
TO THE EDITOR: A letter that I submitted to the Journal was published in the January 25 issue. Because there has been concern about the provenance and authorship of that letter, I request that it be retracted.

Hadi Meeran Hussain, M.B., B.S.
Military Hospital
Rawalpindi 46000, Pakistan

Multiple-Triazole–Resistant Aspergillosis

TO THE EDITOR: The use of voriconazole has become common for the management of invasive aspergillosis. However, therapy with voriconazole still sometimes fails, more often because of unresponsive underlying disease than because of resistance of the fungus. Since the first description of itraconazole resistance in Aspergillus fumigatus, three amino acid substitutions in the 14α-sterol demethylase cyp51A gene, which is the target site forazole drugs, have been described.

Our laboratory receives fungal isolates for identification and susceptibility testing from throughout the Netherlands. Since 2002, using Clinical and Laboratory Standards Institute methodology, we have observed an increase in the number of A. fumigatus isolates with elevated minimum inhibitory concentrations of voriconazole (2 to >16 mg per liter), itraconazole (>16 mg per liter), the investigational azole ravuconazole (4 to >16 mg per liter), and posaconazole (0.5 to 1.0 mg per liter). Thirteen isolates were cultured from nine patients from six hospitals in the Netherlands (Table 1). Primary aspergillosis was diagnosed in four patients, and five patients presented with breakthrough invasive aspergillosis.

A new mechanism of resistance, consisting of a Cyp51A amino acid substitution at codon 98 (L98H) together with a tandem repeat in the gene promoter, was found to be responsible for the azole-resistant phenotype. This resistance mechanism was present in 12 of the 13 isolates. Genotyping of the isolates showed no evidence for clonal spread of a single A. fumigatus genotype.

The prevalence of multiple-triazole resistance was compared with a previously conducted nationwide survey of 170 A. fumigatus isolates collected from 114 patients from 21 Dutch hospitals between 1945 and 1998. In this period, no patients with multiple-triazole–resistant isolates were found as compared with 10 of 81 patients in the period since 2002 (P<0.001).

Although the emergence of this new resistance mechanism coincides with the approval of voriconazole, the factors that may explain this phenomenon remain unclear. Four patients became infected with a multiple-triazole–resistant strain during long-term prophylaxis with itraconazole, a drug that has been widely available for clinical use since 1991. The recovery of multiple-triazole–resistant strains in patients who had not been previously treated with azoles suggests that alternative sources of azoles, such as the use of azole compounds in agricultural environments, might play a role.

Our observation underscores the need to make an etiologic diagnosis of invasive mold infection
Table 1. Characteristics of Nine Patients from Whom *A. fumigatus* Resistant to Multiple Triazoles Was Cultured.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Yr of Age</th>
<th>Underlying Disease</th>
<th>Date of Isolation</th>
<th>Site of Isolation</th>
<th>Disease Classification*</th>
<th>Previous Azole Exposure</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15</td>
<td>X-linked chronic granulomatous disease</td>
<td>April 4, 2002</td>
<td>Sputum</td>
<td>Breakthrough invasive pulmonary aspergillosis, proven</td>
<td>Prophylaxis with itraconazole (for 6 yr)</td>
<td>Voriconazole (high-dose)</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>None</td>
<td>Dec. 3, 2003</td>
<td>Ear swab</td>
<td>Invasive aspergillosis of mastoid cavity, proven</td>
<td>None</td>
<td>Surgery and topical therapy</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>Hyper-IgE syndrome</td>
<td>Nov. 19, 2004</td>
<td>Bronchoalveolar-lavage fluid</td>
<td>Breakthrough invasive pulmonary aspergillosis, proven</td>
<td>Treatment with voriconazole (for 2 yr)</td>
<td>Surgery and posaconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>Female</td>
<td>76</td>
<td>Pulmonary fibrosis</td>
<td>June 26, 2005</td>
<td>Sputum</td>
<td>Invasive pulmonary aspergillosis, possible</td>
<td>None</td>
<td>Voriconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>Chronic granulomatous disease</td>
<td>Nov. 1, 2005</td>
<td>Lung aspirate</td>
<td>Breakthrough invasive pulmonary aspergillosis, probable</td>
<td>Prophylaxis with itraconazole (for &gt;10 yr)</td>
<td>Caspofungin and posaconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>Female</td>
<td>68</td>
<td>Acute myeloid leukemia</td>
<td>Feb. 14, 2006</td>
<td>Bronchoalveolar-lavage fluid</td>
<td>Disseminated invasive aspergillosis, probable</td>
<td>None</td>
<td>Voriconazole</td>
<td>Died</td>
</tr>
<tr>
<td>Female</td>
<td>62</td>
<td>Chronic obstructive pulmonary disease</td>
<td>April 5, 2006</td>
<td>Bronchoalveolar-lavage fluid</td>
<td>Invasive pulmonary aspergillosis, possible</td>
<td>None</td>
<td>Voriconazole, amphotericin B, and posaconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>Chronic granulomatous disease</td>
<td>April 15, 2006</td>
<td>Bone</td>
<td>Breakthrough aspergillus osteomyelitis, proven</td>
<td>Prophylaxis with itraconazole (for &gt;2 yr)</td>
<td>Voriconazole, caspofungin, and posaconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
<td>Acute myeloid leukemia and allogeneic hematopoietic stem-cell transplantation</td>
<td>May 11, 2006</td>
<td>Nose swab</td>
<td>Breakthrough aspergillus sinusitis, proven</td>
<td>Prophylaxis with itraconazole (for 4 wk)</td>
<td>Posaconazole</td>
<td>Died</td>
</tr>
</tbody>
</table>

* Diseases were classified according to consensus criteria defined by the European Organisation for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.

† Information about this patient is from Warris et al.3
and to determine antifungal drug activity in clinically relevant A. fumigatus isolates. Furthermore, international surveillance programs are warranted to investigate the spread of resistance in A. fumigatus.

Paul E. Verweij, M.D.
Radboud University Nijmegen Medical Center
6500 HB Nijmegen, the Netherlands
p.verweij@mmb.umcn.nl

Emilia Mellado, Ph.D.
Instituto de Salud Carlos III
28220 Madrid, Spain

Willem J.G. Melchers, Ph.D.
Radboud University Nijmegen Medical Center
6500 HB Nijmegen, the Netherlands


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