Comparison of the In Vitro Activities of Newer Triazoles and Established Antifungal Agents against Trichophyton rubrum

Shuwen Deng, Chao Zhang, Seyedmojtaba Seyedmousavi, Shuang Zhu, Xin Tan, Yiyang Wen, Xin Huang, Wenzhi Lei, Zhaojing Zhou, Wenjie Fang, Shuashuai Shen, Danqi Deng, Weihua Pan, Wanqing Liao

Shanghai Institute of Medical Mycology, Department of Dermatology, Changzheng Hospital, Second Military Medical University, Shanghai, China; Department of Medical Microbiology, Radboudumc, Nijmegen, The Netherlands; Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands; Invasive Fungi Research Center, Mazandaran University Medical Center, Sari, Iran; Department of Dermatology, The Second Affiliated Hospital of Kunming Medical University, Kunming, China; Department of Dermatology, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China

One hundred eleven clinical Trichophyton rubrum isolates were tested against 7 antifungal agents. The geometric mean MICs of all isolates were, in increasing order: terbinafine, 0.03 mg/liter; voriconazole, 0.05 mg/liter; posaconazole, 0.11 mg/liter; isavuconazole, 0.13 mg/liter; itraconazole, 0.26 mg/liter; griseofulvin, 1.65 mg/liter; and fluconazole, 2.12 mg/liter.

Dermatophytosis caused by Trichophyton rubrum is the most common cutaneous fungal infection worldwide (1), which represents the cause of between 80% and 90% of all chronic and recurrent infections (2). These infections establish an important public health problem because of the prolonged treatment required for the disease, because of the frequent recurrence of infection, and because they are generally considered difficult to manage (3). Reliable in vitro susceptibility testing would therefore be useful for selecting the most suitable antifungal treatment. For many years, griseofulvin was the only approved systemic antidermatophytic agent (4). However, nowadays, many potent antifungal agents are available for the treatment of dermatophytosis, such as allylamines and triazoles, which have more potent activity and fewer side effects (5–19). The expansion of information on in vitro susceptibility testing of dermatophytes to new antifungal agents will help in the selection and development of antifungal drug regimens.

The aim of the current study was to compare in vitro the activities of three newer triazoles, voriconazole, posaconazole, and isavuconazole, and four established antifungal agents against T. rubrum infection. One hundred eleven clinical isolates of T. rubrum were collected from seven dermatology clinics in Shanghai, China. Morphological identifications were confirmed by sequence-based analysis of the internal transcribed spacer of the rRNA gene region. The in vitro activities of seven antifungal agents were determined according to the CLSI reference guideline M38-A2 (20), with minor modifications. Two reference strains, Trichophyton mentagrophytes (strain ATCC MYA-4439) and Candida parapsilosis (strain ATCC 22019), were included as quality controls. Student’s t test with the statistical SPSS package (version 9.0) was used, and P values of <0.05 were considered statistically significant.

Table 1 lists the MIC ranges, geometric mean (GM) MICs, MIC<sub>50</sub>s, and MIC<sub>90</sub>s of seven antifungal agents against 111 T. rubrum strains. Terbinafine, voriconazole, posaconazole, isavuconazole, itraconazole, and griseofulvin had low MICs against all tested strains, whereas fluconazole did not show inhibitory effects. Similar results have been achieved in other studies (Table 2); however, limited data are available for the newer triazoles isavuconazole and posaconazole.

Terbinafine was one of the most effective antifungal agents against T. rubrum among the 7 fungal agents tested, and our findings confirm those of previous studies (5–19) (Table 2).

We compared the in vitro activities of the 3 newer triazoles isavuconazole, posaconazole, and voriconazole with that of itraconazole. Three newer triazoles offered good in vitro activity against T. rubrum (Table 1). All isolates were far more susceptible to the 3 newer triazoles than to itraconazole (Table 1) and comparable to those reported by other studies (7, 9, 10, 14, 17, 18).

Isavuconazole is a novel broad-spectrum triazole agent and has the same mechanism of action as the other triazoles. Several studies have supported its efficacy in invasive Candida species, Cryptococcus neoformans, Aspergillus species, and Mucorales isolates.
<table>
<thead>
<tr>
<th>Method for testing</th>
<th>MICs (mg/liter)</th>
<th>Fluconazole</th>
<th>Posaconazole</th>
<th>Voriconazole</th>
<th>Itraconazole</th>
<th>Isavuconazole</th>
<th>Griseofulvin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T. rubrum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incubation time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of strains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td></td>
</tr>
<tr>
<td>MIC90</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td>0.016 10 111</td>
<td></td>
</tr>
</tbody>
</table>

Incubation time is in hours, unless otherwise stated.

GM, geometric mean.
agents against the T. rubrum isolates investigated. These results might help clinicians to develop appropriate therapies for treating dermatomyositis caused by T. rubrum. However, further clinical investigations must be conducted in order to develop interpretive breakpoints.

ACKNOWLEDGMENTS

This study was supported in part by program no. 973 (grants 2013CB531601 and 2013CB531606), by fund no. 2013ZX10004612 of the Program of Severe Infectious Disease of China, and in part by fund no. 14dz2272900 from the Shanghai Key Laboratory of Molecular Medical Mycology; it was also partially supported by the Chinese National Nature Science Fund grants 31171039 and 81471926.

Seyedmohbata Seyedmousavi received travel grants from Astellas and Gilead Sciences. All other authors have no conflicts of interest.

REFERENCES