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• CME article

Drug photosensitivity, idiopathic photodermatoses, and sunscreens

Ernesto González, MD, and Salvador González, MD Boston, Massachusetts

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Journal of the American Academy of Dermatology CFAD v. Anacor, IPR2015-01776 ANACOR EX. 2050 - 7/11

Treatment of Candida nail infection with terbinafine

Rina Segal, MD,^a Aharon Kritzman, MD,^a Lia Cividalli, PhD,^b Zmira Samra, PhD,^b and Michael David, MD^a *Petah Tiqva, Israel*

Background: Terbinafine is a highly potent drug against dermatophytes. Data regarding its effectiveness against *Candida* species are few and variable.

Objective: Our purpose was to evaluate the efficacy and safety of oral terbinafine in patients with *Candida* nail infection.

Methods: In an open-label uncontrolled study, 20 patients completed 16 weeks of treatment with terbinafine, 250 mg/day, and an additional 8 weeks with placebo. Efficacy was assessed clinically and mycologically at weeks 0 (baseline), 4, 8, 16, 24, 36, and 48. Routine laboratory studies were performed at baseline and weeks 4, 8, and 16.

Results: At the end of the trial 60% of target nails were cured clinically and mycologically; in 10% there was mycologic cure with residual clinical signs, in 25% a moderate improvement (>50%), and failure in only 5% (one patient). Most nails were infected by *Candida parapsilosis*. Two of 28 patients showed mild reversible elevation of liver enzymes 1 month after initiation of terbinafine treatment.

Conclusion: The administration of terbinafine for 16 weeks is effective in the treatment of *Candida* nail infection. Liver enzyme values should be determined during the first month of treatment.

(J Am Acad Dermatol 1996;35:958-61.)

The role of *Candida* species as a cause of nail disease has been well established.¹ They cause 1% to 32% of toenail infections and 51% to 70% of fingernail infections, either as the sole pathogen or in combination with dermatophytes or molds.²⁻⁴

Candida albicans accounts for $50\%^3$ to $83\%^4$ of *Candida* species causing nail infections, although *C. parapsilosis* is emerging now as the main pathogen in various centers.*

Terbinafine is the first orally active antifungal drug of the allylamines class.⁵ The in vitro minimal inhibitory concentration values of terbinafine against dermatophytes are extremely low (0.001 to 0.01 μ g/ml), but the in vitro activity against *Candida* is more variable and species dependent, ranging from 0.1 to 12.5 μ g/ml and even higher.^{6, 7} It is fungistatic

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against *C. albicans* and fungicidal against *C. para-psilosis*.

Numerous studies have confirmed the beneficial effect of the drug against dermatophytes.⁵ However, there have been only a few reports on its efficacy against *Candida* nail infection. It was the purpose of this study to evaluate the efficacy and safety of oral terbinafine in patients with a nail infection caused by *Candida* species.

PATIENTS AND METHODS

This study was carried out as an open-labeled uncontrolled study. The subjects had to have mycologically proven candidal onychomycosis, with or without paronychial disease, to be older than 18 years of age, and to have the values of hematologic tests and blood chemistry within the normal range. All gave informed consent. Excluded from the trial were pregnant or lactating women, patients with a history of peptic ulcer, renal or hepatic dysfunction, immunosuppressed patients with psoriasis or other dermatoses, and patients who had received systemic antifungal therapy during the preceding 6 weeks.

The study was divided into two phases. In phase A, terbinafine, 250 mg/day, was given for 16 weeks. In phase B, a placebo was given for an additional 8 weeks, followed by an off-treatment period of 24 weeks. Patients were assessed mycologically every 4 weeks for the first 24 weeks and every 12 weeks in the remaining 24 weeks.

From the Departments of Dermatology^a and Microbiology,^b Beilinson Medical Centre, Petah Tikva, and the Sackler Faculty of Medicine, Tel-Aviv University.

Supported by a grant from Sandoz Pharma Ltd, Basel, Switzerland.

Reprint requests: Rina Segal, Department of Dermatology, Beilinson Medical Center, Petah Tikva, 49100, Israel.

^{*}Abramson C, Berlin S. Increased incidence of nondermatophyte filamentous fungi in skin and toenail infections. Abstracts of the International Summit on Cutaneous Antifungal Therapy, Boston, 1994.

			We	ek 16				Week 24 Week 48														
	Target nail		-		-		0		Toe- nails		Target nail		Finger- nails		Toe- nails		Target nail		Finger- nails		Toe- nails	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%				
Complete cure	2	10	3	15.5	0	0	6	30	4	21	0	0	12	60	12	64	7	36				
Mycologic cure or marked improvement (>90%)	1	5	4	21	0	0	3	15	6	31	1	5	2	10	1	5	2	11				
Moderate improvement (>50%-<90%)	6	30	3	15.5	4	21	7	35	2	10	10	53	5	25	3	15.5	7	37				
Failure (<50%)	11	55	9	48	5	79	4	20	7	38	8	42	1	5	3	15.5	3	16				

Table I. Response to treatment with terbinafine in *Candida* onychomycosis

Target nail = 17 fingernails, 3 toenails; fingernails = (other than target nails), in 19 patients; toenails = (other than target nails) in 19 patients.

Method of assessment

Before treatment, the location of each nail infection was identified and a target nail was selected for mycologic testing and clinical evaluation. All the other infected nails were also assessed clinically at each visit. At each visit, the percentage of nail involvement was recorded and the severity of hyperkeratosis, color changes, and paronychial inflammation were graded on a 0 to 3 scale (0 = none; 1 = mild; 2 = moderate; 3 = severe) for each nail. The mycologic examination of the target nail included potassium hydroxide (KOH) wet mount, culture on Sabouraud media with chloramphenicol, with and without actidione, and identification of candidal species. The clinical response was evaluated statistically with the following scale:

- 1 = Complete cure: No residual clinical signs and negative results of mycologic examination
- 2a = Mycologic cure for target nail, with mild residual clinical signs but negative culture and microscopic findings
- 2b = Marked improvement for all nails other than the target nail, with more than 90% clinical improvement
- 3 = Moderate improvement: Clinical signs and symptoms decreased by more than 50% and less than 90%
- 4 = Failure: Clinical improvement of less than 50%

Statistical analysis

The average improvement per week of the target nail, fingernails, and toenails was calculated. The results were analyzed with the two-sample t test for difference in means. The t test retains the null hypothesis at the 0.05 level of significance.

RESULTS

Of the 28 patients who entered the study, eight did not complete it: two (7%) because of a reversible liver enzyme elevation after 1 month of medication, two because of dizziness and nausea, and four because of lack of compliance. Of the 20 patients who completed the 48 weeks of the study, 13 were women and 7 were men (age range, 21 to 68 years [mean, 49.9 years]). In these subjects, the side effects were gastric fullness (two) and dizziness (one).

Table I presents the response to treatment of the target nail and all other fingernails (in 19 patients) and toenails (in 19 patients; five also grew Trichophyton rubrum). At the end of the study, 12 target nails (60%) were cured, in two (10%) there was a mycologic cure, in 5 there was moderate improvement, and treatment failed in 1. Of the three target toenails, one was cured and two showed moderate improvement (>80%). A similar response was observed in the infected fingernails (Table I). The response of the toenails was less favorable and improvement was observed only after a longer time, with a complete cure or marked improvement (>90%) in only 49%. Overall, of a total of 75 affected fingernails, 58 (77%) were cured; 85 (67.5%) of the 126 infected toenails were cured.

In 18 of the 20 target nails it was possible to identify the candidal species (Table II). Only three patients were infected with *C. albicans* and in two of them *C. parapsilosis* was also isolated. *C. parapsilosis* was found in 16 of 18 nails: six of them alone and in the rest, in combination with *C. albicans* (two), *C. tropicalis* (four), or *C. lypolytica*, *C. fumata*, or *C. rugosa* (four). *C. tropicalis* alone was identified in only one patient. *C. parapsilosis* and *C. tropicalis* infection was manifested mainly as primary distal and lateral onychodystrophy. Total nail involvement was observed in five patients; three of them had paronychial involvement.

Mycologic cure (negative potassium hydroxide and culture) was obtained in 18 patients after a mean

			Туре	e of clinical infe	ection	Time of	Response to treatment (week 48) (scale of response)*				
Candida sp.	No.	%	Proximal Distal Total nail nail onychia nail onychia involvement		mycologic cure (wk)	1	2a	3	4		
C. albicans	1	5.5			$1\dagger$	36	1				
C. parapsilosis	6	34		5	1	21.3	4		2	_	
C. tropicalis	1	5.5		1		24	1			_	
C. albicans, and C. parapsilosis	2	11	2			38	1	1			
<i>C. parapsilosis</i> and <i>C. tropicalis</i>	3	17	_	2	$1\dagger$	22.6‡	2		1		
C. parapsilosis and C. lypotica, C. fumata, or C. rugosa	5	27.5	_	3	2†	30.6‡	1	1	2	- 1	

Table II. Distribution of *Candida* species, type of clinical infection, and response to treatment

*Scale of response: 1 = Cure; 2a = mycologic cure; 3 = moderate improvement; 4 = failure.

[†]Total nail involvement with paronychia.

‡Two patients did not achieve mycologic cure.

time of 25.8 ± 2.3 weeks (range, 4 to 40 weeks) (Table II). The mycologic cure time for *C. albicans* was 37.7 weeks and for *C. parapsilosis* and *C. tropicalis* was an average of 22 to 24 weeks. The combination of *C. lypolytica, C. fumata*, or *C. rugosa* lengthened the time for mycologic cure to an average of 30.6 weeks. The most rapid response was in infections caused by *C. parapsilosis*, whereas the response by *C. albicans* was obvious only after 24 weeks of treatment.

During the follow-up period of 8 months only one patient had a relapse and this occurred at approximately 48 weeks.

DISCUSSION

Therapy with oral terbinafine for 3 months produces a cure rate of more than 80% in dermatophytosis of the nails.⁸ For candidial nail infections, however, differing results have been reported.^{9, 10}

Our results showed that fingernail infections responded better to terbinafine than toenail infections. The continuing clinical and mycologic improvement after cessation of treatment and the relatively low relapse rate imply that terbinafine continues to be active in the nailplate for more than 6 months. However, no studies have been done of the presence of terbinafine in the nailplate more than 90 days after its discontinuation.^{11, 12}

Onychomycosis caused by *Candida* species is relatively frequent in Israel. In our study group, *C*.

parapsilosis was more common than *C. albicans* as the pathogen. Most patients had distal nail dystrophy; none of them had peripheral vascular disease.

Evaluation after 16 weeks of treatment showed an earlier and better response to treatment by *C. parapsilosis* than by *C. albicans*, but after 48 weeks the end results were almost identical. This pattern of response can be explained by the fact that terbinafine is fungicidal for *C. parapsilosis* and fungistatic for *C. albicans*. Nails infected with rather rare species of *Candida (C. lypolytica, C. fumata, C. rugosa)* showed mild or moderate improvement. Unfortunately, we were unable to determine the minimal inhibitory concentration values for the various species of *Candida*.

Only two previous studies have evaluated the efficacy of terbinafine for *Candida* nail infection. The first by Roberts et al.⁹ gave terbinafine for 12 weeks or up to 24 weeks in nonresponders. The improvement after 12 weeks was not significant, and follow-up results were not conclusive. Nolting, Brautigam, and Weidinger¹⁰ treated their patients for 48 weeks. Clinical and mycologic cures were achieved in 52% of toenails and in 65% of fingernails. The cure rates according to pathogen were 63% for *C. parapsilosis* and 54% for *C. albicans*. Our results are in accord with these.

Overall, in our study terbinafine was well tolerated. The only relevant adverse reaction was a reversible elevation of liver enzymes in 2 (7%) of 28 patients. Journal of the American Academy of Dermatology Volume 35, Number 6

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