Chronic granulomatous disease (CGD) is characterized by life-threatening bacterial and fungal infections. Treatment with posaconazole led to a complete response in 7 of 8 patients with CGD and invasive mold infections (7 proven cases and 1 possible case) after failure or intolerance of treatment with standard antifungal agents. In this preliminary study, salvage treatment with posaconazole was safe and effective.

Chronic granulomatous disease (CGD) is an inherited disorder of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex in which phagocytes are defective in generating the reactive oxidant superoxide anion and its downstream metabolites. Activation of preformed granule proteases is likely to be principally responsible for the NADPH oxidase-mediated host defense against pathogens [1, 2]. CGD is characterized by recurrent life-threatening bacterial and fungal infections and by abnormally exuberant inflammatory responses leading to granuloma formation, such as granulomatous enteritis, genitourinary obstruction, and wound dehiscence [3, 4]. CGD affects ~1 in 200,000 live births.

People with CGD are susceptible to a broad spectrum of opportunistic infections with filamentous fungi. Invasive aspergillosis is the most significant cause of mortality in people with CGD [5–7]. Patients with X-linked CGD appear to be at increased risk for invasive aspergillosis, compared with patients with autosomal recessive forms [8, 9]. The routine use of antibacterial prophylaxis has significantly reduced the frequency of severe bacterial infections in CGD [10–12]. However, fungal infections have remained a persistent problem, with an incidence of 0.1 fungal infections per patient year [7].

Posaconazole (Schering-Plough) is an orally administered, second-generation triazole with a broad spectrum of activity against opportunistic yeasts and molds. Here, we report results for 8 patients with CGD and invasive filamentous fungal infections who were enrolled in an open-label, limited-access study of posaconazole treatment for invasive fungal infections (Protocol P02095; so far unpublished).

**Methods.** Patients with CGD received care at the National Institutes of Health Clinical Center (Bethesda, Maryland). All patients or their guardians gave written informed consent, and written assent was obtained from minors. The diagnosis of CGD was established on the basis of results of either abnormal nitroblue tetrazolium reduction testing, or abnormal-flow cytometry assay with the dihydrorhodamine 123 probe, or both [13].

To participate in the study, patients were required to meet criteria for proven, probable, or possible invasive fungal infection, as they are defined by the European Organization for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [14]. One of the following criteria also must have been met for enrollment in the study: fungal infection refractory to therapy with standard agents; intolerance of standard therapy; or invasive fungal infection with no proven effective antifungal therapy.

Seven of 8 patients in this series fulfilled the criteria for proven invasive mold infection, and 1 patient had possible fungal pneumonia. All patients with refractory infection experienced persisting or worsening infection-related symptoms and/or radiographic abnormalities and/or had fungal cultures that were persistently positive for causative organisms after receiving at least 10 days of therapy with a drug active against molds. A successful outcome was defined as a complete or partial response at the end of therapy and at 1 month after discontinuation of therapy.

Oral posaconazole solution was provided by Schering-Plough under protocol P02095, a multicenter, open-label study of treat-
Table 1. Baseline characteristics of 8 patients with chronic granulomatous disease invasive mold infection who were treated with posaconazole.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years, sex</th>
<th>Patient CGD genotype</th>
<th>Pathogen</th>
<th>Site of infection</th>
<th>Diagnosis</th>
<th>Received itraconazole prophylaxis</th>
<th>Prior antifungal therapy</th>
<th>Reason for enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17, M</td>
<td>X-linked</td>
<td><em>Phaeoacremonium parasiticum</em></td>
<td>Lung</td>
<td>Biopsy proven</td>
<td>Yes</td>
<td>Caspofungin, then ABLC, then voriconazole</td>
<td>Infection refractory to prior therapy</td>
</tr>
<tr>
<td>2</td>
<td>17, M</td>
<td>X-linked</td>
<td><em>Paecilomyces variotti</em></td>
<td>Lung</td>
<td>Biopsy proven</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Infection refractory to prior therapy</td>
</tr>
<tr>
<td>3</td>
<td>18, F</td>
<td>X-linked</td>
<td><em>Scedosporium apiospermum</em></td>
<td>Lung</td>
<td>Biopsy proven</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Intolerance of prior therapy</td>
</tr>
<tr>
<td>4</td>
<td>9, M</td>
<td>X-linked</td>
<td>None cultured</td>
<td>Lung</td>
<td>Possible¹</td>
<td>Yes</td>
<td>Itraconazole</td>
<td>Infection refractory to prior therapy</td>
</tr>
<tr>
<td>5</td>
<td>18, M</td>
<td>X-linked</td>
<td>None cultured</td>
<td>Lung and lymph node</td>
<td>Biopsy proven</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Infection refractory to prior therapy</td>
</tr>
<tr>
<td>6</td>
<td>9, M</td>
<td>X-linked</td>
<td><em>Phaeoacremonium parasiticum</em></td>
<td>Lung</td>
<td>Biopsy proven</td>
<td>Yes</td>
<td>LAMB, then ABLC, then voriconazole</td>
<td>Infection refractory to prior therapy</td>
</tr>
<tr>
<td>7</td>
<td>36, F</td>
<td>p47^{exo-/-}</td>
<td><em>Aspergillus fumigatus</em></td>
<td>Lung</td>
<td>Biopsy proven</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Infection refractory to prior therapy</td>
</tr>
<tr>
<td>8</td>
<td>12, M</td>
<td>X-linked</td>
<td>A. <em>fumigatus</em></td>
<td>Lung</td>
<td>Biopsy proven</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Infection refractory to prior therapy</td>
</tr>
</tbody>
</table>

**NOTE.** ABLC, amphotericin B lipid complex; LAMB, liposomal amphotericin B.

¹ Intolerance of treatment with voriconazole was associated with anxiety and mental status changes.

² See Results.
ment with posaconazole in patients with invasive fungal infections with limited or no alternative treatment options. Posaconazole was administered at a dosage of 400 mg twice daily, with a dose reduction for children that was determined according to each child’s weight.

Results. Eight patients (6 males and 2 females) with CGD who had invasive mold infection were enrolled (table 1). Seven patients had X-linked CGD, and 1 patient had autosomal p47phox–/– CGD. One of the patients with X-linked CGD was a female carrier with extreme skewing in favor of NADPH oxidase-defective cells [15]. The mean age of patients was 17 years (range, 9–36 years).

Six patients had proven fungal pneumonia, and 1 patient had fungal cervical adenitis. Pathogens isolated from culture included Aspergillus fumigatus (n = 2), Phaeoacremoniumparasiticum (n = 2), Paecilomyces variotti (n = 1), and Scedosporium apiospermum (n = 1). The only patient with a possible invasive fungal infection (patient 4) had received a diagnosis of right lower–lung pneumonia due to an Acremonium species 9 months prior to enrollment. After responding to treatment with itraconazole, a new right upper–lung infiltrate developed, and the patient was enrolled in this study. Because no definitive diagnosis was made regarding the right-upper–lung infiltrate, this case was classified as a possible fungal infection.

All of the patients had received itraconazole prophylaxis prior to receiving the diagnosis of fungal infection. After receiving the diagnosis, 5 patients received voriconazole as primary therapy, and 2 received voriconazole after failure of treatment with a lipid formulation of amphotericin B. Six of these patients had an infection that was refractory to voriconazole therapy, and 1 patient was intolerant of voriconazole (table 1). The duration of voriconazole therapy ranged from 10 days to 14 months.

Response to posaconazole. Treatment with posaconazole led to a complete response in 7 patients; treatment failed for 1 patient because of persistent pneumonia due to P. variotti (table 2). Posaconazole was administered for a mean duration of 10 months (range, 4–19 months). Chest CT scans for one patient because of persistent pneumonia due to P. variotti led to a complete response in 7 patients; treatment failed for 1 patient (patient 8) with a successful response to treatment with posaconazole are shown in figure 1.

One patient (patient 3) with S. apiospermum pneumonia had a complete response to treatment with posaconazole but developed A. fumigatus pneumonia after 11 months of treatment with posaconazole. This case was classified as a complete response on the basis of the outcome of the initial fungal infection for which the patient was enrolled in the study.

Three patients were treated with surgery after study enrollment. One patient (patient 1) underwent lung-wedge resection, which showed Nocardia pneumonia without evidence of residual fungal pneumonia. Another patient (patient 2) underwent wedge resection of a new pulmonary lesion, a specimen of which grew P. variotti, and was classified as experiencing therapeutic failure. A third patient (patient 5) with a pulmonary infiltrate and invasive fungal infection of the cervical lymph nodes was treated with lymphadenectomy after having received posaconazole for 1 month. Histologic examination of a tissue specimen showed invasive hyphae, but cultures were sterile. Both the infiltrate and the adenopathy subsequently responded to treatment with posaconazole. Only 1 patient received adjunctive recombinant interferon-γ (IFN-γ) with posaconazole. No patient received granulocyte transfusions.

Treatment with posaconazole was well tolerated, with nausea and gastrointestinal symptoms being the most common adverse events attributed to it. No patient was withdrawn from the study because of drug intolerance or adverse events. Three patients developed serious bacterial infections requiring hospitalization while receiving treatment with posaconazole. Intercurrent infections are common in people with CGD and were not considered to be related to posaconazole therapy.

Discussion. Treatment with posaconazole led to a complete response in 7 of 8 patients with CGD and invasive mold infection (7 proven cases and 1 possible case) after failure or intolerance of therapy with standard antifungal agents. All patients had received prior itraconazole prophylaxis, and 6 had a mold infection refractory to treatment with voriconazole. Thus, in this preliminary study, posaconazole was a safe and effective salvage therapy for invasive mold infections in patients with CGD, despite the prior use of azoles active against molds.

Second-generation triazoles have excellent in vitro activity.
against Aspergillus species and some activity against other pathogenic molds [16]. Posaconazole was active in vitro against some Aspergillus species with reduced susceptibility to amphotericin B, itraconazole, and voriconazole [17]. Among Aspergillus isolates selected in the laboratory for voriconazole resistance, cross-resistance to posaconazole was minimal [18]. Azole resistance in A. fumigatus has been associated with decreased drug accumulation. However, there is growing appreciation of specific enzyme mutations that confer resistance to individual azoles, rather than to the entire class [18, 19].

In a trial of posaconazole salvage therapy that enrolled 330 patients, treatment with posaconazole was successful against a wide variety of refractory fungal infections, and outcomes compared favorably with those for contemporaneous control subjects [20]. Most refractory infections involved prior therapy with an amphotericin B formulation. Posaconazole therapy was successful in 4 of 8 patients with an invasive fungal infection refractory to voriconazole [21], which is consistent with outcomes in our series. This study supports a large body of in vitro and animal studies showing that posaconazole has a broad spectrum of antifungal activity [16, 22–29] and demonstrates the efficacy of posaconazole in treating serious fungal infections refractory to standard therapy.

All of the patients in our series had received itraconazole prophylaxis. A European open-label study of itraconazole prophylaxis found a reduced rate of Aspergillus infection, compared with historical controls [6]. A recently conducted randomized, double-blind, placebo-controlled crossover study confirmed the efficacy and tolerability of itraconazole prophylaxis in people with CGD [30]. In our series, breakthrough infections in patients receiving itraconazole prophylaxis may have been related to intrinsic resistance in the pathogens isolated, which would indicate that there was a subset of patients more prone to fungal infections than were those enrolled in the prophylaxis trial, or poor medication compliance.

In this series, only 1 patient received adjunctive rIFN-γ therapy with posaconazole. Prophylaxis with rIFN-γ reduced the number of serious infections by >70% in a randomized, placebo-controlled study [31]. However, the value of rIFN-γ in established infection is undetermined and its use is, therefore, not our practice. In contrast to findings of our previously published series of cases of invasive aspergillosis in patients with CGD [8], no patient in the current series received granulocyte transfusions; this change is likely because we used more effective antifungal agents.

In a landmark study of patients with invasive aspergillosis, treatment with voriconazole was more effective than treatment with amphotericin B and was associated with improved survival [32]. Most patients had a hematologic malignancy or had undergone stem cell transplantation. Walsh et al. [33] evaluated compassionate-use treatment with voriconazole in 58 children with invasive fungal infection, 13 of whom had CGD. Eight (62%) of the patients with CGD had a successful outcome. Voriconazole is now the drug of choice for initial treatment of invasive aspergillosis in patients with CGD at our center. For patients with CGD and mold infection refractory to voriconazole, our preliminary results suggest that treatment with posaconazole is safe and effective.

Acknowledgments

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Figure 1. Chest CT scans obtained prior to treatment with posaconazole (A) and at 4 months after the start of posaconazole therapy (B) for patient 8, a 12-year-old boy with X-linked chronic granulomatous disease with Aspergillus fumigatus right upper-lung pneumonia refractory to treatment with voriconazole. The infection completely resolved after posaconazole therapy.
References


