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

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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, MIC50s, and MIC90s 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 1 Geometric mean MICs, MIC ranges, MIC50s, and MIC90s obtained by susceptibility testing of antifungal agents against 111 T. rubrum clinical isolates

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC/MIC (mg/liter)</th>
<th>Range</th>
<th>50%</th>
<th>90%</th>
<th>Geometric mean</th>
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<tbody>
<tr>
<td>Griseofulvin</td>
<td>1–4</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Fluconazole</td>
<td>0.125–64</td>
<td>2</td>
<td>64</td>
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<td>Itraconazole</td>
<td>0.031–16</td>
<td>0.5</td>
<td>2</td>
<td>0.26</td>
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<tr>
<td>Voriconazole</td>
<td>0.031–16</td>
<td>0.031</td>
<td>0.125</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>0.016–1</td>
<td>0.125</td>
<td>0.5</td>
<td>0.11</td>
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<tr>
<td>Isavuconazole</td>
<td>0.031–4</td>
<td>0.06</td>
<td>0.125</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Terbinafine</td>
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<td>0.031</td>
<td>0.06</td>
<td>0.03</td>
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TABLE 2  Summarized data on susceptibility of *Trichophyton rubrum* to antifungal drugs in different studies from 2000 to 2014

<table>
<thead>
<tr>
<th>Method for testing</th>
<th>Incubation time (h)</th>
<th>Incubation temp (°C)</th>
<th>Reference</th>
<th>No. of strains</th>
<th>G30</th>
<th>M10</th>
<th>M125</th>
<th>M78</th>
<th>M64</th>
<th>M16</th>
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<td>111</td>
<td>96</td>
<td>96</td>
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</tbody>
</table>

Incubation time is in hours, unless otherwise stated.

a PDA, potato dextrose agar; OA, oatmeal agar.

b GM, geometric mean.

c (28–30).

The excellent activity of voriconazole against *T. rubrum* has been observed by B. Fernández-Torres et al. (17) and A. J. Carrillo-Muñoz et al. (9), with sample sets of 144 and 139 isolates, respectively (GM for both, 0.06 mg/liter). Our findings with 111 isolates have confirmed this good activity (GM, 0.05 mg/liter). There were, however, some discrepancies; in two of the previous reports, voriconazole appeared to be less active than itraconazole (7, 18). This could be attributed, at least partially, to the different methodology employed and the lack of standardized protocols. Our previous study (24) revealed that voriconazole had potent activity against *T. violaceum*.

For itraconazole, significant variations are shown in the published literature (Table 2). Overall, the geometric mean MIC of itraconazole for half of the isolates was <0.1 mg/liter, and the highest GM was 0.59 mg/liter (16), followed by 0.42 mg/liter (8). Our results showed good in vitro activity of itraconazole against *T. rubrum* (GM, 0.26 mg/liter); however, itraconazole was less active than the three new triazoles tested.

Griseofulvin was the first-line antifungal agent for the treatment of dermatophytes for many years; today, it is used less due to griseofulvin-resistant isolates of dermatophytes and the existence of strains with elevated MICs to griseofulvin (6, 25–27). With our results, the MICs of griseofulvin for *T. rubrum* were in agreement with those reported by Adimi et al. (7) and Perea et al. (18). Griseofulvin was less active than the rest of the agents tested except for fluconazole against *T. rubrum*. Nevertheless, all strains were more susceptible to griseofulvin than to fluconazole (Table 1).

Among the studies reported in Table 2, fluconazole also was effective against *T. rubrum*, except in a study by Adimi et al. (7). Of all the agents tested in the current study, fluconazole showed the lowest activity, which was consistent with previous studies (9, 10, 16); although *T. rubrum* is not susceptible to fluconazole, it is recommended for the management of some dermatophytes (28–30).

In conclusion, terbinafine, voriconazole, posaconazole, and isavuconazole were shown in vitro to be the most potent antifun-
gal agents against the *T. rubrum* isolates investigated. These results might help clinicians to develop appropriate therapies for treating dermatophytosis caused by *T. rubrum*. However, further clinical investigations must be conducted in order to develop interpretive breakpoints.

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