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Twelve weeks of continuous oral therapy for toenail onychomycosis caused by dermatophytes: A double-blind comparative trial of terbinafine 250 mg/day versus itraconazole 200 mg/day

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Background: Dermatophyte infections of the toenail have been difficult to treat, requiring long courses of therapy and having high recurrence rates. New oral antifungal agents with better outcomes and minimal adverse events are needed.
Objective: The purpose of this study was to compare two newer antifungal compounds, terbinafine and itraconazole, for efficacy and safety in toenail onychomycosis caused by dermatophytes.
Methods: The study was randomized and double-blind. It compared 12 weeks of continuous oral treatment with terbinafine 250 mg/day or itraconazole 200 mg/day for confirmed toenail dermatophyte onychomycosis. Clinical symptoms and mycologic outcome were assessed at weeks 4, 8, 12, 24, 36, and 48. A total of 372 patients (186 in each group) with dermatophyte infection confirmed by microscopy and culture were included in the intent-to-treat analysis.
Results: At week 48, a statistically significantly greater percentage of the terbinafine group than itraconazole group showed negative mycology (73% [119 of 163] vs 45.8% [77 of 168]; $p < 0.0001$) (difference = 27.2%; 95% CI = [17.0%, 37.3%]). The difference was also confirmed clinically ($p = 0.001$) in the patients who were clinically cured or had only minimal symptoms at the end of the study (76.2% [125 of 164] vs 58.1% [100 of 172]) (difference = 18.1%; 95% CI = [8.24%, 27.9%]). The geometric mean length of healthy nail of the big toe was significantly greater in the terbinafine than itraconazole group (8.1 vs 6.4 mm; $p = 0.026$). Tolerability was good to very good in almost 90% of patients in both groups, and all reported adverse events were known for these compounds.
Conclusion: Terbinafine produced higher rates of clinical and mycologic cure at follow-up than did itraconazole. (J Am Acad Dermatol 1998;38:S57-63.)

Toenail onychomycosis is a common disease, affecting more than 2% of the population.[1] The causal agent is most frequently a dermatophyte, and the infection is difficult to treat. Newer antifungal compounds such as terbinafine, an allylamine and a new chemical entity, and itraconazole have reduced the duration of treatment to 3 months as compared with the extensive treatment necessary with the older antifungal agents griseofulvin and ketoconazole. The cure rates with these older compounds, which had to be taken until the whole nail had grown out, were low.[2] Hepatotoxicity and drug interactions were not uncommon, especially with ketoconazole.[2]

Terbinafine inhibits squalene epoxidase,[3,4] a key enzyme in ergosterol synthesis of the fungal cell membrane. Inhibition of this enzyme leads to deficient production of membrane sterol and accumulation of squalene within the fungal cell. This dual action is believed to lead to rapid death of the fungal cell. Therefore this primary fungicidal activity of terbinafine, i.e., its ability to kill fungi at minimal inhibitory concentrations (MIC), is believed to lead to the high cure rates obtained in

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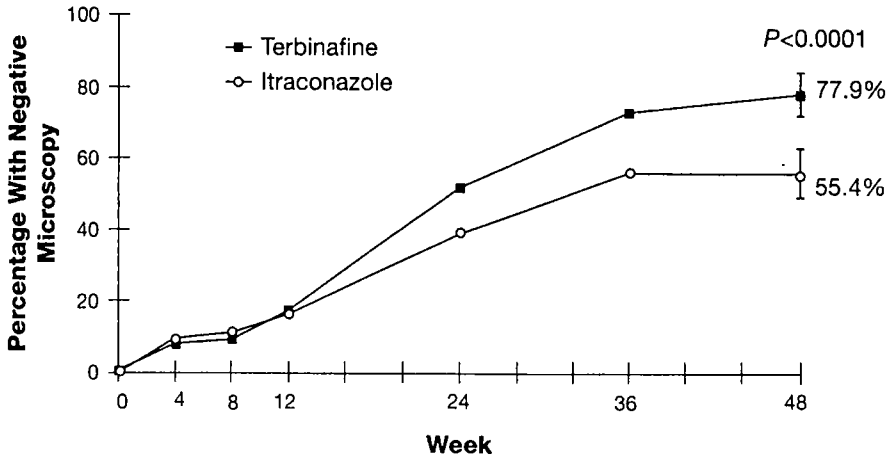

Fig. 1. Percentage of patients with negative microscopy (± 95% CI at week 48).

skin and nail fungal infections with short courses of treatment. The triazole, itraconazole, interrupts ergosterol synthesis by a different mechanism.[5] Itraconazole interferes with the demethylation of lanosterol to ergosterol by inhibiting a cytochrome P-450–dependent enzyme. The interference with the cytochrome P-450 metabolic pathway has led to interactions with drugs metabolized by this system.

The pharmacokinetics of the two drugs are comparable.[6-8] High concentrations are achieved rapidly in the nail plate and remain high for several months after discontinuation of oral treatment.

The aim of this study was to compare the efficacy and safety of 12 weeks of continuous therapy with oral terbinafine 250 mg daily and itraconazole 200 mg daily.

METHODS

This multicenter, double-blind, parallel-group study enrolled patients with fungal toenail infections. The protocol was approved by the local ethics committees, and oral informed consent was obtained from all patients.

Male and female patients 18 years or older who had a clinically suspected subungual dermatophyte infection that was then confirmed by direct microscopy and dermatophyte culture at a central laboratory were eligible for inclusion in the study. Coculture of other fungi with a dermatophyte in a few patients was not grounds for exclusion.

Patients with clinically relevant abnormalities in baseline values for creatinine, ALT, AST, γ-glutamyltransferase, alkaline phosphatase, and total bilirubin were excluded. Other exclusion criteria were nondermatophytic onychomycosis; pregnancy or breast feeding; women of childbearing potential if they were not using a reliable contraceptive method; concomitant diseases or conditions interfering with absorption from the gastrointestinal tract; significant kidney or liver disease; alcohol abuse; radiotherapy; and treatment with systemic cytostatic agents or immunosuppressive drugs (including corticosteroids taken in the preceding 2 weeks or during the study). Patients receiving oral antifungal treatment 4 months before the start of the study or any topical antifungal treatment 1 month before were excluded. No other antifungal therapy was allowed during the study. Patients with known hypersensitivity to allylamines or azoles or those unwilling to comply with the study requirements were excluded at the start of the study.

Eligible patients received a numbered box containing the study medication. The randomization list was computer-generated in balanced blocks of four. A double-dummy technique was used: Each daily dose was either a 250 mg terbinafine tablet (250 mg/day dose) and placebo capsules or two 100 mg itraconazole capsules (200 mg/day dose) and a placebo tablet. Patients were instructed to take two capsules and one tablet daily after the evening meal for 12 weeks. These instructions were printed on each medication blister pack.

Follow-up visits were scheduled at weeks 4, 8, 12, 24, 36, and 48. Concomitant medication and adverse events were recorded at each visit. One nail was selected as the target nail at the start of the study. Samples taken from this target nail were sent to the mycology laboratory of the Institute of Tropical Medicine in Antwerp for microscopy of potassium hydroxide (KOH) preparations and culture on Sabouraud 2% dextrose agar (with chloramphenicol 0.05% and with and

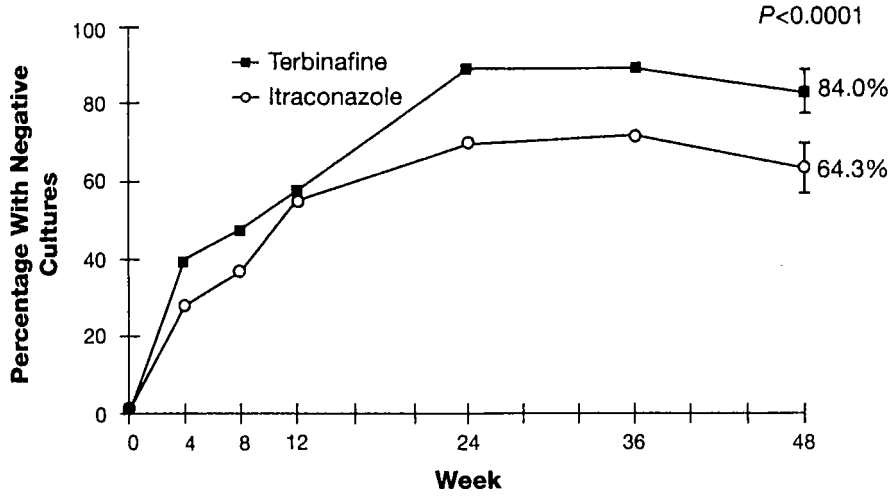

Fig. 2. Percentage of patients with negative dermatophyte culture (± 95% CI at week 48).

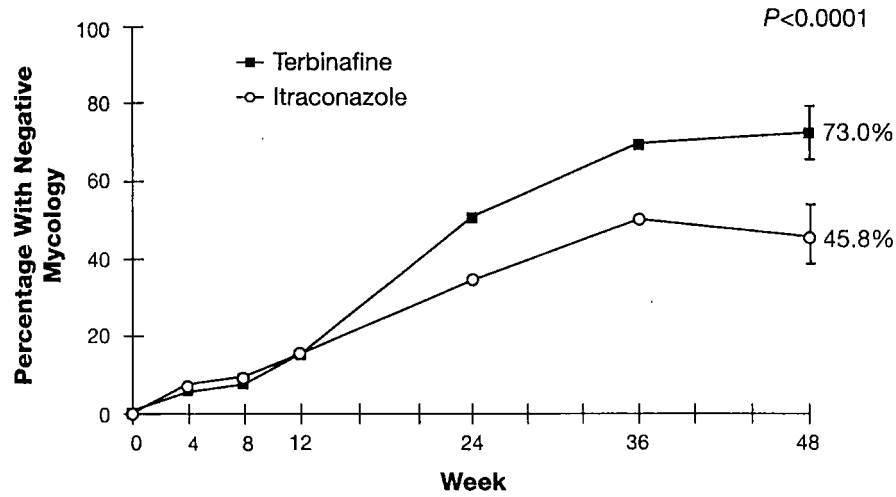

Fig. 3. Percentage of patients with negative mycology (negative microscopy plus negative dermatophyte culture) (± 95% CI at week 48).

without cycloheximide 0.5%) at room temperature for 4 weeks. Clinical signs and symptoms were recorded for the same target toenail throughout the study. This included measurements of the length of the healthy nail and scoring of hyperkeratosis, onycholysis, and paronychial inflammation on a 4-point scale (absent, mild, moderate, and severe). During the treatment period, tests of kidney and liver function were performed and drug compliance was checked. At the end of the study, the global clinical efficacy of treatment for the target nail was rated on a 4-point scale (cleared, minimal symptoms, slightly improved, failure). In addition, both investigators and patients rated the overall efficacy and overall tolerability of the treatment on a 5-point scale (very good, good, moderate, poor, very poor).

The intent-to-treat statistical analysis compared the two treatment groups for baseline characteristics, efficacy parameters, overall assessment of efficacy, drug compliance, adverse events, and biochemical laboratory tests. The end point chosen for the calculation of sample size was the percentage of patients with a negative culture at week 48. On the basis of a two-sided significance level of 0.05 and a power of 90% (Solo Power Analysis[9]), the two-sample binomial test applied to the primary end point requires 129 patients in each arm of the study for an estimated success rate of 75% with itraconazole and of 90% with terbinafine. All other analyses were labelled as exploratory. For the analysis of the primary end point, the center effect was taken into account by a Mantel-Haenzel test. Heterogeneity was tested by the Breslow-Day test. The effect of the dropout rate of

Table I. Cure rates of the target nail at week 48 (%)

	Terbinafine		Itraconazole		*p* value	95% CI of difference
Negative microscopy (%)	77.9		55.4		< 0.0001	22.6% [12.7%, 32.4%]
Negative culture (%)	84.0		64.3		< 0.0001	19.8% [10.6%, 28.9%]
Mycologic cure (%)	73.0		45.8		< 0.0001	27.2% [17.0%, 37.3%]
Geometric mean healthy nail length of big toe (mm)	8.1		6.4		0.026	0.238 [0.29, 0.45] (ratio)
Global clinical evaluation (%)						
Cleared	40.9	76.2	33.1	58.1	0.001	18.1% [8.24%, 27.9%]
Minimal symptoms	35.4		25.0			
Slightly improved	11.0		12.8			
Failure	12.8		29.1			
Significant improvement (%)		64.2		37.5	< 0.0001	26.7% [16.3%, 37.0%]
Total cure (%)		37.7		23.2	0.004	14.4% [4.62%, 24.3%]

Mycologic cure = negative microscopy and negative culture for dermatophytes; significant improvement = mycologic cure and cleared or minimal clinical symptoms; total cure = mycologic cure and cleared symptoms.

analysis and a worst-case for terbinafine/best-case for itraconazole analysis. Although these analyses often do not simplify the interpretation of the results, here they confirmed the primary analysis (necessarily) without including the outcome of the dropouts. The reported measurements analysis of the length of healthy nail was performed with the SAS procedure MIXED, which partially takes the dropouts into consideration. All analyses were done with the statistical package SAS.[10]

RESULTS

A total of 378 patients were randomly assigned treatment and entered in the study. Six patients were excluded from the intent-to-treat analysis because they had fingernail infection only (two in the terbinafine group and one in the itraconazole group) or had clinically relevant abnormalities in liver function tests at baseline before beginning study treatment. These patients immediately stopped taking medication (one in the terbinafine group and two in the itraconazole group). Thus 372 patients were included in the intent-to-treat analysis, 186 in each treatment arm. The distributions of sex, age, height, and weight in the two groups were equivalent. In 79.1% of the patients the big toe was selected as the target nail.

Trichophyton rubrum was isolated in about 92% of the patients. The remaining isolates were primarily *T. interdigitale*. At week 48 the percentage of patients with negative microscopy was statistically significantly higher in the terbinafine group than in the itraconazole group (77.9% [127 of 163] vs 55.4% [93 of 168], $p < 0.0001$; Fig. 1). There was a similar difference favoring the terbinafine group for negative dermatophyte culture (84% [137 of 163] vs 64.3% [108 of 168], $p < 0.0001$; Fig. 2). Negative mycology results (Fig. 3) were obtained in 73% (119 of 163) of the patients in the terbinafine group and 45.8% (77 of 168) in the itraconazole group ($p < 0.0001$; difference = 27.2%; 95% CI = [17.0%, 37.3%]) at week 48.

Table II. Most frequently reported adverse events; some patients reported several adverse events

	No. of adverse events	
	Terbinafine	Itraconazole
Gastric	33	19
Intestinal	11	8
Skin	9	9
Abnormal liver function test	4	11
Taste disorder	4	0
Headache	5	6
Vertigo	3	4
Miscellaneous	45	53

At baseline, the geometric mean length of healthy nail for the big toenail (on the basis of log [healthy nail length + 1]) was 2.1 mm in the terbinafine group and 1.9 mm in the itraconazole group (difference not significant). At week 48 (Fig. 4), there was a significant difference in the geometric mean length of healthy nail for the big toenail (8.1 mm for terbinafine vs 6.4 mm for itraconazole; $p = 0.026$) but not for the small target nails. Onychomycosis is a slowly evolving condi-

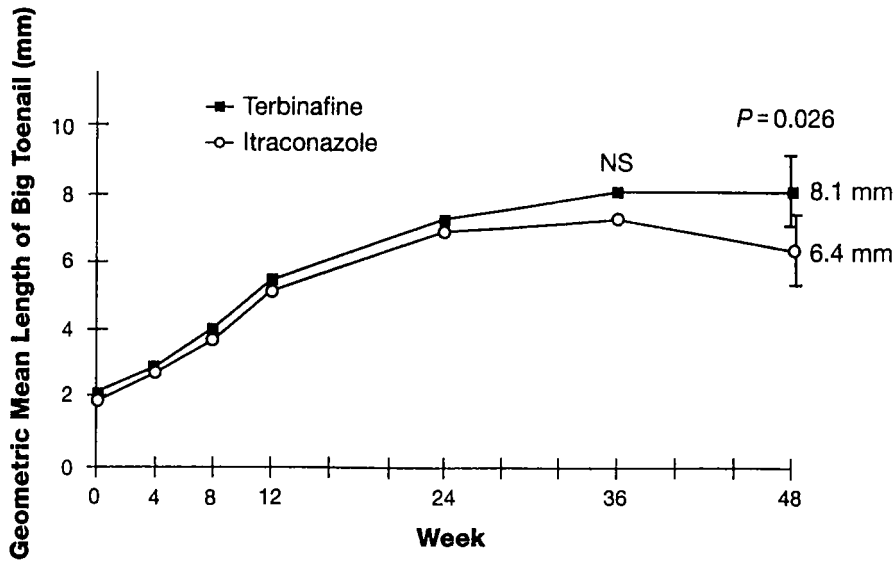

Fig. 4. Geometric mean length (mm) of healthy nail for target big toenail (± 95% CI at week 48).

tion; this may explain why the between-drug difference in healthy nail outgrowth appeared some time after the mycological difference was present.

At the end of the study, the difference between the onycholysis scores for the treatment groups was statistically significant ($p = 0.001$) in favor of terbinafine. The hyperkeratosis scores were slightly better for terbinafine, but the difference was not statistically significant ($p = 0.27$). Paronychial inflammation was absent in the majority of the patients in both groups. The results of the global clinical evaluation of the target nail at week 48 (Table I) was significantly better ($p = 0.001$) for the terbinafine group, 76.2% (125 of 164) of whom had cleared or had only minimal symptoms versus 58.1% (100 of 172) of patients in the itraconazole group (difference = 18.1%; 95% CI = [8.24%, 27.9%]).

When the mycologic cure rates were combined with the global clinical cure rates of the target nail, the results still favored terbinafine. The percentages of patients with total cure and significant improvement are given in Table I.

The overall assessment of the tolerability made by both the patients and investigators was good to very good for over 90% of patients. Adverse events were reported in 38.6% of the terbinafine-treated patients and in 35.4% of the itraconazole-treated patients. The mean values of biochemical parameters did not change significantly during the treatment period. Table II lists the most frequently reported adverse events.

DISCUSSION

This double-blind study shows that 12 weeks of oral treatment with terbinafine in patients with toenail infection caused by dermatophytes results in higher cure rates at follow-up than does itraconazole and is as well tolerated. These findings confirm the recently presented results of a similar large-scale double-blind study in Germany[11] comparing these two new antifungal drugs, which used the same treatment duration and a follow-up period extending 4 weeks longer. Except for other small-scale or open studies,[6,12] no other double-blind comparative studies with a sufficient number of patients that could demonstrate statistical significance have been published so far to our knowledge. Our findings confirm the results of previous studies[13–17] with terbinafine at the same dosage and treatment duration.[16,17] For itraconazole, few data[18,19] on this dose and treatment duration have been published, but our study results are comparable to those for the same dose and treatment duration given in the US package insert for itraconazole (product leaflet)[20]: 54% negative mycology; 35% significant improvement; and 14% total cure.

Because the two drugs have similar pharmacokinetic profiles and both rapidly reach high concentrations in the nail plate that last for several weeks after treatment is stopped, we believe that the sig-

nificantly better results obtained with terbinafine may be because of the efficient primary fungicidal activity of this molecule.[5] Apparently, during the initial treatment period, the two patient groups respond equally well to treatment. However, after treatment is completed, a significant difference in mycologic cure rate is observed by week 24. This difference also is reflected by a difference in the clinical outcome in the long term (week 48). It would be interesting to follow-up for another year those patients whose infections were cured at the end of this study to determine whether cure continued over the long term. Some data for patients followed up for at least 2 years after treatment suggest that most terbinafine-treated patients remain cured of their infection.[21]

These clinical findings should have a significant impact in any economic evaluation of treatments for onychomycosis. The treatment costs per patient with terbinafine are lower than those with itraconazole because of the better outcome. Formal economic assessments and recommendations that terbinafine be used as first-line treatment for onychomycosis have appeared elsewhere.[22–25] These new clinical data support the conclusions of these assessments. Therefore, terbinafine should continue to be the first choice for the treatment of toenail onychomycosis, a fungal infection known to be common that is usually caused by dermatophytes and, until recently, difficult to cure.

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