

Long-term Effectiveness of Treatment With Terbinafine vs Itraconazole in Onychomycosis

A 5-Year Blinded Prospective Follow-up Study

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Objective: To examine long-term cure and relapse rates after treatment with continuous terbinafine and intermittent itraconazole in onychomycosis.

Design: Long-term prospective follow-up study.

Setting: Three centers in Iceland.

Subjects: The study population comprised 151 patients aged 18 to 75 years with a clinical and mycological diagnosis of dermatophyte toenail onychomycosis.

Interventions: In a double-blind, double-dummy study, patients were randomized to receive either terbinafine (250 mg/d) for 12 or 16 weeks or itraconazole (400 mg/d) for 1 week in every 4 for 12 or 16 weeks (first intervention). Patients who did not achieve clinical cure at month 18 or experienced relapse or reinfection were offered an additional course of terbinafine (second intervention).

Main Outcome Measures: The primary efficacy criterion was mycological cure, defined as negative results on

microscopy and culture at the end of follow-up and no requirement of second intervention treatment. Secondary efficacy criteria included clinical cure without second intervention treatment and mycological and clinical relapse rates.

Results: Median duration of follow-up was 54 months. At the end of the study, mycological cure without second intervention treatment was found in 34 (46%) of the 74 terbinafine-treated subjects and 10 (13%) of the 77 itraconazole-treated subjects ($P < .001$). Mycological and clinical relapse rates were significantly higher in itraconazole- vs terbinafine-treated patients (53% vs 23% and 48% vs 21%, respectively). Of the 72 patients who received subsequent terbinafine treatment, 63 (88%) achieved mycological cure and 55 (76%) achieved clinical cure.

Conclusion: In the treatment of onychomycosis, continuous terbinafine provided superior long-term mycological and clinical efficacy and lower rates of mycological and clinical relapse compared with intermittent itraconazole.

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ONYCHOMYCOSIS is a common disease, and recent population studies have shown a prevalence of between 2% and 8%.¹⁻³ This disease is more common in older age groups and in selected populations, such as swimmers and individuals with diabetes mellitus or psoriasis.⁴⁻⁶ Onychomycosis can be an infection reservoir for dermatomycoses of the adjacent skin, such as interdigital or plantar ("moccasin type") tinea pedis. Studies have shown that onychomycosis can have severe impact on quality of life,⁷ and this disease should not be trivialized.⁸

For several years treatment of onychomycosis was limited to griseofulvin, which provided low cure rates and long treatment times. Modern antifungal agents, such as terbinafine and itraconazole, are significantly more effective with shorter treatment times. It has previously been demonstrated in a randomized controlled,

multicenter, double-blind, double-dummy study (the Lamisil vs Itraconazole in Onychomycosis [LION] study) that patients treated with continuous terbinafine achieved significantly superior mycological and clinical cure rates compared with patients treated with intermittent itraconazole.^{9,10}

While both itraconazole and terbinafine have proven to be effective against onychomycosis, very little is known about the long-term maintenance of cure and relapse rates observed with both drugs.¹¹ The objective of the present study was to examine long-term mycological and clinical cure rates after treatment with terbinafine and itraconazole for onychomycosis. Similarly, mycological and clinical relapse rates were examined. A secondary objective was to evaluate the effect of subsequent treatment with terbinafine in patients who experienced relapses or failed the original treatment with terbinafine or itraconazole.

PATIENTS AND METHODS

PROTOCOL

Study Outline

Patients were recruited from a multinational, prospective, randomized, double-blind, double-dummy study comparing the safety and efficacy of continuous terbinafine with intermittent itraconazole treatment in onychomycosis. The clinical courses of 496 patients were followed up to month 18.^{9,10} Of these 496 patients, 144 from the 3 Icelandic centers were followed up prospectively (**Figure 1**). Iceland was the most suitable country to do this follow-up because there was a large number of patients enrolled in the trial, and patients were easy to follow-up for long periods because of the unique geographic location.

Inclusion and Exclusion Criteria

The study population comprised men and women aged between 18 and 75 years with a clinical diagnosis of onychomycosis of the toenail confirmed by positive mycological culture and microscopic (potassium hydroxide examination) findings for a dermatophyte.^{9,10} All patients belonging to the intention-to-treat population were followed up prospectively.

Planned Interventions

First Intervention. Terbinafine was given at a dosage of 250 mg/d for 12 or 16 weeks; itraconazole, at a dosage of 400 mg/d for 1 week every 4 for 12 (3 cycles) or 16 (4 cycles) weeks. The 4 treatment groups were compared at baseline, and at weeks 4, 8, 12, 16, 32, 48, and 72 (LION study). The cure rates at month 18 (week 72) were very similar for both terbinafine groups and both itraconazole groups. Therefore, in view of the smaller number of patients in the follow-up study, only 2 treatment groups were considered for prospective analysis, namely, patients treated with terbinafine (for 12 or 16 weeks) and patients treated with itraconazole (for 3 or 4 cycles). Patients included in the follow-up study were checked for clinical and mycological status at approximately 6-month intervals for up to 5 years (LION Icelandic Extension Study).

Second Intervention. From month 18 onward, an additional 12-week course of oral terbinafine, 250 mg/d, was offered on clinical signs of reinfection. If necessary, further additional courses of terbinafine were offered on signs of reinfection or if previously negative mycological findings became positive with signs of clinical disease. Patients with positive mycological findings but with normal nails were not treated.

Mycology and Ethics

All mycological examinations were undertaken at a single laboratory (Mycology Reference Centre, Leeds, England). The study protocol conformed to good clinical practice: all patients gave written informed consent to participate, and the study protocol was subjected to approval by the institutional review board.

Primary and Secondary Efficacy Criteria

The primary efficacy criterion was the proportion of patients who remained mycologically cured at the end of follow-up without requiring second intervention treatment with terbinafine. Mycological cure was defined as negative results on both microscopy and culture of samples taken from the target toenail. Secondary efficacy criteria included (1) clinical cure (defined as 100% normal-appearing nail) at the end of follow-up without the requirement of second intervention treatment, (2) complete cure defined as mycological plus clinical cure, (3) clinical and mycological relapse over time, (4) mycological and clinical cure over time, and (5) the effect of subsequent terbinafine treatment on clinical and mycological outcome. A mycological relapse was defined as a patient who achieved mycological cure at month 12 but had mycologically positive test results at any time thereafter. A clinical relapse was defined as a patient who achieved clinical cure at month 18 and showed clinical signs of infection at any time thereafter. The difference in times for the assessment of mycological and clinical cure can be explained by the slow growth rate of nails. A duration of 18 months is needed to assess clinical cure, whereas 12 months is adequate to assess mycological cure.⁹

Rationale and Methods for Statistical Analysis

All efficacy assessments were based on the intention-to-treat population defined as all randomized patients who satisfied all inclusion criteria and had at least 1 primary efficacy measurement at month 6. Treatment comparisons for mycological cure rate and mycological relapse rate were made by the Fisher exact test, using the SAS statistical package (SAS Institute Inc, Cary, NC). The "last observation carried forward" method was used to impute missing observations.¹²

ASSIGNMENT AND BLINDING

Details on assignment and blinding have been described previously.⁹ After 18 months the study continued to be blinded to patients and investigators until an interim analysis was performed in September 1999, after 4 years of follow-up on average.

RESULTS

PARTICIPANT FLOW AND FOLLOW-UP

A total of 268 patients were screened in Iceland (**Figure 2**), 110 of whom were excluded because of negative results on mycological examination, withdrawal of consent, protocol violations, or failure to return to the clinic. The 158 remaining patients were randomized for

treatment, 151 of whom comprised the intention-to-treat population (the 7 patients excluded violated the inclusion or exclusion criteria or did not have sufficient follow-up). Of these 151 patients, 143 completed the first 18 months of the study, and the clinical courses of 144 were followed up to 58 months. The median duration of follow-up was 54 months (range, 8-58 months), with 142 (94%) of the 151 patients followed up for more than 43 months. The treatment groups were comparable with re-

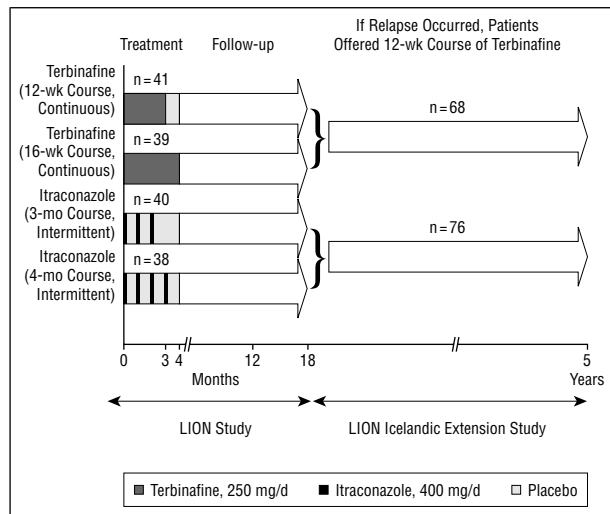


Figure 1. Study flowchart. Of 158 subjects randomized to treatment, 151 belonged to the intention-to-treat population and were entered into the study. Of these 151 subjects, 144 could be followed up for up to 5 years. LION indicates Lamisil vs Itraconazole in Onychomycosis.

gard to demographics and the extent and duration of nail disease at baseline (**Table 1**).

CAUSAL AGENTS

The dermatophyte species isolated at screening were *Trichophyton rubrum* alone (146 patients [97%]), *T rubrum* plus a nondermatophyte mold (4 patients [3%]), and *Trichophyton mentagrophytes* alone (1 patient [1%]).

LONG-TERM CURE RATES AFTER FIRST INTERVENTION

At the end of follow-up, 34 (46%) of the 74 patients originally treated with terbinafine had negative mycological examination results without the need for a second intervention (**Table 2**). Significantly fewer patients treated with itraconazole maintained mycological cure (10 [13%] of 77; $P < .001$). When clinical cure rates were considered, 31 (42%) of the 74 terbinafine-treated patients remained clinically cured at the end of follow-up compared with 14 (18%) of the 77 itraconazole-treated patients ($P < .002$; Table 2). Regarding complete cure, significantly more patients treated with terbinafine maintained complete cure at the end of follow-up without the need for a second intervention ($P < .005$; Table 2).

RELAPSE RATES

After 12 months, 57 (77%) of the 74 patients taking terbinafine had achieved mycological cure, and the corresponding rate for itraconazole was 32 (42%) of 77 patients. Six months later (at 18 months), 5 (9%) of 57 terbinafine-treated patients and 7 (22%) of 32 itraconazole-treated patients had relapsed mycologically. The relapses in the itraconazole-treated patients continued to increase between months 18 and 36 (**Figure 3**), while relapses in terbinafine-treated patients increased

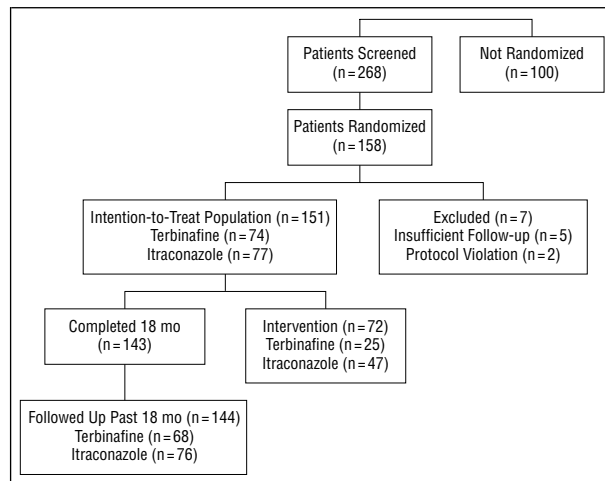


Figure 2. Distribution of participants in the Lamisil vs Itraconazole in Onychomycosis Icelandic Extension Study.

Table 1. Baseline Characteristics

Characteristic	Terbinafine Group (n = 74)	Itraconazole Group (n = 77)	Total (N = 151)
Mean age, y	48	48	48
Male sex, No. (%)	47 (64)	53 (69)	100 (66)
Mean % of <i>Trichophyton rubrum</i>	97	96	97
Mean weight, kg	81	81	81
Mean No. of infected toenails	5.4	5.6	5.5
Mean duration of onychomycosis, y	12.8	11.8	12.3
Mean % of nail involvement	77	76	76

Table 2. Mycological and Clinical Cure Rates*

Criteria of First Intervention	Month 18	End of Study Without Second Intervention
Terbinafine (n = 74)		
Mycological cure	58 (78)	34 (46)
Clinical cure	39 (53)	31 (42)
Complete cure	37 (50)	26 (35)
Itraconazole (n = 77)		
Mycological cure	35 (46)	10 (13)
Clinical cure	29 (38)	14 (18)
Complete cure	23 (30)	11 (14)

*All data given are number (percentage) of patients.

only slightly. After 31 to 36 months, very few mycological relapses were seen in both groups. At the end of the study, significantly fewer terbinafine-treated patients had experienced a mycological relapse compared with itraconazole-treated patients (13 [23%] of 57 vs 17 [53%] of 32; $P < .01$). Clinical relapse showed a similar pattern. At the end of the study, 8 (21%) of the 39 terbinafine-treated patients had a clinical relapse, while the corresponding relapse rate for the itraconazole-treated patients was 48% (14 of 29 patients) ($P < .05$; Figure 3).

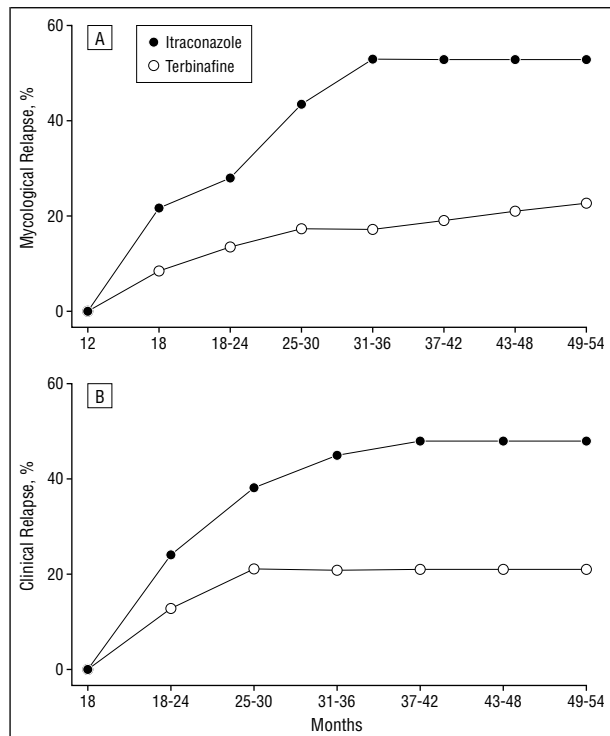


Figure 3. Mycological (A) and clinical (B) relapse rates.

RESPONSE TO SECOND INTERVENTION WITH TERBINAFINE

Patients with clinical signs of onychomycosis after 18 months were offered treatment with terbinafine in an open manner. Details about the 72 patients receiving second intervention treatment are given in **Table 3**. At the end of follow-up, 23 (92%) of 25 patients who originally received terbinafine as first intervention and 40 (85%) of 47 patients who originally received itraconazole achieved mycological cure. Regarding clinical cure, 19 (76%) of 25 patients who originally received terbinafine and 36 (77%) of 47 patients who received itraconazole were clinically cured at the end of follow-up. All 6 patients originally treated with terbinafine who did not achieve clinical cure had 10% or less dystrophy at the end of follow-up. Among the patients originally treated with itraconazole, 5 of 11 patients who did not achieve clinical cure had 10% or less dystrophy at the end of follow-up. Complete cure was achieved in 52 (72%) of 72 patients overall.

COMMENT

Many studies have addressed the efficacy of modern antifungal drugs on onychomycosis.¹³⁻¹⁹ Most studies have concentrated on 9 to 12 months' outcome. Few studies have addressed the long-term efficacy or relapse rates after antifungal treatment. Considering that toenails can take 12 to 18 months to grow out, many clinicians consider that 1 year is too short to assess clinical effectiveness.¹¹ Most of the studies that have followed the clinical courses of patients beyond 12 months have been small with no possibility for meaningful comparisons between treatment groups, have not followed the clinical

Table 3. Subjects Receiving Second Intervention With Terbinafine at Month 18

Detail	Nature of First Intervention		
	Terbinafine (n = 74)	Itraconazole (n = 77)	Total (N = 151)
No. (%) of patients receiving an additional course of terbinafine treatment	25 (34)	47 (61)	72 (48)
Mean ± SD duration of subsequent terbinafine treatment, mo	4.2 ± 1.6	4.3 ± 2.2	4.3 ± 2.0
Minimum, maximum of terbinafine therapy, mo	3, 8	2, 11	2, 11
No. (%) of patients achieving mycological cure	23 (92)	40 (85)	63 (88)
No. (%) of patients achieving clinical cure	19 (76)	36 (77)	55 (76)
No. (%) of patients achieving complete cure	18 (72)	34 (72)	52 (72)

courses of patients beyond 3 years, or have used different end points for cure. Few studies have addressed relapse rates.²⁰⁻²³

In the present study, we have shown that terbinafine achieves significantly higher long-term mycological and clinical cure rates than itraconazole in onychomycosis. To our knowledge, this study represents the longest prospective follow-up of patients treated for toenail onychomycosis. The study was done in Iceland, and it is possible that the results would differ with a more heterogeneous study population. We do not find this likely. The patients were recruited from the multinational LION study, and in this study no difference in cure rates was found between individual countries.^{9,10}

It can be argued that the cure rates observed at 54 months are suboptimal, with 34 (46%) of the 74 terbinafine-treated and 10 (13%) of the 77 itraconazole-treated patients achieving mycological cure. However, toenail onychomycosis is recognized to be a difficult condition to treat, and most of the patients studied had long-standing and widespread disease as shown by the duration of disease and number of nails involved. Moreover, we used very stringent criteria for analysis, taking the intention-to-treat population as the denominator for assessment of long-term effectiveness. The differences between itraconazole- and terbinafine-treated patients, however, are marked and of clinical importance regarding treatment decisions.

Interestingly, we have demonstrated that the relapse rate is significantly higher among patients treated with itraconazole (Figure 3). It is striking to see that itraconazole-treated patients experience a rapid increase in mycological relapses up to months 31 to 36, with a stable condition thereafter. In the terbinafine-treated patients the situation is more stable with constant and low relapse rates during the entire follow-up period. It is well recognized that both itraconazole and terbinafine can persist for months after treatment at clinically relevant concentrations in treated nails.²⁴ Terbinafine is primarily fungicidal in its mode of action as opposed to itraconazole, which is primarily fungistatic. It is tempting to speculate that the

fungicidal activity of terbinafine enables it to kill the fungus more rapidly at low concentrations and that this may account for the lower relapse rate observed in this study. Also, the concentration of terbinafine achieved in the nails is much higher relative to the concentration required to kill the fungus than it is for itraconazole.²⁴ With current techniques, it is impossible to distinguish between a reinfection and a recurrence of a previous infection. Because the drugs have disappeared from the nails at this time, it is very unlikely that the reinfection rate is different between the 2 patient groups. The only logical explanation for the differences between the 2 groups is that the itraconazole-treated patients experience more recurrences (not reinfections) than the terbinafine-treated patients.

The results of the second intervention with terbinafine show that many patients who fail to respond to conventional 3- to 4-month treatment with terbinafine or 3- to 4-cycle treatment with itraconazole can be treated successfully with prolonged treatment or additional courses of terbinafine. This is valid for patients failing the initial treatment with terbinafine or itraconazole. It is likely that a subgroup of patients who fails to respond adequately to conventional treatment needs a more individualized treatment approach. In this study an individualized approach was used in a difficult-to-treat subgroup of patients who failed to respond to conventional treatment, and good cure rates were achieved. Further research is needed to optimize cure rates in onychomycosis. Patients likely to respond poorly to conventional treatment could benefit from a more individualized approach. Considering the cost of treatment with antifungal agents today, more research is needed to identify such patients with refractory disease.

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