred for surgery.

Thus, voriconazole is a new option for the treatment of bone aspergillosis. In the present study, favorable responses were seen in more than one-half of the patients treated, despite factors such as disseminated disease and compromised immune function, which are usually associated with poor outcomes. The majority of patients received voriconazole at a relatively early stage of the drug’s development, and since that time, clinical data have led to voriconazole becoming the new standard for first-line therapy for invasive aspergillosis [30]. Although the majority of patients described here received voriconazole as salvage therapy, it is likely that, in the future, patients with bone aspergillosis will receive first-line therapy with voriconazole on the basis of results from this study. The ability to switch the means of administration of voriconazole from intravenous to oral and the generally favorable tolerability of long-term therapy with this agent are additional benefits for the management of Aspergillus bone infection.

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