Infection Due to Non-Aspergillus Fungi in Immunocompromised Patients Receiving Itraconazole

Str—Chariyalertsak et al. [1] recently reported the efficacy of oral itraconazole prophylaxis for prevention of systemic fungal infections (particularly cryptococcosis and penicilliosis) in patients with advanced HIV infection included in a controlled trial. We also previously reported that oral itraconazole was effective for the prevention of invasive orofacial aspergillosis in neutropenic patients with acute leukemia [2]. At the Hiroshima Red Cross and Atomic Bomb Survivors Hospital, orofacial aspergillosis has not been seen in immunocompromised patients since itraconazole prophylaxis began to be routinely administered to such patients in 1997. However, we recently saw 3 patients with invasive orofacial infections caused by non-Aspergillus fungi that had high itraconazole MICs on in vitro susceptibility testing.

The first patient was a 39-year-old woman with acute myelogenous leukemia who developed invasive stomatitis due to Exophiala dermatitidis in January 1999. The patient was successfully treated a combination of surgery and parenteral amphotericin B. All patients received itraconazole capsules (200 mg/day) as antifungal prophylaxis for 27–40 days before a diagnosis of invasive fungal infection was made on the basis of clinicohistological and microbiological evidence. All causative organisms were finally identified by sequencing of the rDNA internal transcribed domain.

In vitro susceptibility studies revealed that the causative organisms in these 3 cases had itraconazole MICs that were higher than those for isolates from oral Aspergillus infections, for which the range is 0.125–0.25 µg/mL (table 1) [3]. All causative fungi isolated from samples from our patients were susceptible to amphotericin B. These results suggest that fungi with low susceptibility to itraconazole were present in the environment and might have colonized patients, resulting in the development of invasive orofacial infections while the patients were receiving itraconazole as antifungal prophylaxis. Chariyalertsak et al. [1] described a case of penicilliosis in the group of patients in that study who were receiving itraconazole prophylaxis, but the in vitro susceptibility data for the causative fungi were not clear; such data are needed if infections are to be treated effectively.

In conclusion, it should be noted that invasive fungal infections that develop in severely immunocompromised patients who do not respond to itraconazole prophylaxis need to be managed with intensive antifungal treatment with other effective drugs, such as amphotericin B, that should be selected on the basis of the results of in vitro susceptibility testing.

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References

Table 1. In vitro activity of itraconazole and amphotericin B against fungal isolates recovered from patients with invasive orofacial infections.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age in years, sex</th>
<th>Underlying disease</th>
<th>Causative organism</th>
<th>MIC, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39, F</td>
<td>Acute myelogenous leukemia</td>
<td><em>Exophiala dermatitidis</em></td>
<td>4.0</td>
</tr>
<tr>
<td>2</td>
<td>66, F</td>
<td>Malignant lymphoma</td>
<td><em>Trichoderma longibrachiatum</em></td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>29, M</td>
<td>Aplastic anemia</td>
<td><em>Mucor racemosus</em></td>
<td>2.0</td>
</tr>
</tbody>
</table>

NOTE. AmB, amphotericin B; Itr, itraconazole.
Reply

Sr.—The experience reported by Myoken et al. [1] of superinfection with fungal organisms resistant to itraconazole in patients who are receiving the drug as prophylaxis is of interest. We have not seen superinfections with resistant organisms in immunocompromised HIV-infected patients receiving prophylacticitraconazole. In our experience [2] and in that of others who have reported in vitro testing results [3–5], *Penicillium marneffei* strains have been uniformly susceptible to itraconazole. However, resistance to flucconazole is not uncommon. In our double-blind trial [6], 1 (1.6%) of 63 subjects assigned to receive itraconazole developed a disseminated *P. marneffei* infection, and 11 (16.7%) of the 66 persons who received placebo developed a systemic fungal infection (7 of these patients developed cryptococcal meningitis, and 4 developed *P. marneffei* infection). We have not done in vitro testing of isolates from these patients. Because the study was blinded, we were not aware of which regimen the patients were receiving at the time that infection was diagnosed. However, the lower rates of *P. marneffei* infection seen among patients receiving itraconazole suggest that the drug may have been effective. Whether the breakthrough infection that occurred in the single patient who became infected with *P. marneffei* could have been due to dosing or pharmacokinetic issues, rather than to resistance of the organism to itraconazole, is unclear. We agree with Myoken et al. [1] that monitoring of patients receiving itraconazole who develop fungal infections and susceptibility testing of isolates from these patients could be important.

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Variable Number Tandem Repeat Polymorphism of the Interleukin-1 Receptor Antagonist Gene in Meningococcal Disease

Sr.—We read with interest the article by Witkin et al. [1] that described the role of the variable number tandem repeat (VNTR) polymorphism of the IL-1 receptor antagonist (IL-1Ra) gene in different disease states. The role of the IL-1Ra VNTR polymorphism in meningococcal disease (MCD) has not, to our knowledge, previously been studied, and therefore we aimed to determine whether this polymorphism might influence susceptibility to disease, disease severity, or disease type.

One hundred forty-four children with a diagnosis of MCD who were admitted to a single tertiary children’s hospital were prospectively studied between December 1997 and March 1999. Informed consent was obtained from the parents of all children included in the study and from controls, and the study protocol was approved by the Local Research Ethics Committee of the Royal Liverpool Children’s National Health Service Trust. Cases were defined and investigated as described elsewhere [2]. Severity of disease was assessed using the Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) [3, 4]. Severe disease was defined by a GMSPS of ≥8. Anonymous healthy blood donors (n = 95) were used as controls; of these, 52 (53%) were male.

IL-1Ra concentrations were determined using a commercially available solid-phase enzyme-amplified sensitivity immunoassay performed on microtiter plates (Medgenix IL-1Ra EASIA Kit; Biosource). If the IL-1Ra concentrations in a blood sample were higher than the upper limit of the standard curve, additional dilutions were not performed. In the statistical analysis, nonparametric tests for ranked or ordinal data were used to account for this. A primer set was used to amplify the 86-base tandem repeat region contained in intron 2 of the IL-1Ra gene. The primer set consisted of primer 1 (5′–CTC AGC AAC ACT CCT AT-3′) and primer 2 (5′–TCC TGG TCT GCA GGT AA-3′). PCR was performed in a Progene Thermal cycler (Techne) programmed for 45 cycles of 50 s at 95°C, 40 s at 57.5°C, 30 s at 72°C, and 3 min at 72°C. The PCR product was electrohoresed using a 100-hp DNA ladder as a marker, at 100 V and 100 mA for 45 min on a 2% agarose gel, and the gel was