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Oral Terbinafine in Toenail Dermatophytosis

A Double-blind, Placebo-controlled Multicenter Study with 12 Months' Follow-up

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The treatment of onychomycosis has previously often been protracted and unsuccessful. Terbinafine has been shown to be effective in short-term regimens. In this double-blind, placebo-controlled study, 148 patients with toenail dermatophytosis were randomized to treatment with either 250 mg terbinafine daily or placebo for 3 months. An additional treatment was given for 3 months to patients whose infection had not responded. The patients were followed clinically and mycologically through 12 months. After 3 months 82% of the terbinafine-treated group, versus 5% of the placebo group, showed significant improvement, i.e. negative culture and growth of unaffected nail more than 2 mm ($p = <0.0001$). After 12 months clinical and mycological cure was seen in 40% of the patients treated with terbinafine for 3 or 6 months, while 67–81% were clinically cured, but with positive microscopy. Side-effects occurred in 13.5% of the terbinafine group, versus 5.4% of the placebo group, and were mild.

250 mg terbinafine daily for 3 months was significantly more effective than placebo. The efficacy did not appear to improve with additional treatment for 3 months. ***Key words: onychomycosis; short-term treatment; additional treatment.***

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Terbinafine (Lamisil®), one of the allylamine group of antifungal agents, is a lipophilic compound which is active orally as well as topically. The mode of action is inhibition of fungal squalene epoxidase. This enzyme is active in the synthesis of ergosterol, an essential lipid component of the fungal cell wall. The accumulation of squalenes following inactivation of squalene epoxidase seems to be fatal for the fungus, thus accounting for the in vitro fungicidal action of terbinafine (1).

In vitro terbinafine is active against a wide range of fungi, including dermatophytes, dimorphic and dematiaceous moulds and yeasts. The most susceptible fungal species are the dermatophytes, but terbinafine is also active in vitro against *Aspergillus* species and other pathogenic filamentous fungi infecting the skin, nails and cornea. Its action against yeasts is more variable. Clinical investigations have primarily dealt with dermatophytosis (2, 3).

Onychomycosis, caused by dermatophytes, constitutes 50% of all nail diseases and is a therapeutic challenge. In the United Kingdom (4) 2.7% of the population suffers from onychomycosis, predominantly caused by *Trichophyton rubrum* (*T. rubrum*). In the United States an increase in the number of patients with onychomycosis has been reported (5). Previously, griseofulvin was the drug of choice for this disorder. This drug cures 70% of fingernail onychomycosis but less than 40% of toe nail infections (6–8).

Pharmacokinetic studies have shown that terbinafine diffuses rapidly into the nail and that it can be detected in the distal part of the nail 3 to 18 weeks after the initiation of therapy (9–11). Previous studies have shown terbinafine to be effective in onychomycosis with mycological cure rates of 70–100% and clinical cure rates of 42–100% after treatment for 3 to 6 months (12–17).

The purpose of the present investigation was to compare the efficacy of 250 mg terbinafine taken daily for 3 months with a placebo for the treatment of dermatophytosis of the toenails. In addition, the results of an additional 3-month treatment with terbinafine to non-responders were evaluated.

MATERIALS AND METHODS

Study design

The investigation was carried out as a double-blind, controlled, multicenter study in 15 dermatology clinics and 5 hospital dermatology departments. Patients who were 18 years or older with proven modest to severe dermatophyte infection of one or both great toenails (positive microscopy and culture) were included. Patients with impaired liver and kidney function as well as pregnant or lactating women were excluded.

After a 1-month wash-out period with no topical or systemic treatment the patients were randomized to receive either oral 250 mg terbinafine or placebo daily for 3 months. Based on the clinical evaluation at that point, and without breaking the code, 250 mg terbinafine daily for an additional 3-month period was given to the patients who had not responded satisfactorily according to the clinical score. All patients were followed for 6 or 9 months after treatment was discontinued.

Evaluation

Clinical and mycological evaluations were carried out at baseline and after 6 weeks and 3, 6, 9, and 12 months. The clinical evaluation at baseline included percent of nail affected (less than 25%, 26–50%, 51–75%, 76–100%), and degree of subungual keratosis of target nail, i.e. one of the great toenails (none, modest, moderate or extensive) according to a score system. At the following visits the same clinical parameters were evaluated. In addition, regrowth of unaffected nail was measured. The number of other infected toenails and the severity of the infection were also noted.

For mycological identification nail material underwent fluorescence microscopy using calcofluor white (18) and culture on Sabouraud dextrose agar with and without cycloheximide and with chloramphenicol

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col. The target toenail infection was considered cured at the final visit after 12 months, only if there was no clinical trace of disease and the mycology (microscopy and culture) was negative.

Any adverse reactions were noted at each visit during treatment.

RESULTS

Patients

Two hundred and thirty-seven patients were examined in the screening phase. One hundred and forty-eight entered the protocol; 75 were randomized to treatment with terbinafine, 73 to placebo. Twenty-one (12 received terbinafine and 9 placebo) patients left the study during or at the end of the initial 3-month treatment period due to: a) lack of efficacy, b) side-effects (4 from terbinafine, 2 from placebo), or c) various other reasons (6 received terbinafine, 6 placebo). One hundred and twenty-seven patients completed the study, (63 received terbinafine and 64 placebo).

The baseline demographic data for the patients did not show significant differences between the two groups. There were fewer females and more patients with fingernail mycosis in the terbinafine group.

Mycology

T. rubrum was the cause of infection in 65, *T. mentagrophytes* in 7, and *T. tonsurans* in 3 patients treated with terbinafine. In the placebo-treated group the pathogenic organisms were *T. rubrum* in 66, *T. mentagrophytes* in 3, and *T. tonsurans* in 4 individuals. In 34 patients from the terbinafine group and 29 from the placebo group moulds, *Candida* or bacteria were cultured along with the dermatophytes.

Evaluation after 3 months

Clinical evaluation. The target toenails of 74 patients who received terbinafine and 73 who received placebo were evaluated after 3 months. With regard to length of unaffected nail, subungual keratosis and percent of nail affected, significantly greater improvement was seen in the terbinafine group than in the placebo group ($p=0.0001$, $p=0.001$, $p=0.01$, respectively, chi square test). The total score for toenail onychomycosis was significantly reduced in the terbinafine group compared with the placebo group ($p=0.01$, t-test).

Lack of efficacy, defined as non-improvement or deterioration, was observed in 26 terbinafine-treated patients and in 57 who received placebo. In accordance with the protocol, these patients were treated for a further 3 months with terbinafine. Sixteen patients who had received placebo had improved markedly and thus did not get further treatment.

Mycological evaluation. Negative culture was obtained in 49 of 74 (66%) terbinafine-treated patients versus 24 of 73 (33%) on placebo ($p=0.011$, Fig. 1). Negative microscopy and culture was present in 2 and 4%, respectively, at the 3-month follow-up.

Efficacy after 3 months. A combination of negative culture (Fig. 1) and the growth of 2 mm or more unaffected nail (Fig. 2) was considered a relevant measure of efficacy. This combination was seen in 42% (31 of 74) of terbinafine-treated patients and in 5% (4 of 73) of patients who received placebo ($p<0.01$ chi square test).

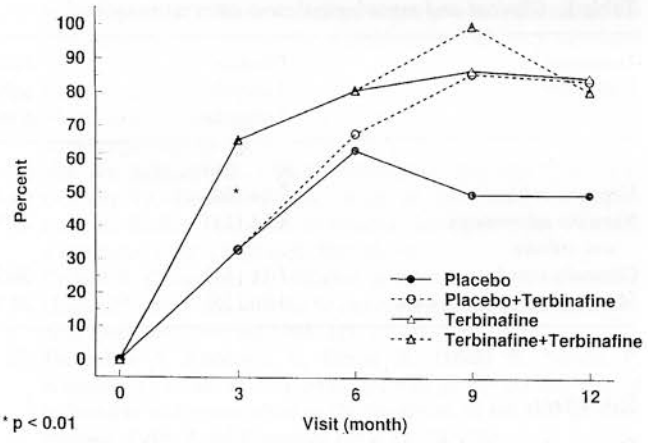

Fig. 1. Negative culture during the entire observation period.

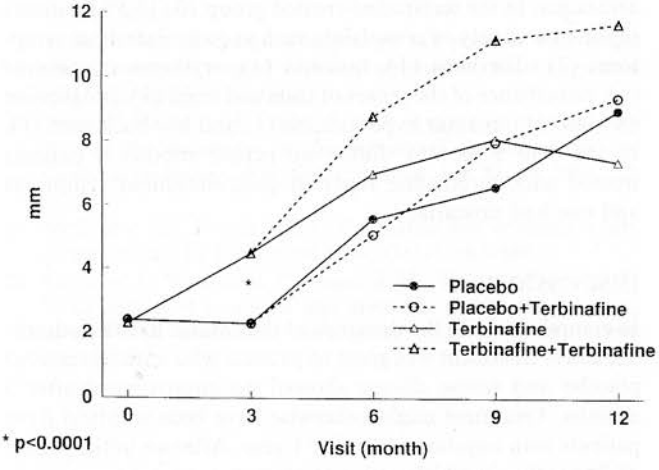

Fig. 2. Length of unaffected target nail during the entire observation period.

Evaluation after 12 months

Clinical evaluation. No differences between the four groups with regard to area of nail affected or total score were found, but the results in the group treated with terbinafine for 6 months were slightly better than in the remaining groups. The clinical cure rates for the placebo group, the placebo/terbinafine group, the terbinafine for 3 months and the terbinafine for 6 months groups were 44%, 67%, 63% and 81%, respectively (Table I).

Mycological evaluation. Cure, defined as negative microscopy and culture, was observed in 4 of 12 (33%) patients who received placebo, in 28 of 57 (49%) who received placebo for 3 months followed by terbinafine for 3 months, in 19 of 48 (40%) treated with terbinafine for 3 months, and in 12 of 26 (47%) treated with terbinafine for 6 months. There was negative culture with or without positive microscopy in 50%, 84%, 85% and 81%, respectively.

Overall evaluation. There was a discrepancy between efficacy defined as clinical and mycological cure with higher cure rates for the clinical response compared with the mycological response. Clinical and mycological cure was seen in 25% of the placebo group compared with 40, 38 and 42% in the terbinafine-treated groups (Table I).

Table I. *Clinical and mycological cure rates at month 12*

Treatment Follow-up	Placebo 3 months 9 months	Placebo + 3 months terbinafine 6 months	Terbinafine 3 months 9 months	Terbinafine 3 + 3 months 6 months
	n (%)	*n* (%)	*n* (%)	*n* (%)
Negative culture	8/16 (50)	48/57 (84)	41/48 (85)	21/26 (81)
Negative microscopy and culture	4/16 (25)	28/57 (49)	19/48 (40)	12/26 (46)
Clinically cured	7/16 (44)	38/57 (67)	30/48 (63)	21/26 (81)
Mycological + clinical cure	4/16 (25)	23/57 (40)	18/48 (38)	11/26 (42)

Side-effects

During the initial 3-month treatment period, side-effects were reported by 4 patients (5.4%) in the group who received placebo. Three had gastrointestinal complaints and one had arthralgia. In the terbinafine-treated group 10 (13.5%) patients reported a variety of complaints such as gastrointestinal symptoms (3), diarrhoea (1), urticaria (1), erythema multiforme (1), disturbance of the senses of taste and smell (1), progressive psoriasis (1), plantar hyperhidrosis (1) and low back pain (1). In the 6 to 9 months' follow-up period another 4 patients treated with terbinafine reported gastrointestinal symptoms and one had urticaria.

DISCUSSION

In compliance with the demands of the Danish health authorities, active treatment was given to patients who initially received placebo and whose disease showed no improvement after 3 months. Treatment might otherwise have been withheld from patients with onychomycosis for 1 year. After an initial period of 3 months, in which active treatment or placebo was given in an Australian study (19), there was a 3-month intermission without treatment. Such a design, with an evaluation of the 3-month treatment at month 6, would have made possible a better evaluation, as the clinical differences between treated and untreated nail at this point would probably have been more distinct.

Significant differences between the terbinafine-treated and the placebo groups were seen after 3 months for the following parameters: negative culture, area of unaffected nail, per cent of affected target nail, subungual keratosis and total score for toenail onychomycosis. After 12 months the number of patients in each of the four groups was too small for statistical evaluation.

Microscopy was positive for most patients both after 6 weeks and after 3 months and was therefore not useful in the evaluation of a positive response at month 3. It is noteworthy that many terbinafine-treated patients were still microscopy-positive at month 12. The pathogenic potential of these mycelia is unknown and a longer follow-up period might have revealed to which degree these elements could cause relapse. Two of the investigators in the current study did reexamine 22 patients after a further 2 years. A predictive value of a positive microscopy at the end of treatment as to cure versus clinical relapse at the end of the additional follow-up, however, was impossible to evaluate (unpublished data). A microscopy method with which it is possible to discriminate between viable and non-viable filaments (20) might provide a more reliable means of evaluating cure. *T. rubrum* was the pathogen in all the patients who were not cured. All patients with infections caused by *T. tonsurans* were identified in Iceland. All these patients and those infected with *T. mentagrophytes* were cured.

Although the clinical and mycological cure rates were relatively low compared to other studies, the methods of evaluation used were generally the same as in the most recent clinical investigations (11–16). Only the group of 26 patients treated actively for 6 months showed a clinical response comparable to previous reports. However, it has to be pointed out that, in contrast to several other investigations, clinical cure in this study was only considered present if no trace of disease was observed. In terms of mycology, the three groups showed identical results, characterized by persistent positive microscopy. The use of fluorescence microscopy with calcofluor white is probably a more sensitive method and may explain this finding (18).

Four of 16 patients in the placebo group were clinically as well as mycologically cured after 12 months. One of these had had minimal clinical infection with *T. rubrum* when included in the study. He was culture-negative at month 3 and microscopy-negative at month 9. Two patients had had moderate infections for one and a half and 4 years, respectively; they were both culture-negative at month 6 and microscopy-negative at month 12. The fourth patient had had severely affected nails for 10 years; he was culture-negative at month 6 and microscopy-negative at month 9. As far as the investigators know none of these 4 patients received other treatments during the study. This finding indicates that spontaneous cure may occur in onychomycosis. Previous reports of such a high proportion are not available.

Side-effects were more frequent among patients who received active treatment. All were familiar side-effects of terbinafine treatment (7). None were serious, and all disappeared rapidly after cessation of treatment. It should be noted that rare, severe cases of erythema multiforme, Stevens-Johnson's syndrome and toxic epidermal necrolysis have been described during treatment with terbinafine and that careful surveillance during therapy is called for (21, 22).

The following conclusions can be drawn from this study: 250 mg oral terbinafine taken daily for 3 months is significantly more effective than placebo in the treatment of toenail onychomycosis. Side-effects occurred in 13.4% of those treated with terbinafine compared with 5% of those who received placebo. None of the side-effects were serious. The follow-up period of only 6 months, after which some patients were evaluated, may be too short to obtain complete clinical cure and negative microscopy.

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