

Original Article

## Treatment Outcome and Relapse with Short-term Oral Terbinafine (250 mg/day) in Tinea Pedis

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### Abstract

A total of 168 patients with tinea pedis, but without onychomycosis, were treated with 1 cycle of terbinafine (TBF) (1 cycle: defined as 250 mg/day for 1 week). KOH preparation for direct microscopy was performed 4, 8 and 12 weeks after starting therapy to determine if testing was positive for tinea. Patients with no negative results on KOH examination or no evidence of obvious clinical improvement at 8 weeks, another cycle of the therapy was prescribed. The “cure,” “no cure,” “dropout,” and “discontinuation/unevaluable” rates were 89.3%, 4.8%, 4.8% and 1.2%, respectively. The number of cycles required for cure in the plantar type was 1 cycle in 65.9% and 2 cycles in 54.5% of cases; in the interdigital type, 1 cycle in 79.1% and 2 cycles in 20.9% of cases; and mixed type, 1 cycle in 29.1% and 2 cycles in 60.9% cases. Among patients who were followed for at least 3 years after cure, the relapse rates were about 10% each year: 1 year, 11.3%; 2 years, 8.9%; and 3 years, 11.2%. The relapse rate of about 10% each year over a 3-year period suggests that reinfection may be likely.

**Key words:** oral terbinafine, treatment outcome, relapse rate, tinea pedis

### Introduction

When treating tinea unguium using terbinafine (TBF), we have noticed that accompanying tinea pedis is very easily treated, and recurrence is rare. In other countries, there have been many reports on the therapeutic effects of oral TBF on tinea pedis<sup>1–4</sup>. However, few reports of oral TBF for tinea pedis have been published in Japan because the use of TBF for tinea pedis of conventional form is not covered by health insurance.

We now report treatment outcome in these patients. In addition, among patients who were followed for at least 3 years after cure, relapse rates at 1 to 3 years were calculated.

### Patients and Methods

Over a 5-year period from January 1998 to December 2002, 168 patients diagnosed with tinea pedis, based on clinical features and KOH examination, were treated with 1 cycle of oral terbinafine (TBF) (1 cycle defined as 250 mg/day for 1 week) by the Department of Dermatology, Showa University Fujigaoka Hospital.

The patients in this study had no evidence of onychomycosis. Of the 168 patients with tinea pedis, 93 had a plantar-type, 51 had an interdigital-type and the remaining 24 had both plantar- and interdigital-type (mixed-type).

Follow-up examinations at 4, 8 and 12 weeks after starting treatment included clinical and KOH examination. In general, regardless of the findings on KOH examination at 4 weeks, KOH examination was again performed at 8 weeks to determine if testing was positive for tinea. In patients with no negative results on KOH

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examination or no evidence of obvious clinical improvement at 8 weeks, another cycle of the therapy was prescribed.

In the present study, cure was defined as follows: at either 8 or 12 weeks after the start of treatment, improved clinical symptoms were seen, and KOH examinations of scales collected from several places and stratum corneum samples harvested using a scalpel under a microscope did not show any fungal elements. Continued negative results on KOH examination at 12 weeks, even in the absence of marked improvement on clinical examination, was also defined as a "cure." Positive results on KOH examination at 12 weeks or later after starting treatment, regardless of whether clinical examination showed improvement, were defined as "no cure." Treatment in these patients was changed.

To evaluate relapse in patients judged as cured, an attempt was made to schedule follow-up evaluations including KOH examination. The presence or absence of a relapse in the patients who achieved a cure was evaluated by a clinic visit or contacting the patient by phone or e-mail each year from late August to early September. Eighty two of the patients were evaluated through contact by phone or e-mail; the other 68 patients were evaluated at a clinic visit.

## Results

The results of the 168 patients treated with oral TBF are summarized in Table 1. Treatment produced a "cure" in 150 patients and "no cure" in 8. There were 8 "dropouts" who started treatment but did not return to clinic for follow-up. Treatment was discontinued or unevaluable in 1 patient each. If the 8

Table 1. Treatment outcome of tinea pedis with intermittent cycles of 1-week oral TBF (250 mg/day)

	Number (%)
Cure	150 (89.3)
No cure	8 (4.8)
Dropout	8 (4.8)
Discontinued/Unevaluable	2 (1.2)
Total	168 (100)

Table 2. Number of cures for each tinea pedis clinical type

Clinical type	Number
Plantar type	84
Interdigital type	43
Mixed type	23
Total	150

dropouts are excluded, the "cure" rate was 93.8% and the "no cure" rate was 5.0%. The discontinued and unevaluable rates were both 0.6%.

Of the 150 patients cured of tinea pedis, 84 had the plantar type, 43 had the interdigital type and 23 had the mixed type (Table 2). Among patients with a cure, 29 with the plantar type, 9 with the interdigital type and 14 with mixed type received two treatment cycles (Table 3).

Of the 8 patients without a cure, 1 patient judged as having a cure 8 weeks after cycle 1 of treatment had a relapse 1 month later. In each of the other patients, KOH examination was positive at 4 to 8 weeks after cycle 2 of treatment. Five of the patients had the interdigital type, 2 had both the interdigital and plantar types, and 1 had the plantar type.

There were 115 patients who were followed for at least 3 years after completing treatment. Figure 1 depicts the changes in relapse rates from 1 to 3 years in these patients. At 1 year, among 115 patients, 101 (87.8%) had no relapse, 13 (11.3%) had a relapse, and in one (0.9%), the status was unknown. At 2 years, among 101 patients, 89 (88.1%) had no relapse, 9 (8.9%) had a relapse, and the status was unknown in 3 (3.0%). At 3 years, 74 of 89 patients (83.1%) had no relapse, 10 (11.2%) had a relapse, and in 5 (5.6%), the status was unknown.

Of the 115 patients followed for at least 3 years, there were 58 cases of plantar type, 16 cases of interdigital type and 21 cases of mixed type. The number of relapses over 3 years was 15 in the plantar type, 15 in the interdigital type and 2 in the mixed type.

## Discussion

In addition to clinical examination and KOH examination by direct microscopy, culture findings have been regarded as essential to evaluate a "cure". However, not all lesions can be cultured or examined with KOH, so complete evaluation of microbiological cure is nearly impossible. A better clinical indicator is whether the patient again develops tinea pedis the following summer<sup>1)</sup>.

Table 3. Number of cycles of treatment until cure

	1 cycle	2 cycles	Total
Plantar type	55	29	84
Interdigital type	34	9	43
Mixed type	9	14	23
Total	98	52	150

In the present study, we decided to use a marked improvement on clinical examination and findings on KOH examination as evaluation criteria for "cure". Even if KOH examination was positive, mycological culture of skin materials was not performed from all patients as a basis for initial diagnosis. We cannot deny that there was a slightly insufficient basis for the initial diagnosis.

The "cure" "no cure" and "dropout" rates in our study were 89.3%, 4.8%, and 4.8%, respectively (Table 1). Of the patients who did not return for follow-up and were considered "dropouts," 13 patients were judged to be "cured" based on telephone interviews or examination 2 years or later when they visited our clinic for another disorder. Therefore, most of the 8 dropout patients, in fact, likely were cured of tinea pedis. If we exclude the 8 dropout patients, the "cure" rate was 93.8% and the "no cure" rate was 5.0%. Treatment was discontinued in 1 patient because of abdominal pain. In the unevaluable patient, *T. rubrum* was cultured at the initial evaluation, but *Candida* was found at the same site 2 months later. Because of the microbial substitution, rating this patient as "cured" may have been appropriate, but clinical examination showed no change, so the rating was "unevaluable."

In a study of oral TBF in tinea pedis, Barnetson *et al.*<sup>2)</sup> compared 1 week of oral TBF (250 mg/day) with 4 weeks of topical clotrimazole. The cure rates 4 weeks after completing therapy in both groups were approximately 72% and not significantly different. After 16 weeks with clotrimazole cream there was still no significant difference, but the cure rate was only 54.9% in the TBF group. In our study, if we assume treatment was completed after 1 week of therapy, the cure rate for both plantar type and interdigital type tinea pedis was 66.2% (114 of 172 cases). This is not considerably different from the rate reported by Barnetson *et al.*<sup>2)</sup> In another study of oral TBF in tinea pedis, Hay *et al.*<sup>3)</sup> compared 2 weeks of oral TBF (250 mg/day) with 4 weeks of oral itraconazole (100 mg/day). After 16 weeks, the cure rate with TBF was 78%. Keyser *et al.*<sup>4)</sup> treated 184 patients with oral TBF (250 mg/day) for 2 weeks and reported a clinical cure rate of 94.1% and microbiological cure rate of 88.6% after 2 months. Using a similar regimen, White *et al.*<sup>5)</sup> treated patients with tinea pedis and tinea manuum and reported microbiological cure rates of 64% after 4 weeks and 86% after 8 weeks. The results in our study are similar to

the data reported in these 2-week continuous treatment studies. However, in our treatment regimen, an additional cycle of therapy was prescribed only when clinical or KOH examination after 8 weeks showed no obvious improvement. As shown in Table 3, among patients with a cure, 29 with the plantar type, 9 with the interdigital type and 14 with the mixed type received two cycles of treatment. However, in 7 cases with the plantar type, 3 of the interdigital type and 4 of the mixed type, KOH examination at 8 weeks after the starting cycle (corresponding to the scheduled day for starting cycle 2) was negative, and clinical examination also showed improvement. Nevertheless, these patients requested that another cycle of treatment be prescribed. If all these patients were judged as being "cured" after 1 cycle, two cycles of treatment were required for a cure in 22 patients with the plantar type, 6 patients with interdigital type and 10 patients with mixed type. The majority of patients responded after 1 cycle of treatment. Surprisingly, fungal elements of dermatophytes were detected in plantar callosity of six patients, but KOH examination was negative after 1 cycle of treatment. In 1 patient, there was a relapse during the following year; there were no relapses in the other patients.

Five of the 8 patients with "no cure" had only the interdigital type. In another patient with both the plantar and interdigital type, there was recurrence only on the interdigital region. This suggests that interdigital tinea pedis may be more refractory to treatment than plantar tinea pedis. Furthermore, over a 3-year period, the relapse rate for the interdigital type (29.8%) was higher than for the plantar type (15.2%). Of the 8 patients with "no cure" 3 patients stopped coming to the clinic, so their clinical course is unknown. One patient continued topical therapy but had repeated infections. In 4 patients, continuous treatment with TBF (125 mg/day) was prescribed. Two patients had a cure with 1 month of treatment, but the other 2 patients had no response to therapy. With continuous oral TBF (250 mg/day), a cure was judged after 5 weeks and after 8 weeks.

In many cases, there was disagreement between the patient and physician regarding a relapse; preference was given to the opinion of the physician. Although patients who had a relapse often came back to the clinic, there were relatively few who returned every year merely to show whether or not they had has a relapse. Therefore, we had to evaluate these patients by phone or e-mail interview. Of thoses

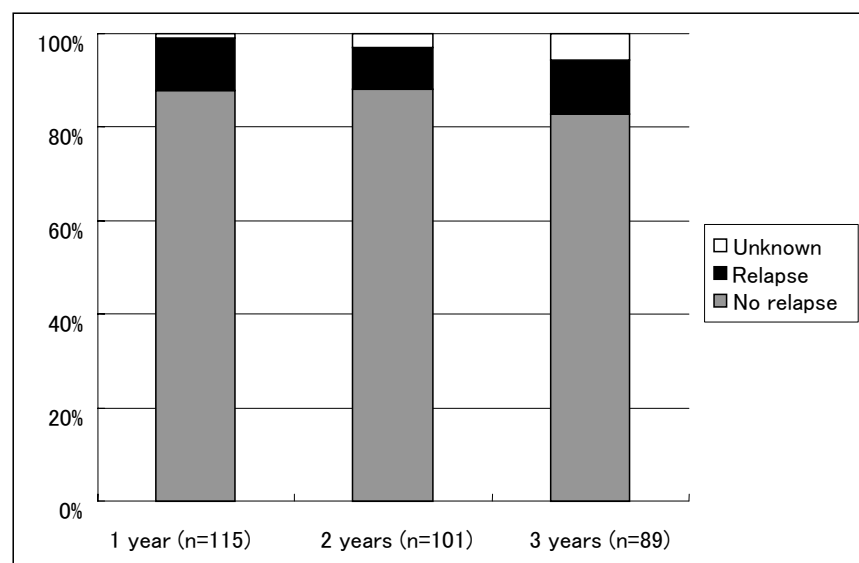


Fig. 1. Relapse rates over the 3-year period after cure

The figure depicts results in 115 patients who were followed for at least 3 years after cure.

evaluated by phone or e-mail, about 90% said they had “no relapse” and 10% said they had had a “relapse.” However, of the patients evaluated at a clinic visit, about one half had “no relapse” and one half had a “relapse.”

The number of patients lost to follow-up increased each year and reached more than half the cases by 4 years after treatment. This would not be statistically meaningful, so we decided to evaluate the presence or absence of relapse in patients followed for 3 years or longer, which included at least 100 patients. Although the number lost to follow-up increased each year, we found that over a 3-year period, approximately 85% of patients had “no relapse” and approximately 10% of patients had a “relapse” each year (Fig. 1).

Topical therapy has been regarded as relatively ineffective for hyperkeratotic tinea pedis<sup>6)</sup>, but a fungus negative conversion rate of 80.6% for lesions with some degree of keratinization has also been reported<sup>7)</sup>. This is not substantially different from our results, but few reports have addressed the issue of relapse after topical therapy. In 380 patients with tinea pedis who were treated during the summer of 1993, Nishimoto<sup>8)</sup> reported a cure in only 27 cases. In that study, the principal clinical problem was that despite treatment for several to over 10 years, many patients still had recurrent relapses. In addition, several studies following patients after cure for at least 1 year found relapse rates of approximately 50% at 1 year and thereafter<sup>9-11)</sup>. In our study, the relapse rates of approximately 10% each year with oral TBF are

relatively low compared to topical therapy. Although health insurance coverage may be a problem, the fact that many patients only require 2 or 3 clinic visits means a savings in costs. This, combined with the very low relapse rates, makes oral TBF, in our opinion, the best treatment of choice for many patients with tinea pedis. However, misdiagnosis may be a potential problem. Accurate diagnosis at the initial evaluation should preferably include fungal cultures, or at a minimum, the presence of fungal elements on direct KOH examination.

The issue of recurrence versus reinfection must always be considered in patients with relapse<sup>1</sup>. Our findings of an approximately 10% relapse rate each year over a 3-year period suggest that reinfection is more likely than recurrence.

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