Treatment of Invasive Aspergillosis with Itraconazole

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Purpose: Invasive aspergillosis in the immunocompromised host is one of the most difficult therapeutic problems. Itraconazole, a new oral triazole, is inhibitory as well as fungicidal against Aspergillus species in vitro. It is active against Aspergillus infections in animal models. We present our experience with itraconazole therapy of 21 patients with aspergillosis.

Patients and Methods: Eighteen of the 21 patients received 400 mg of itraconazole orally per day; the other three received 100 to 200 mg daily. Serum concentrations of itraconazole were measured and susceptibility testing was performed according to previously described methods.

Results: Of 15 evaluable patients, responses were produced in 12. Four of five with invasive pulmonary disease, two of two with skeletal disease, one of two with pleural disease, one of one with pericardial, sinus, mastoid, or hepatosplenic aspergillosis, and one of one with onychomycosis responded. One patient with carotid artery disease did not show a response, although results of cultures were negative at autopsy. One responder with joint disease had a possible relapse three months after completing 12 months of therapy. Ten of these patients who died; this observation suggests that hematologic recovery governs response more than does amphotericin B therapy. Recently, efforts at earlier diagnosis, usually using invasive methods such as bronchoscopy, combined with more aggressive amphotericin B therapy have improved survival.

In our laboratory, 29 of 83 (35%) Aspergillus isolates, tested previously by the same methods described in this report, had a minimal inhibitory concentration (MIC) to amphotericin B of 4 μg/mL or higher, a level usually considered resistant. In addition, amphotericin B causes considerable morbidity and has to be administered intravenously. There is potential utility for alternative therapy of aspergillosis, which has led to the study of a new triazole, itraconazole.

In this report, we describe our experience with 21 patients with aspergillosis treated with itraconazole. Eleven of these patients, who had invasive disease, are reported in detail and for the first time. Eight of these were immunocompromised. On the basis of our experience, we believe that itraconazole has considerable promise as a new therapeutic agent for Aspergillus infection, and merit further study.

Patients

Patients with a diagnosis of aspergillosis, excluding patients in whom amphotericin B therapy had been initiated by their primary physician and who had an apparent response, were potential candidates for the study. Approval for the use of itraconazole was given by the relevant Institutional Review Boards. Informed consent in writing was obtained after discussion with the patient and the patient's family. No patients in whom itraconazole therapy for aspergillosis was offered declined to be treated.

Laboratory Studies

Serum concentrations of itraconazole were determined by bioassay methods described previously [9,10]. Susceptibility testing was performed as described previously [10].

Results

In Vitro Susceptibility Testing

Of 28 isolates studied in our laboratory, 26 had an MIC to itraconazole of 6.3 μg/mL or less, and 18 had an
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Figure 1. Minimum inhibitory concentrations (MIC) of 27 Aspergillus isolates, with corresponding minimum fungicidal concentrations (MFC) for 10 isolates.

MIC of 3.1 μg/mL or less. Itraconazole was also fungicidal for all but one of the 10 isolates tested, with a minimum fungicidal concentration (MFC) ranging between 1.6 pg/mL and 25 pg/mL (median, 6.3 pg/mL) (Figure 1).

Serum Itraconazole Levels
Itraconazole exhibits steady-state kinetics after two weeks of therapy, and data from patients in this report confirm this (data not shown). Mean steady-state serum concentrations are displayed in Table I. Individual samples ranged from less than 1 μg/mL to 26 μg/mL (median, 6.3 μg/mL) (Figure 1).

CASE REPORTS

Patients
Case histories are given in this section for each newly detailed evaluable patient. Four of these patients were treated at the Santa Clara Valley Medical Center, San Jose, California, three at Stanford University Hospital, Stanford, California, and one each at University Hospital, Oregon Health Sciences University, Portland, Oregon; Methodist Hospital, Houston, Texas; Wenatchee Valley Clinic, Wenatchee, Washington; and Bakersfield Memorial Hospital, Bakersfield, California. Summaries on these patients, and those of previously reported cases presently updated, are given in Table I. These data are compiled as of February 1989.

Patient 1
This 76-year-old man developed aspergillosis involving the 10th and 11th thoracic vertebrae (T10/11). He is transfusion dependent due to severe sideroblastic anemia. In March 1987, he developed adult respiratory distress syndrome following a transfusion reaction. This was treated with five days of high-dose glucocorticoids (520 mg methylprednisolone), and he recovered after a long hospital stay (including intubation). In July 1987, two small pulmonary nodules were noted on chest radiograph. In August, severe back pain developed and a lesion was demonstrated at T10/11 by radiography, computed tomographic (CT) scanning, bone scanning, and magnetic resonance imaging. Percutaneous biopsy was done, and only Aspergillus fumigatus was cultured (two to 10 colonies). Cultures for aerobic and anaerobic bacteria and mycobacteria were negative. Histologic examination of the specimen showed chronic inflammatory changes. Itraconazole, 200 mg twice daily, was initiated. His back pain improved over the next two months, partially attributable to a brace. No change on CT scan was noted over four months. Because of this and the potential instability of his back due to the lesion, anterior vertebrectomy at T10/11 was performed, with spinal fusion using autologous bone grafts and posterior stabilization with Harrington rods. He recovered well from this operation. Histologic examination of the excised bone showed granulomatous inflammation and no hyphal elements. Fungal cultures of the specimen were negative. He completed 12 months of itraconazole therapy and remains well six months after discontinuation of itraconazole.

Patient 2
This 69-year-old man had chronic lymphocytic leukemia (CLL) of 10 years duration, and had undergone splenectomy. He became neutropenic (i.e., neutrophil count 500 × 10^6/L) for at least two weeks due to chemotherapy (cyclophosphamide, vincristine, prednisone) and developed an Escherichia coli bacteremia. This responded to antibiotics, but fever again developed coincidental with a rise in his peripheral neutro-
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Site of Disease</th>
<th>Underlying Disease</th>
<th>Daily Itraconazole Dose (mg)</th>
<th>Time to Response (months)</th>
<th>Duration of Therapy (months)</th>
<th>Mean Serum Concentrations (µg/mL)</th>
<th>MIC (µg/mL)</th>
<th>MFC (µg/mL)</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thoracic spine</td>
<td>Previous steroid treatment</td>
<td>400</td>
<td>&lt;4</td>
<td>12</td>
<td>11.5</td>
<td>1.5</td>
<td>50</td>
<td>Response</td>
<td>Cultures negative after four months of itraconazole</td>
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<tr>
<td>2</td>
<td>Lung</td>
<td>CLL</td>
<td>400</td>
<td>&lt;0.3</td>
<td>3.5</td>
<td>ND</td>
<td>1.5</td>
<td>3.1</td>
<td>Response</td>
<td>Died of CLL with no evident fungal disease</td>
</tr>
<tr>
<td>3</td>
<td>Lung</td>
<td>ALL</td>
<td>400</td>
<td>&lt;2</td>
<td>12</td>
<td>21.0</td>
<td>1.5</td>
<td>6.3</td>
<td>Response</td>
<td>Switched from amphotericin B because of toxicity</td>
</tr>
<tr>
<td>4</td>
<td>Sinusoc and carotic artery</td>
<td>Renal transplant</td>
<td>400</td>
<td>-</td>
<td>1.5</td>
<td>1.3</td>
<td>ND</td>
<td>ND</td>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Lung</td>
<td>Renal transplant</td>
<td>400</td>
<td>&lt;2</td>
<td>12</td>
<td>4.3</td>
<td>6.3</td>
<td>12.5</td>
<td>Failed</td>
<td>Died: Embolosis at autopsy</td>
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<td>6</td>
<td>Liver and spleen</td>
<td>AML/ALL</td>
<td>400</td>
<td>&lt;2</td>
<td>12</td>
<td>4.6</td>
<td>3.1</td>
<td>25</td>
<td>Response</td>
<td>Amphotericin B failed before itraconazole was given</td>
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<tr>
<td>7</td>
<td>Lung</td>
<td>Steroid treatment</td>
<td>400</td>
<td>4.0</td>
<td>4.6</td>
<td>ND</td>
<td>1.5</td>
<td>1.5</td>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pleura</td>
<td>Pneumonectomy</td>
<td>400</td>
<td>4.0</td>
<td>4.6</td>
<td>14.5</td>
<td>3.1</td>
<td>3.1</td>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Sphenoid sinus/pterygopalatine space</td>
<td>None</td>
<td>400</td>
<td>4.0</td>
<td>1.0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Response</td>
<td>Surgery possibly contributed to response</td>
</tr>
<tr>
<td>10</td>
<td>Pericardium</td>
<td>Hodgkin's disease (probably cured)</td>
<td>400</td>
<td>4.0</td>
<td>4.6</td>
<td>2.7</td>
<td>6.3</td>
<td>12.5</td>
<td>Response</td>
<td>Mastoidectomy removed part of disease</td>
</tr>
<tr>
<td>11</td>
<td>Mastoid</td>
<td>Chronic otitis externa</td>
<td>400</td>
<td>0.5</td>
<td>2.6</td>
<td>9.9</td>
<td>1.5</td>
<td>12.5</td>
<td>Response</td>
<td>Mastoidectomy possibly contributed to response</td>
</tr>
<tr>
<td><strong>Updated patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>12</td>
<td>Lung</td>
<td>AML</td>
<td>200</td>
<td>1</td>
<td>12</td>
<td>2.5</td>
<td>ND</td>
<td>ND</td>
<td>Cured</td>
<td>Amphotericin B failed before itraconazole was given; Thirty months of posttreatment follow-up. Update from [8]</td>
</tr>
<tr>
<td>13</td>
<td>Pleura</td>
<td>Hodgkin's disease; splenectomy</td>
<td>200</td>
<td>-</td>
<td>0.5</td>
<td>NU</td>
<td>0.8</td>
<td>NU</td>
<td>No response</td>
<td>Amphotericin B subsequently failed. Pleural disease at autopsy. Update from [8]</td>
</tr>
<tr>
<td>14</td>
<td>Nails of hands and feet</td>
<td>None</td>
<td>100</td>
<td>2</td>
<td>6</td>
<td>0.2</td>
<td>1.5</td>
<td>ND</td>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Right knee</td>
<td>Diabetes</td>
<td>400</td>
<td>3</td>
<td>12</td>
<td>6.3</td>
<td>6.3</td>
<td></td>
<td>Response</td>
<td>Clinical response, cultures negative. Three months after therapy was completed, inflammation of joint recurred. Patient refused arthrocentesis. Update from [10]</td>
</tr>
</tbody>
</table>

ND = not done.
* Continuing therapy.
phil count. A right mid-lung field lesion appeared on a chest radiograph (Figure 2). Cytologic examination of a bronchoalveolar lavage specimen showed organisms characteristic of aspergilli, and cultures grew two strains (two to 10 colonies each) of *Aspergillus*, one *A. fumigatus* and the other not *fumigatus*, *flavus*, or *terreus*. Treatment with itraconazole, 200 mg twice daily, was initiated. No other antimicrobial agents were given. He became afebrile within a few days. Two weeks after therapy was begun, marked improvement was noted on a chest radiograph. After one month of therapy, his chest radiograph was normal (Figure 3). He continued to receive chemotherapy for CLL, which worsened, and he died 14 weeks after institution of itraconazole treatment with no radiologic or clinical evidence of aspergillosis. An autopsy was not performed.

**Patient 3**

A 63-year-old man with acute undifferentiated (presumed lymphocytic) leukemia (ALL) was receiving his first course of aggressive chemotherapy in July 1987. He became profoundly neutropenic (i.e., neutrophil count 100 × 10^6/L), and fever, sweats, and coughing developed. A chest radiograph showed a right lower lobe infiltrate. He remained febrile despite gentamicin and imipenem therapy. Three days later, when the chest radiograph showed progression of the infiltrate, bronchoscopy was performed. Bronchial washings showed hyphal elements and later grew *Aspergillus* species (not *flavus*, *fumigatus*, or *ruiger*). He received 800 mg of amphotericin B over the next 12 days. Initially he became afebrile, but fever again reappeared as his neutrophil count improved. Chest radiography showed marked deterioration, with bilateral extensive disease, and his serum creatinine level rose to 300 mmol/L. Another bronchoscopy was unrevealing, and itraconazole (200 mg twice daily) was commenced. Despite further chemotherapy (which continued over the next six months) with daunorubicin and cytosine arabinoside, resulting in a decrease of his absolute neutrophil count from more than 2,000 × 10^6/L to 1,316 × 10^6/L, appearances on chest radiography progressively improved and were virtually normal 10 weeks later. He completed 12 months of itraconazole therapy and his leukemia remains in remission, with intermittent antileukemia therapy, six months after discontinuation of itraconazole.

**Patient 4**

A 24-year-old man developed diplopia, anisocoria, and hyponatremia one year after receiving a successful cadaveric renal transplant. His immunosuppressive regimen included cyclosporine and prednisone. Cerebral arteriography and magnetic resonance imaging revealed a large right supraclinoid mass invading the sella turcica, compressing the internal carotid artery, and abutting the optic chiasm. Right transantral sphenoidectomy and ethmoidectomy were performed. Hyphal elements were seen on histopathologic examination and *A. fumigatus* was cultured. Amphotericin B (1,700 mg) was given over six weeks, but the patient developed progressive obtundation. Cerebrospinal fluid obtained by lumbar puncture revealed a leukocyte count of 980 × 10^6/L with a lymphocytic predominance, results of fungal and bacterial cultures were negative. CT scanning demonstrated an extensive area of edema in the right temporal lobe, acute hemorrhage in the right hippocampus, and hydrocephalus. Itraconazole (200 mg twice daily) therapy was initiated. A ventriculostomy was placed, and multiple culture specimens of cerebrospinal fluid were obtained during treatment. All these culture specimens were negative for fungus. Repeat CT scanning one week after initiation of itraconazole therapy showed extension of the cerebral edema into the right frontal lobe with a slight increase in hydrocephalus. High-dose dexamethasone therapy was started. Removal of part of the right maxilla, and ethmoid and sphenoid sinus re-exploration, showed no evidence of fungus by histopathologic examination or culture. One month after initiation of therapy, CT scan demonstrated an increase in hydrocephalus. The patient had a decline in mental status, developed major gastrointestinal bleeding due to erosive esophagitis, and died of cardiopulmonary arrest after six weeks of itraconazole therapy. At necropsy, infarction of the brain served by the right internal carotid artery and diffuse anoxic encephalitis of both hemispheres were noted. Fungal elements consistent with *Aspergillus* were seen within both cavernous sinuses and surrounding both internal carotid arteries, with invasion of the adjacent leptomeninges and occlusion of the right internal carotid artery. Fungi were...
not observed in the nasal sinuses. Cultures of the sella turcica, basilar leptomeninges, orbits, and ethmoid and maxillary sinuses did not grow Aspergillus.

Patient 5
A 47-year-old insulin-dependent diabetic man with hypertensive and atherosclerotic renal disease received a cadaveric renal transplant in November 1987. Immunosuppression consisted of cyclosporine, prednisone, and azathioprine. In late January 1988, he had an inter-loop ileal abscess, requiring emergency partial ileal resection and multiple antibiotics. Despite improvement of this abdominal infection, he remained febrile and developed bilateral pulmonary infiltrates a week after surgery. Bronchoscopic washings showed hyphal elements and subsequently grew A. fumigatus. Amphotericin B was given for three days, but concern about renal function led to its substitution by itraconazole in early February, initially 400 mg twice daily (five days) and then 200 mg twice daily. He became afebrile, but his pulmonary lesions progressed and cavitated, and sputum samples repeatedly showed growth of A. fumigatus. Immunosuppression was initially reduced and then completely stopped after three weeks of itraconazole therapy. In the fifth week of therapy, he had a focal seizure and became confused. A CT scan showed a left parietal hemorrhage. He died two days later. Autopsy indicated disseminated aspergillosis with mitral valve, cerebral, myocardial, and bilateral pulmonary involvement. Autopsy cultures were not done.

Patient 6
A 40-year-old woman with biphenotypic leukemia (AML and ALL) received chemotherapy and became profoundly neutropenic. She developed pulmonary aspergillosis (diagnosed histologically on bronchoscopic biopsy and by culture of bronchoalveolar lavage fluid) and persistently elevated results of liver function tests. Treatment over four weeks with amphotericin B (2 g) and rifampin stabilized her pulmonary disease, but pulmonary nodules persisted on radiography and did not change after amphotericin B was stopped. Results of liver function tests, abnormal at the end of amphotericin B therapy, worsened after the drug was discontinued (alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels increased to 2.5, 6.3, and 3.4 times normal, respectively). CT scan of the abdomen revealed multiple low-density lesions within the liver and fewer lesions in the spleen (5 to 15 mm in diameter) (Figure 4). CT-guided biopsy was performed, and histologic sections revealed typical Aspergillus hyphal elements, although results of cultures were negative. Itraconazole therapy was started, and over the next eight weeks, marked improvement was noted on liver and spleen CT scanning and chest radiography. Ankle edema developed two weeks after itraconazole treatment was begun, and this condition has persisted. Levels of serum electrolytes were normal, and renin and aldosterone levels were not obtained. Ten weeks after initiation of itraconazole, she received intensification chemotherapy with cytosine arabinoside and became profoundly neutropenic for three weeks. Immediately after this period, another CT scan showed continued improvement and her liver function test results became normal. Repeat CT scan-guided biopsy after six months of itraconazole therapy garnered material in which fungi were absent by culture and histologic examination. A further cancer chemotherapy course after nine months of itraconazole produced profound neutropenia for 16 days. Another liver CT scan then demonstrated reduction in number and size of the lesions. At present, her condition is not in hematologic remission and she is undergoing salvage cytotoxic chemotherapy.

Patient 7
A 32-year-old woman with a four-year history of sarcoidosis treated with intermittent high-dose prednisone (10 to 60 mg daily) developed progressive hemoptysis and multiple, thin-walled pulmonary cavitats with surrounding infiltration. Transbronchial biopsy revealed invasive pulmonary aspergillosis by histopathology and culture (A. fumigatus). She received 3 g of amphotericin B over the following six months with a resolution of cough and hemoptysis. These symptoms recurred within two weeks of discontinuation of amphotericin B, and expectorated sputa were culture-positive twice for A. fumigatus. Baseline chest radiography revealed progressive extensive bilateral cavitation with bronchiectasis. Treatment with oral itraconazole (400 mg/day) resulted in resolution of all clinical symptoms within four months; she returned to work for the first time in one year. She has had no toxicity attributable to itraconazole.

Patient 8
Twenty-two months after left pneumonecnectomy for carcinoma of the bronchus, a 58-year-old white man presented with a four-week history of cough and night sweats. A chest radiograph showed air in the post-pneumonecnectomy space, and a bronchopleural fistula was diagnosed. Fluid aspirated from this space grew A. fumigatus only. An attempt to close the fistula by bronchoscopy was unsuccessful, and fever and night sweats persisted, so an open, anterior drainage of the pleura was surgically achieved and resulted in a bronchopleurocutaneous fistula. Biopsy specimens of the pleura showed many hyphal organisms typical of Aspergillus species, and tissue cultures grew A. fumigatus. A potassium hydroxide preparation of the tissue showed hyphae. Itraconazole, 400 mg/day orally, was begun and the cavity was irrigated twice daily with...
sive anterior mediastinal mass that extended from the irradiation. A CT scan of the thorax showed an extension of disease and was presumed secondary to mediastinal radiotherapy. In 1983, she developed stage II nodular sclerosing Hodgkin's disease of the mediastinum with superior vena cava obstruction, which required thoracic irradiation and chemotherapy. Six years later, she returned for evaluation with shortness of breath, fever, and orthopnea. A diagnosis of constrictive pericarditis was made, presumed secondary to mediastinal irradiation. A CT scan of the thorax showed an extensive anterior mediastinal mass that extended from the base of the pterygoid bone. Histopathologic examination of a small piece of mastoid tissue showed chronic inflammation and a polyp. Itraconazole, 400 mg daily, was commenced three weeks postoperatively, and was discharged home taking itraconazole 400 mg daily. Follow-up revealed continued improvement in her respiratory symptoms and general level of energy, and absence of fever. Furosemide prescribed for ankle edema and shortness of breath was discontinued. Four months after itraconazole therapy was begun, findings on CT scanning of the chest were significantly improved, with marked clearing of pleural effusions, resolution in size of the anterior mediastinal shadows, and partial clearing of the pulmonary atelectasis. Two pulmonary nodules, 1.0 cm in diameter or less, were first apparent on this scan, having been obscured by the pleural effusions. The echocardiographic dimension of the posterior pericardium was unchanged at 3 mm. The only adverse effect has been a loss of body weight four months postoperatively, almost certainly attributable to telogen effluvium.

Patient 10

A 36-year-old male physician with chronic otitis externa secondary to swimming developed an increasing discharge from his left ear while vacationing in the tropics. The discharge continued despite antibacterial therapy; he developed night sweats and fever; and a tympanic membrane perforation was observed. CT scanning demonstrated opacification of the left mastoid air cells. Culture of mastoid fluid obtained by nitrous oxide insufflation under general anesthesia yielded pus that grew only A. fumigatus. Itraconazole therapy (400 mg/day) was begun and his fevers and night sweats resolved within two weeks; a scant discharge remained that was culture-negative for fungus. After 15 days of itraconazole therapy, he underwent left mastoidectomy. Histopathologic examination of a small piece of mastoid tissue showed chronic inflammation without evidence of fungal elements. Gram stain, stains for acid-fast bacteria, and cultures for bacteria and fungi were negative. The aural discharge resolved promptly and the tympanic membrane sealed spontaneously one month after surgery. He continues to have no clinical symptoms.

Other Patients Treated

Of the other 10 treated patients, five have been previously reported; the four evaluable patients are included in Table I and the information on these patients is updated. Six patients are unevaluable. One patient with vertebral osteomyelitis was lost to follow-up.
up [8]. Two other patients with rapidly progressive disseminated aspergillosis died after three and five days of therapy. Three other patients are unevaluable. One, a drug addict, had bilateral renal aspergillosis caused by *A. fumigatus*. One kidney was removed and the other (renal pelvic disease only) improved with itraconazole 400 mg daily and concurrent amphotericin B irrigation through a nephrostomy tube. The respective roles of itraconazole and amphotericin B are unclear. Another non-immunocompromised patient with maxillary sinusitis took itraconazole for two months after a Caldwell-Luc procedure. He remains disease-free. Another patient with a thalamic astrocytoma treated with corticosteroids developed histopathologically proven pulmonary aspergillosis. After responding to amphotericin B over six weeks, he developed seizures and a new temporal-parietal mass was noted, which on biopsy revealed hyphal elements. Itraconazole was given concurrently with phenytoin and carbamazepine, and after one month of therapy, no itraconazole was detectable in serum. He died seven weeks later, with no CT scan change in the lesion (at two weeks). No autopsy was performed.

**COMMENTS**

Several laboratories have found itraconazole active against several *Aspergillus* species *in vitro*, with MICs [11,12] and even MFCs achievable in blood at presenty studied doses [10,13,14]. The peak mean concentration at steady state (at seven hours after dose) was 5.9 \( \mu \)g/mL in a large series of patients receiving 200 mg itraconazole twice daily [10]. Results of susceptibility testing may be highly variable between laboratories, and there is as yet no standard. Despite this, very few resistant isolates have been found, less than 8% in our and others' studies. Several animal model systems have demonstrated the activity of itraconazole *in vivo* against aspergilli. This is especially noteworthy when oral therapy is used. In a mouse model using intravenous challenge, 17-day courses of itraconazole and amphotericin B were of approximately equal efficacy in their effect on survival and in decreasing the extent of renal infection [14]. Neither drug affected the extent of liver infection. However, comparisons are difficult since only one set dose of both drugs was compared. Together the two drugs showed no interaction (enhancement or decrease of efficacy) *in vivo*. Intranasal challenge produced a more lethal model: itraconazole was ineffective in a four-day course and amphotericin B was not studied. Other workers using an intravenous *A. fumigatus* mouse model found three-day courses of itraconazole prolonged survival after a 100% lethal (LD_{100}) challenge, and produced 14 long-term survivors of 50 animals treated [15]. Eight of these had eradication of all infection at autopsy. In a subsequent study with four different isolates and LD_{100} challenges, five-day courses of itraconazole therapy yielded 0% to 60% survival [13]. Twenty-five to 50% of the survivors had eradication of all residual infection at autopsy. In another murine study, 10 itraconazole doses of 50 mg/kg kept 60% of the animals alive at 21 days after an LD_{100} intravenous *Aspergillus* challenge [16]. Itraconazole, 5 mg/kg/day for 14 days, produced 70% to 92% survival in non-immunocompromised guinea pigs given an LD_{100} intravenous *A. fumigatus* challenge with an isolate whose itraconazole MIC was 10 \( \mu \)g/mL [12]. In an identical experiment with neutrophilic guinea pigs, 50% to 80% survival was produced, the lower figure in those animals whose treatment was started later after challenge [12]. Thus, efficacy was not markedly reduced by neutropenia. However, intravenous infection may result in a model that mimics disseminated aspergillosis, but that is of uncertain relevance to focal (*e.g.*, pulmonary) infection. In a rabbit model of *A. fumigatus* endocarditis, itraconazole at 5 mg/kg/day intraperitoneally for 14 days was superior to amphotericin B, flucytosine, or the combination of the latter drugs [17]. This was a rigorous test of drug efficacy in that therapy was initiated three days after the infection was established. The vegetations were sterilized by itraconazole. However, the relevance of the doses of all drugs used in this study to humans is not known, as blood concentrations were not evaluated.

In the clinical setting, the diagnosis of *Aspergillus* infection is often problematic. Ancillary tools that might assist the process, such as tests for the presence of antibody or antigen, are not widely available, not standardized, and/or not widely accepted as definitive. Because we often cannot proceed with definitive diagnostic procedures due to factors beyond the clinician's control (thrombocytopenia, patient preferences, and so forth) and because we often do not have the luxury of delaying procedures before instituting therapy, decisions about treatment must often be made with incomplete information. The literature on the therapy of aspergillosis must therefore reflect this problem. In addition, bias may be introduced by evaluating only patients with histologically proven disease who are neutropenic, as achieving a histologic diagnosis may necessitate a delay, and such delay has been shown to adversely affect mortality [6]. It is still of interest to know the results of therapy in settings that the clinician will actually confront, i.e., where the diagnosis may only be likely and not definitive, even though it may be possible some cases included may not actually have the diagnosis if definitive methods had been available. The "gold standard" for *Aspergillus* infection should be histologic and culture evidence of etiology. In the new cases detailed here, this ideal was achieved in seven patients (Patients 4 through 10). In one (Patient 1), the diagnosis rests on positive cultures of percutaneous aspirates of involved tissue. In two (Patients 2 and 3), the diagnosis is based on the clinical setting (neutropenia, lung infiltrate, persistent fever, and progression of infection despite broad-spectrum antibiotics) and culture and histology of bronchial washings. The usefulness of cultures [18], specifically bronchoscopic cultures [19], as support for the diagnosis of pulmonary aspergillosis during neutropenia is documented in the literature. In one case (Patient 11), the diagnosis rests on a pure growth of *Aspergillus* from the mastoid fluid obtained by insufflation.

There have been a number of reports of the use of itraconazole in *Aspergillus* infections in humans. The early studies used lower doses (e.g., 50 to 200 mg daily) than those we have used in most of our patients. Many of the reports are only published in abstract form, preventing a complete appraisal of each case. The relation of therapy to the time of recovery of granulocytes in neutropenic patients is unclear in most instances. Recovery of granulocytes may be essential to recovery.
in neutropenic patients even with treatment. In Table II, we have summarized those itraconazole-treated cases of invasive aspergillosis reported by others that have sufficient information to discuss in detail.

Our series included five pulmonary cases, four of which responded. Of the patients in Table II, five of seven with invasive pulmonary infection responded. Itraconazole has been successful in treating invasive pulmonary aspergillosis in other reports. Among eight biopsy-proven cases (treated with 100 to 400 mg itraconazole daily), five apparently improved, but details of these cases are lacking [23]. Among 44 patients with chronic necrotizing pulmonary disease (an unusual, poorly understood entity), 29 apparently responded [23]. Again, pertinent details are missing. Craven et al [24] briefly reported cure of a patient with an endobronchial mass and failure of response of a patient with Aspergillus empyema. In addition, prophylaxis of Aspergillus infections in immunocompromised hosts may be successful [25].

Two well-studied patients with aspergilloma responded to 200 mg of itraconazole daily (Table II) [21]. Colombian investigators briefly reported eight patients with aspergilloma evaluated by means of an objective point score system [26]. Five had minor and three had major improvement by the definitions. Improvements included reversion of culture results to negative. In another patient with an aspergilloma [20], hemoptysis and sputum production decreased with therapy. The variable natural history of pulmonary aspergilloma makes evaluation of response rates difficult.

In addition, allergic bronchopulmonary aspergillosis remitted in two of five patients and improved in two others [20,22,23]. One did not respond. Detailed description of these cases would be required to evaluate the diagnosis and the results of therapy.

Infections other than those in a pulmonary site have also been treated. Two of our two evaluable cases of skeletal infection responded, and one of two cases of skeletal infection in Table II (note also Patient D). It is important to note that no improvement in radiologic appearance was apparent in Patient 1 after four months of therapy, and yet when he underwent surgery, all evidence of fungal disease had resolved. Review of others’ experience with itraconazole or other antifungal chemotherapy emphasizes the point that sterilized lesions may not recalcify radiographically. A high dose of itraconazole may be appropriate in patients with bone disease, as blood supply and therefore drug delivery to infarcted bone will be poor. This may account in part for the emergence of bone loss of infections during itraconazole treatment in Patient D (Table II). It may also be responsible in part for the possible relapse in Patient 15 after a year of therapy. Adjunctive surgical therapy is probably important in this group.

In regard to infections of sinuses and ears, Patient 8 with sinus disease responded. This patient was not immunocompromised. Maxillary Aspergillus sinusitis in this group will respond to surgical drainage alone [27–53]. Our patient had both sphenoid sinusitis (which does not always respond to surgical drainage alone [29,34–36]) and extranasus extension of disease into the pterygomaxillary space and the greater wing of the sphenoid bone. Surgical treatment is probably important in this group, so the relative contribution of itraconazole in our patients’ response is unclear. Our patient with mastoiditis likewise improved before surgery, but cure may necessitate surgery, which may not be successful even when combined with amphotericin B [37–40]. Cure of otitis media has been observed with itraconazole [24], as has cure of one patient with ethmoid sinusitis [23]; pertinent details of these cases are missing.

Two patients with pericardial aspergillosis have responded to itraconazole. Patient 10 (Table I) and Patient C (Table II). Patients previously reported with this manifestation of aspergillosis have died [41–44]. Response after oral therapy in 10 to 12 of 16 Indian patients with corneal ulcers could be inferred, including 10 whose culture results became negative [45]. The 11 cases we have detailed here are different in certain respects from most of the previously reported cases. Ten of these patients were immunocompromised to some degree, five were significantly immunocompromised, and three continued cytotoxic chemotherapy during itraconazole treatment without adverse effects. Patient 6, with hepatosplenic disease, is the only patient described who has been shown to improve with itraconazole during prolonged neutropenia. Hepatosplenic aspergillosis does not usually respond to amphotericin B; thus it is even more remarkable that she should show improvement while neutropenic. Both renal transplant recipients did not respond to therapy. This may be because the degree of compromise of the immune defenses was unchanged, unlike cases of leukemia, in which the degree of compromise varies with time. However, Patient 4 had very poor absorption of itraconazole and extensive disease, including intracerebral disease. Therapy also failed in the only other reported patient with intracerebral disease treated with itraconazole (dose and serum levels not stated) [24], and in the vast majority of these patients treated with amphotericin B. Our other transplant recipient had higher serum concentrations, but unfortunately also a relatively insensitive organism, so even an inhibitory serum level of itraconazole was never achieved. Prior correlations between serum concentrations and outcome have not been made, but these data and those from studies of prophylaxis [25] do suggest that such a correlation may emerge for itraconazole and Aspergillus. The substantial variability of serum itraconazole concentrations noted in our patients may prove a useful observation if such an association is found. It is important to note that results with bioassay and liquid chromatographic (HPLC) assays of serum itraconazole concentrations have been inexplicably discordant, the former giving higher values.

Among our 11 new patients, only one had a side effect. She (Patient 6) developed ankle edema, which required diuretic therapy. In general, itraconazole side effects are uncommon and minor and include mild gastrointestinal complaints, headache, edema, rash, increased levels of liver enzymes, urinary frequency, impotence, gynecomastia, and hypokalemia [10]. No life-threatening side effects have yet been reported for itraconazole.

With the knowledge that itraconazole may be fungicidal at achievable serum concentrations for approximately 60% of isolates and inhibitory for the vast majority of isolates, that it can be superior to other agents in animal models, and that grossly immunocompromised patients with life-threatening aspergillosis have
**TABLE II**

Patients with *Aspergillus* Infection Treated with Itraconazole as Reported in the Literature

<table>
<thead>
<tr>
<th>Patient</th>
<th>Site of Disease</th>
<th>Underlying Disease</th>
<th>Daily Itraconazole Dose (mg)</th>
<th>Time to Response (months)</th>
<th>Duration of Treatment (months)</th>
<th>Mean Serum Concentrations (µg/mL)</th>
<th>MIC (µg/mL)</th>
<th>MFC (µg/mL)</th>
<th>Outcome</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Lung</td>
<td>CML, blast crisis</td>
<td>200</td>
<td>1</td>
<td>4</td>
<td>0.38†</td>
<td>0.05</td>
<td>ND</td>
<td>Cured</td>
<td>Amphotericin B-flucytosine failure, neutropenia</td>
<td>[20]</td>
</tr>
<tr>
<td>B</td>
<td>Lung</td>
<td>ALL</td>
<td>200/100</td>
<td>1</td>
<td>21*</td>
<td>0.24†</td>
<td>ND</td>
<td>ND</td>
<td>Response</td>
<td>ND</td>
<td>[20]</td>
</tr>
<tr>
<td>C</td>
<td>Lung, pericardium</td>
<td>Heart transplant</td>
<td>200</td>
<td>1</td>
<td>19*</td>
<td>ND</td>
<td>0.1</td>
<td>ND</td>
<td>Response</td>
<td>ND</td>
<td>[20]</td>
</tr>
<tr>
<td>D</td>
<td>Lung, cervical and lumbar spine</td>
<td>Heart transplant</td>
<td>200/400</td>
<td>1</td>
<td>22*</td>
<td>0.64†</td>
<td>0.1</td>
<td>ND</td>
<td>Response</td>
<td>ND</td>
<td>[20]</td>
</tr>
<tr>
<td>E</td>
<td>Lung</td>
<td>Renal dialysis, steroid treatment</td>
<td>200</td>
<td>2</td>
<td>2*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Failed</td>
<td>ND</td>
<td>[20]</td>
</tr>
<tr>
<td>F</td>
<td>Lung</td>
<td>Pleuropneumonectomy, respiratory failure</td>
<td>200</td>
<td>—</td>
<td>0.5</td>
<td>0.08†</td>
<td>ND</td>
<td>ND</td>
<td>Failed</td>
<td>ND</td>
<td>[20]</td>
</tr>
<tr>
<td>G</td>
<td>Lung</td>
<td>Tuberculosis</td>
<td>200</td>
<td>3</td>
<td>0.38</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Response</td>
<td>ND</td>
<td>[21]</td>
</tr>
<tr>
<td>H</td>
<td>Sternum</td>
<td>Radiotherapy and steroids</td>
<td>200/100</td>
<td>0.5</td>
<td>5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Failed</td>
<td>ND</td>
<td>[21]</td>
</tr>
<tr>
<td>I</td>
<td>Lung</td>
<td>Radiotherapy</td>
<td>200</td>
<td>4</td>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Response</td>
<td>ND</td>
<td>[21]</td>
</tr>
<tr>
<td>J</td>
<td>Lung (aspergilloma)</td>
<td>Radiotherapy</td>
<td>200</td>
<td>5</td>
<td>5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Response</td>
<td>Clinical but not radiographic improvement</td>
<td>[21]</td>
</tr>
<tr>
<td>K</td>
<td>Lumbar spine</td>
<td>Corticosteroids</td>
<td>200</td>
<td>—</td>
<td>1.5</td>
<td>0.09†</td>
<td>ND</td>
<td>ND</td>
<td>Failed</td>
<td>Low serum concentrations</td>
<td>[22]</td>
</tr>
</tbody>
</table>

*ND = not done or reported.
†Continuing to receive therapy at time of reporting.
‡Concentrations measured by high-pressure liquid chromatography.
been clinically cured, we believe that itraconazole may have a bright future in the treatment of Aspergillus infections. Itraconazole's good bioavailability after oral administration, lack of D-,G-glucosidase, and track record to date make this agent an attractive alternative for patients with aspergillosis. Recent data [46] suggest that toxicity is common with doses of more than 400 mg/day, although such doses may be more efficacious in some circumstances. Whether an initial loading dose would be tolerated and improve outcome is unknown. Further extensive studies, probably multicenter in nature, could assess itraconazole's potential as an alternative for therapy of aspergillosis.

ACKNOWLEDGMENT

We thank Dr. Richard Bryant, University of Oregon; Dr. Paul Croney, Stanford; Dr. Hans Steinb, Bakersfield; Dr. Todd Bagwell, Texas; and Dr. Tim Patton, Wasnuche, Washington, for their collaboration.

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