Oral Treatment of Tinea Corporis and Tinea Cruris with Terbinafine and Griseofulvin: A Randomized Double Blind Comparative Study†

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Griseofulvin, a conventional antifungal therapy, has been the first-line drug for the management of dermatophyte infections for nearly 30 yrs. Resistance to griseofulvin is associated with poor rates of recovery and high rates of relapse in many dermatophyte infections(1). The development of a drug that is able to kill the fungi rather than only inhibit their growth should provide an important clinical step forward in the treatment of these diseases. The new allylamine antifungal terbinafine has this characteristic.

Recently introduced, terbinafine has a primary fungicidal action against a wide range of dermatophytes of the general Trichophyton, Epidermophyton and Microsporum(2-4). It is administered orally and acts through inhibition of squalene epoxidase(5-9). Comparison of standard in vitro mycological tests showed terbinafine to be more effective in the treatment of dermatophyte infection than other currently available antifungals(10). Clinical studies of terbinafine have been based on its high degree of efficacy demonstrated in vitro against a wide spectrum of dermatophytes and on its effectiveness in animal models(11-14).

The purpose of this study was to evaluate the efficacy and tolerability of oral terbinafine in comparison to griseofulvin in patients with tinea corporis and tinea cruris.

MATERIAL AND METHOD

The study was performed from January 1992 to August 1992 at Songklanagarind Hospital, Prince of Songkla University, Thailand. The protocol was approved by the Ethical Committee of the Faculty of Medicine.

Sixty-four patients were clinically diagnosed as tinea corporis or tinea cruris proven by KOH wet mount microscopy and culture were both required before the patients were recruited into the study, the trial was a double-blind study and patients were randomized into one of two treatment groups: terbinafine 250 mg once daily or micronized griseofulvin 500 mg once daily. Neither the clinician nor the patient knew which was being used. Treatment was administered for a period of upto 2 wks; concomitant medication for various chronic diseases, such as cardiac insufficiency, high blood pressure or diabetes mellitus were maintained during the study.

All patients were assessed prior to treatment with a detailed history and clinical exami-
nation. Only patients aged between 17 and 60 yrs having tinea corporis or tinea cruris confirmed by direct microscopy and culture were included in the study. Written consent was obtained from all patients, pregnant women and female patients of child-bearing age not using reliable contraceptive measures, those with dermatophytosis of palms or soles, patients with diseases of the digestive system, conditions which might impair absorption from the gastrointestinal tract, patients with liver disease, nephropathy, blood dyscrasias, disturbances of porphyrin metabolism, patients allergic to griseofulvin, patients receiving radiation therapy, systemic therapy with immunosuppressive drugs, or therapy with other antifungal drugs either at the time of the trial or 12 wks prior to the start of the study were excluded from the trial.

The patients were seen 2 wks after treatment and at follow-up (4 wks post therapy). Parameters of clinical disease activity (erythema, pruritus, scaling, exudation and pustulation) were assessed and scored as: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Scrapings were taken from the target lesion for KOH wet mount and mycological examinations (direct microscopy and culture on Sabouraud's dextrose agar with added chloramphenicol).

Tolerability was assessed by noting adverse events which occurred during treatment, at the end of treatment and at the follow-up period and their severity was graded as mild, moderate or severe.

Haematological investigation (haemoglobin, haematocrit, total WBC with differential and platelet count) and biochemical tests (SGOT, SGPT, alkaline phosphatase, LDH, bilirubin, total protein, albumin, creatinine, glucose, cholesterol and triglycerides) and urine tests (protein, glucose, acetone, bile and sediment) were carried out at the initial examination and after 2 wks of therapy and at 4 wks follow-up.

The assessment of the drug efficacy was evaluated into clinical response alone, mycological response alone and overall assessment combined clinical response and mycological response.

Clinical response: defined as the ability of the drugs to decrease clinical score at each visit during the treatment period and at follow-up.

Mycological response: defined as ability of the drugs to decrease the organism both microscopy and culture.

Overall assessment: can be classified into two categories.

A: complete cure = microscopy and culture negative, no residual clinical signs and symptoms.

B: effective therapy = microscopy and culture negative with mild residual clinical signs and symptoms.

Wilcoxon matched paired rank test was used for comparing mean total score. Fisher's exact two-tailed test was used for evaluation of mycological result.

RESULTS

Sixty-four patients entered the study. Of these, two were drop-outs; one in the terbinafine group for unknown reasons and one in the griseofulvin group because of diarrhea. Each group had 31 patients which were proved statistically to have no significant differences in the age, sex, weight, height, distribution, duration of disease, type and size of lesion (Table 1), predisposing factors, other diseases in past history, family members with fungal infections and prior medication between the groups. The infecting organisms responsible for the infection had an even distribution in both groups (Table 2).

<table>
<thead>
<tr>
<th>Table 1. Study patients' data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine-treated</td>
</tr>
<tr>
<td>(n=32)</td>
</tr>
<tr>
<td>Male /female</td>
</tr>
<tr>
<td>Age (yrs)*</td>
</tr>
<tr>
<td>Height (cm)*</td>
</tr>
<tr>
<td>Weight (kg)*</td>
</tr>
<tr>
<td>Lesion size (cm²)</td>
</tr>
</tbody>
</table>

*Means ± SD

<table>
<thead>
<tr>
<th>Table 2. Organisms isolated in study patients (n)</th>
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</thead>
<tbody>
<tr>
<td>Terbinafine-treated (n=32)</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Trichophyton rubrum</td>
</tr>
<tr>
<td>Trichophyton mentagrophytes</td>
</tr>
<tr>
<td>Epidermophyton floccosum</td>
</tr>
</tbody>
</table>


Clinical result

After 2 wks of active treatment, the reduction in mean total score of clinical symptoms was similar for both groups (Fig. 1). However, after a further 4 wks of follow-up, the score reduction for the two treatments was significantly greater with terbinafine (p<0.05) by using Wilcoxon matched paired rank test.

Mycological result (Table 3)

After 2 wks of terbinafine treatment, 90.3 per cent of patients were mycologically cured (defined as negative microscopy and culture) compared with 80.7 per cent in the griseofulvin-treated group (Fig. 2). These rates changed to 87.1 and 54.8 per cent with terbinafine and griseofulvin respectively at the end of follow-up. Again, the differences were statistically significant (p<0.05), using Fisher's two tailed exact test. There were 8 patients relapsed after mycological cure in the griseofulvin group (25%) at the end of the study. Five of these patients had tinea cruris caused by T. rubrum and the other three had tinea corporis caused by T. mentagrophytes, in the terbinafine group, two patients (6.4%) relapsed at the end of the study. One patient had a groin infection caused by E. floccosum and the other had extensive ringworm of the trunk caused by T. rubrum.

![Fig. 1 Change in mean total score from pretreatment (baseline) value after 2 wks of treatment and after 4 wks of follow-up. * p<0.05](image1)

![Fig. 2 Mycological cure rate at the end of treatment period and at follow-up * p>0.05](image2)

Table 3. Number of patients responding at the end of treatment (week 2) and at follow-up (week 6)

<table>
<thead>
<tr>
<th>Microscopy</th>
<th>Terbinafine (n=31)*</th>
<th>Griseofulvin (n=31)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 2</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Positive</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Positive</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Mycological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cure (%)</td>
<td>0</td>
<td>90.0</td>
</tr>
</tbody>
</table>

*One patient lost to follow-up in each group
Overall assessment of clinical and mycological response

- Complete cure (Table 4)
  After 2 wks of treatment, there was complete cure in 19.4 per cent in the terbinafine group compared with 12.9 per cent in the griseofulvin group. After 6 wks of treatment, there was a complete cure in 83.9 per cent in the terbinafine group compared with 41.9 per cent in the griseofulvin group.

- Effective therapy (Table 4)
  After 2 wks of treatment, there was effective therapy in 77.4 per cent in the terbinafine group compared with 48.4 per cent in the griseofulvin group. After 6 wks of treatment, there was effective therapy in 87.1 per cent in the terbinafine group compared with 54.8 per cent in griseofulvin group.

Tolerability

Four terbinafine-treated patients had mild side-effects possibly related to the drugs in the days of treatment, but they subsided and all were able to complete their full course of treatment; these side-effects consisted of nausea, diarrhea and headache (Table 5). Five griseofulvin treated patients also had mild side effects which later subsided. These were: nausea, diarrhea and indigestion (Table 5).

Table 4. Overall assessment of clinical mycological response

<table>
<thead>
<tr>
<th></th>
<th>Terbinafine</th>
<th>Griseofulvin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>after 2 wks</td>
<td>after 2 wks</td>
</tr>
<tr>
<td></td>
<td>therapy</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Complete cure</td>
<td>19.4%</td>
<td>83.9%</td>
</tr>
<tr>
<td></td>
<td>(6/31)</td>
<td>(26/31)</td>
</tr>
<tr>
<td></td>
<td>12.9%</td>
<td>41.9%</td>
</tr>
<tr>
<td></td>
<td>(4/31)</td>
<td>(13/31)</td>
</tr>
<tr>
<td>Effective therapy</td>
<td>77.4%</td>
<td>87.1%</td>
</tr>
<tr>
<td></td>
<td>(24/31)</td>
<td>(27/31)</td>
</tr>
<tr>
<td></td>
<td>48.4%</td>
<td>54.8%</td>
</tr>
<tr>
<td></td>
<td>(15/31)</td>
<td>(17/31)</td>
</tr>
</tbody>
</table>

Table 5. Side effects reported during the study

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Terbinafine group</th>
<th>Griseofulvin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Indigestion</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

Evaluation of renal function test before and during the treatment with either terbinafine or griseofulvin revealed no clinically relevant drug related changes. In the liver function tests there were some transient changes possibly due to drugs in SGOT (one patient in the terbinafine group 81 IU/L and two in griseofulvin 76 and 84 IU/L) at follow-up, all enzyme activities had returned to normal.

DISCUSSION

The results reported here suggest that oral terbinafine is, in general, comparably safe and more effective than griseofulvin in the overall management of tinea corporis and tinea cruris at the end of treatment, although at long-term follow-up both drugs were comparable.

Data from previous studies comparing terbinafine and griseofulvin in tinea corporis have shown that terbinafine (250 mg/day) given orally
was as effective as griseofulvin (500-1,000 mg/day) over a treatment period of 6 wks\(^{15-17}\). The mycological cure rates at the end of treatment ranged from 78-100 and 83-100 per cent with terbinafine and griseofulvin, respectively. The results in our population were inferior at the end of the treatment to those published because of the shorter duration of treatment.

Interestingly, there was a large number of terbinafine-treated patients who still had residual signs and symptoms and positive culture at the end of the 2 wks treatment who had achieved more clinical and mycological cure at the end of study without using other treatment measures. This result indicated that terbinafine continues to exert a therapeutic effect for a prolonged period even after a short course of treatment, this observation has been previously noted that in using different topical and systemic antifungals, there were a number of patients who still had moderate signs and symptoms at the end of the treatment with positive cultures (carriers) achieved a total clinical and mycological cure a few weeks later\(^{18-20}\). This means that the process of healing of dermatophytosis is complex and therefore not dependent on positive cultures alone.

In our patients, there were no significant differences in terms of tolerance between terbinafine and griseofulvin and the side effects were mild and transient.

**SUMMARY**

Sixty-four patients with clinically and mycologically diagnosed tinea corporis and tinea cruris were randomly allocated to receive either 250 mg of oral terbinafine once daily or 500 mg of griseofulvin once daily for 2 wks. Patients in each group were well matched for age, gender, clinical features and type of dermatophytes.

Clinical and mycological control tests (KOH wet mount and culture) were performed before treatment, at the end of treatment and 4 wks after stopping treatment. In the majority of cases, the infecting agent was identified as *Trichophyton rubrum* (53/64). The remainder comprised *Trichophyton mentagrophytes* (8/64) and *Epidermophyton floccosum* (3/64).

After 2 wks of therapy, there was no significant difference in mycological response in the terbinafine group (90.3%) and griseofulvin group (80.7%). The clinical response in both groups was the same. At 6 wks' follow-up, the mycological cure in terbinafine and griseofulvin group was 87.1 and 54.8 per cent, respectively (\(P < 0.05\)). The clinical response of the terbinafine group was also significantly higher than in the griseofulvin group. A higher relapse rate was observed in the griseofulvin group than in the terbinafine group. No serious side effects were reported in either group.

The result showed that oral terbinafine was more effective than oral griseofulvin in the treatment of tinea corporis or tinea cruris.

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**REFERENCES**

10. Balfour JA, Faulds D. Terbinafine : a review of its pharmacodynamic and pharmacokinetic proper-


