Efficacy and Safety of Terbinafine 1% Solution in the Treatment of Interdigital Tinea Pedis and Tinea Corporis or Tinea Cruris

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Two randomized, double-blind, vehicle-controlled, multicenter studies assessed the efficacy and safety of a new terbinafine 1% solution for the treatment of interdigital tinea pedis and tinea corporis or tinea cruris (tinea corporis/cruris). Patients with interdigital tinea pedis applied terbinafine 1% solution or vehicle twice daily for 1 week with 7 weeks of follow-up (N=153), and patients with tinea corporis/cruris applied terbinafine 1% solution or vehicle once daily for 1 week with 3 weeks of follow-up (N=66). Efficacy was assessed mycologically and clinically at the end of treatment and throughout follow-up. In the tinea pedis study, 66% of patients were effectively treated with terbinafine compared with 4% of the group treated by vehicle (P<.001; Mantel-Haenszel test). In the tinea corporis/cruris study, treatment was effective in 65% of the terbinafine group compared with 8% of the vehicle group (P<.001). There were no significant differences in the frequency of cutaneous adverse events between the 2 groups in either study. We conclude that one week of therapy with terbinafine 1% solution is highly effective, superior to vehicle, and safe for use in superficial fungal infections.

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Supported by Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.
Presented in part at the 55th Annual Meeting of the American Academy of Dermatology, San Francisco, California, March 21–26, 1997.
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Terbinafine (Lamisil®; Novartis Pharma AG), an allylamine, is a broad-spectrum, fungicidal drug that is used for the treatment of dermatophytes. It is therapeutically effective at low concentrations[1] and is highly effective in vitro against *Trichophyton*, *Epidermophyton*, *and Microsporum* organisms, which are common dermatophyte pathogens.[2,3] In a 1% cream formulation, terbinafine promotes the clinical and mycologic cure of tinea pedis, corporis, and cruris.[4] Recently, terbinafine was formulated as an easy-to-apply solution for topical use. Topical creams, however, may not be convenient for all patients or application sites. We report the results of 2 double-blind, multicenter, prospective, vehicle-controlled, parallel group studies investigating the safety and efficacy of terbinafine 1% solution for the treatment of interdigital tinea pedis and tinea corporis or tinea cruris (tinea corporis/cruris).

Methods

Study Populations—In the tinea pedis study, patients with interdigital tinea pedis were randomly selected for treatment with terbinafine or vehicle at a 2:1 ratio. Eligible patients were males or nonpregnant females at least 12 years of age with clinically diagnosed interdigital tinea pedis confirmed by positive microscopy. Exclusion criteria included chronic plantar tinea pedis, radiation therapy or systemic therapy with cytostatic or immunosuppressive drugs at time of study or within

2 weeks of initiation of study drug, active treatment for another dermatomycosis with a drug other than the study drug, immunodeficiency, a history of drug or alcohol abuse, allergies necessitating treatment, or hypersensitivity to any drug. Also excluded were patients who had been treated with oral antifungal agents within the previous 6 weeks, topical antifungal agents within the previous 2 weeks, or another investigational drug within the previous 8 weeks.

In the tinea corporis/cruris study, patients from 3 centers in the United States were randomized to treatment with terbinafine 1% topical solution or vehicle at a 1:1 ratio. Eligible patients were males or females at least 5 years of age with clinically diagnosed tinea corporis/cruris confirmed by positive microscopy. Clinical signs were to be localized to the pilose skin of the trunk, inguinal region, extremities, or head and neck. Pregnant or breast-feeding women were excluded, as were persons taking antibacterial, antiviral, or anthelmintic drugs within 2 weeks of initiation of study drug. Other exclusion criteria included anticipated unwillingness or inability to comply with requirements of the study, concomitant nondermatophyte infection, and radiation therapy or systemic therapy with cytostatic or immunosuppressive drugs.

Study Medication and Administration—Patients in both studies were given either 1% terbinafine in a vehicle solution of propylene glycol-1,2, cetomacrogol 1000, ethanol, and demineralized water or vehicle solution alone in identical 20-mL bottles. Tinea pedis patients were instructed to apply the solution to all affected areas twice daily, and tinea corporis/cruris patients were instructed to apply it to all fungal lesions once daily. All patients were told to cover the entire affected area and extend the solution over an approximately 1-inch-wide margin of apparently healthy skin. For each patient, a target lesion (the site with the most extensive disease) was designated for clinical and mycologic assessment. Patients in both studies were instructed to return all unused study medication and all empty bottles so that compliance could be assessed. They also were asked for the exact number of applications during the study period.

Study Schedule—In the tinea pedis study, study drug or vehicle was applied for 7 consecutive days, with a relatively long posttreatment follow-up (7 weeks). Treatment began on the morning after the baseline visit. Mycologic and clinical efficacy variables were measured at baseline and at weeks 1 (end of treatment), 2, 4, 6, and 8. Samples of the designated target lesion were taken at those times for microscopic examination and culture. Any adverse events or changes in concomitant medications were recorded. End of study was defined as the visit supplying the last available data for a patient.

In the tinea corporis/cruris study, the study drug or vehicle was applied once daily for 7 days, with a 3-week posttreatment follow-up. Mycologic sampling and clinical assessments were carried out at the baseline visit, at the end of treatment (week 1), and at weeks 2 and 4. End of study was defined as week 4 or time of last available data for a patient.

Safety—Adverse events, defined as any symptoms, physical signs, syndromes, or diseases that either newly occurred or worsened during the study, were recorded at all study visits. Cause and possible relationship to study medication were assessed. In the tinea pedis study, tolerability was based on investigators' and patients' overall ratings using a scale of *very good, good, moderate, poor,* and *very poor.*

Statistical Analyses—In the tinea pedis study, safety and demographic analyses were performed on patients who were randomized, had received at least one application of the study drug, and had at least one post-baseline safety assessment. Patients were excluded who showed inadequate compliance, took disallowed concomitant medication, had inadequate disease severity or localization, or missed a visit at week 8 or later.

In the tinea corporis/cruris study, criteria for the safety and intent-to-treat (ITT) populations were the same as those for the tinea pedis study. The valid-subject population included all patients with positive mycologic cultures at baseline who completed the study without violating the protocol in any way liable to influence the efficacy outcome. Because no subjects violated the protocol, the ITT and valid-subject populations were identical. Patients who discontinued because of treatment failure were considered as ineffectively treated in the valid-subject population.

Results

Patient populations and demographics for the 2 studies are shown in Tables 1 and 2.

Tinea Pedis Study—All of the patients excluded from the ITT population met the criteria for delayed exclusion. A large proportion of patients had varying degrees of disease involvement of the thick plantar skin and were excluded from the valid-subject population. Demographics between the terbinafine and vehicle groups did not differ significantly except for the proportions of whites versus nonwhites (P=.026; Mantel-Haenszel test).

Of the 153 patients randomly selected, 34 discontinued prematurely (23 from the terbinafine group and 11 from the vehicle group). The reasons for discontinuation in both groups, in descending order of frequency, were treatment failure, failure to return for scheduled visits, protocol violations, and withdrawal of consent.

Table 1.

Number of Patients in Each Study Population

	Tinea Pedis Study		Tinea Corporis/Cruris Study	
	Terbinafine	Control	Terbinafine	Control
Total randomized (safety)	104	49	32	34
Intent-to-treat population	58	28	26	26
Valid subject population	34	15	26	26

Table 2.

Patient Demographics (Intent-to-Treat Population at Baseline)

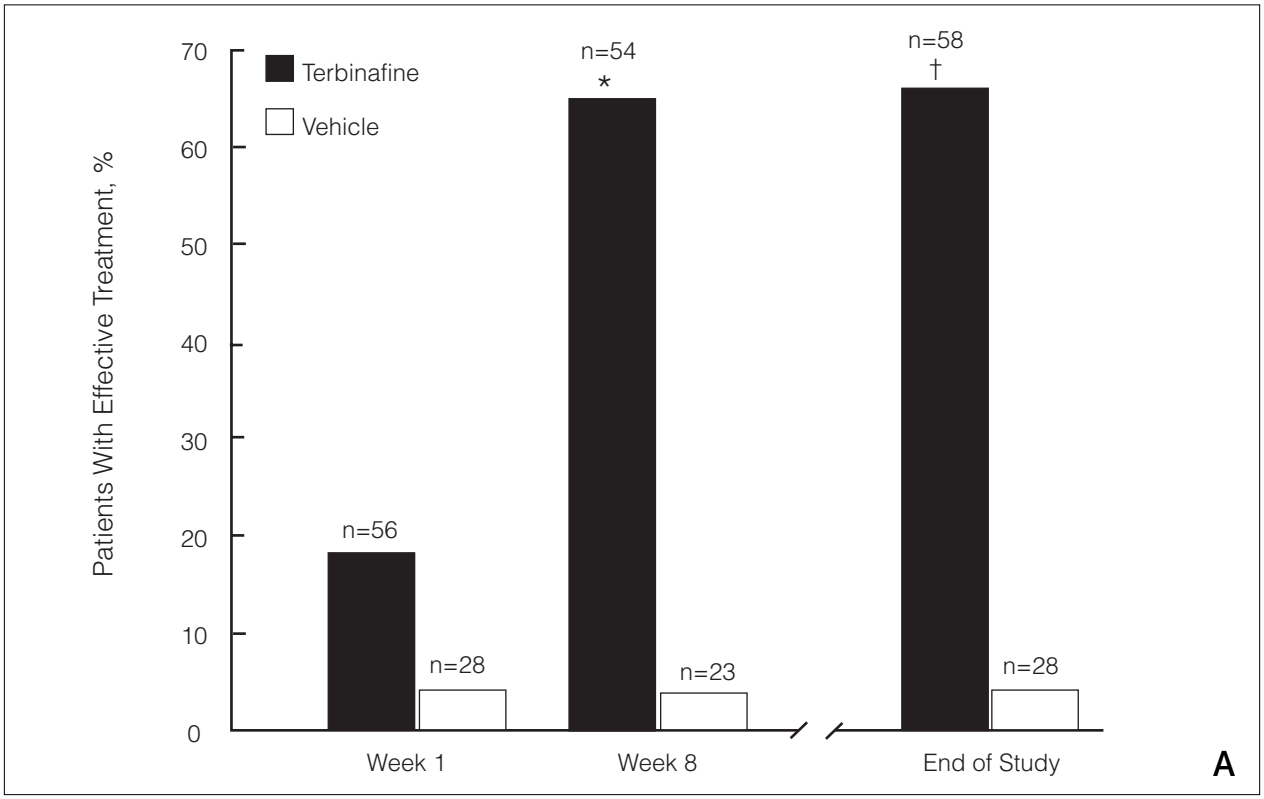
	Tinea Pedis Study		Tinea Corporis/Cruris Study	
	Terbinafine n (%)	Control n (%)	Terbinafine n (%)	Control n (%)
Gender				
Male	47 (81)	18 (64)	17 (65)	18 (69)
Female	11 (19)	10 (36)	9 (35)	8 (31)
Race				
White	35 (60)	23 (82)	21 (81)	20 (77)
Black	17 (29)	3 (11)	1 (4)	0 (0)
Other	6 (10)	2 (7)	4 (15)	6 (23)
Age, y				
Mean	41	43	41.1	43.5
Range	12–83	25–72	9–82	6–71

Tinea Corporis/Cruris Study—No significant between-group differences were found. Of the 66 patients randomly selected, 15 discontinued prematurely (3 from the terbinafine group and 12 from the vehicle group). Two patients from the vehicle group discontinued because of negative baseline cultures, and one discontinued because of exacerbation of untreated areas. Three patients from the terbinafine group and 9 from the vehicle group who discontinued treatment were considered treatment failures.

Efficacy Outcomes

Tinea Pedis Study—Percentages of patients considered effectively treated are shown in Figure 1A. Efficacy results favored terbinafine at all time points, becoming significant at week 4 (data not shown) and remaining significant until the end of the study. The valid-subject analysis yielded superior results (71% versus 7%; $P<.001$), probably because of the exclusion of patients with more recalcitrant plantar involvement. A subgroup analysis of patients with plantar involvement showed effective treatment in 55% of the terbinafine group versus 0% of the vehicle group, demonstrating that terbinafine is effective even in more severe cases.

These results were supported by mycologic testing. After one week, culture was negative in 96% of patients treated with terbinafine compared with 36% of patients treated with vehicle (Figure 2A). Microscopy response rates, which indicate the presence of hyphae regardless of viability, were significantly higher with terbinafine than with vehicle for most of the study.



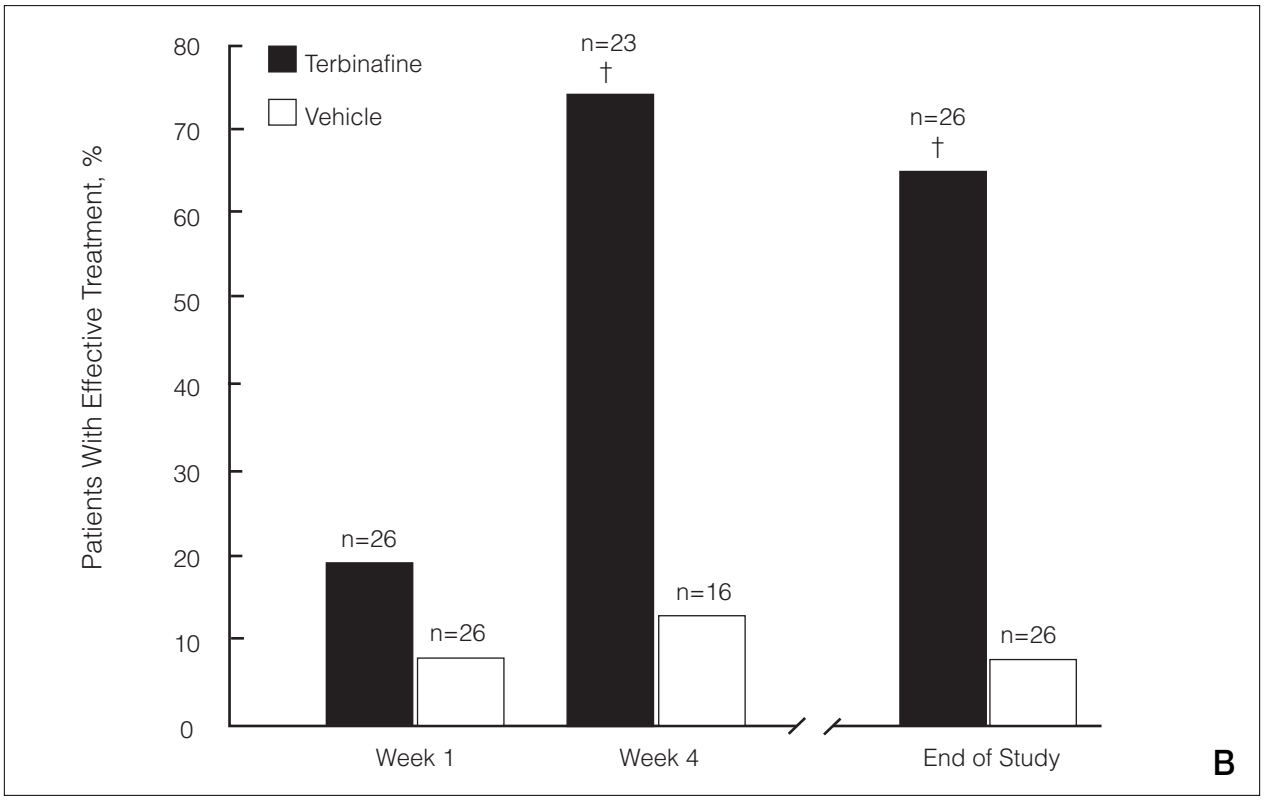


Figure 1. Percentages of patients in the intent-to-treat population who achieved effective treatment in the tinea pedis (A) and tinea corporis/cruris studies (B). Asterisk indicates *P*<.01 vs vehicle; dagger, *P*<.001 vs vehicle.

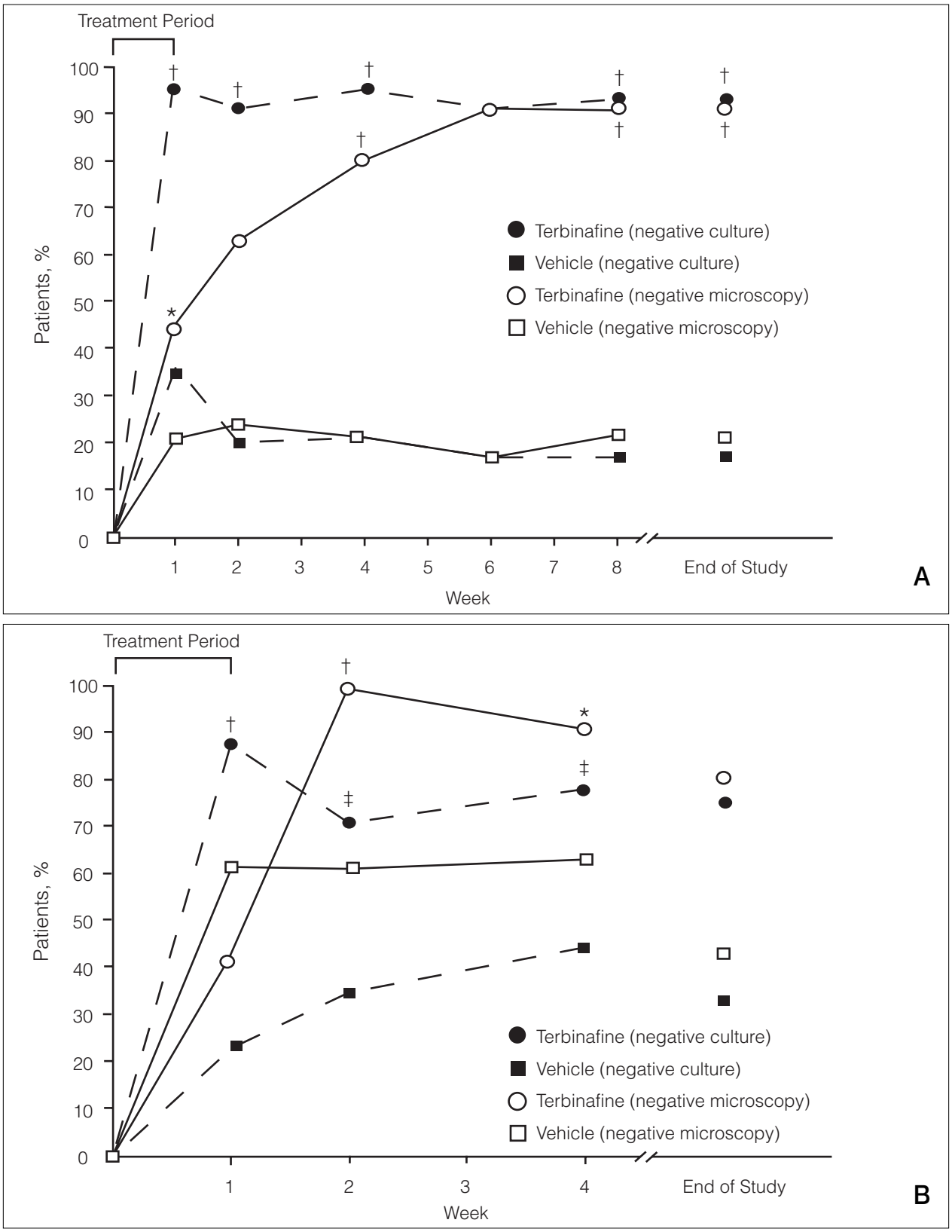


Figure 2. With mycology testing to measure viability, the culture becomes negative earlier than with microscopy, indicating the presence of hyphae regardless of viability. Tinea pedis study (intent-to-treat population)(A) and tinea corporis/cruris studies (valid-subject population)(B). Asterisk indicates *P*<.05 vs vehicle; dagger, *P*<.001 vs vehicle; double dagger, *P*<.01 vs vehicle.

Clinical and mycologic recurrence (relapse or reinfection) occurred in only 7% of patients treated with terbinafine in both the ITT and valid-subject populations despite long follow-up periods.

Tinea Corporis/Cruris Study—In the tinea corporis/cruris study, treatment was effective in 19% of patients at week 1, increasing to 74% at week 4 (Figure 1B). Corresponding values for vehicle were 8% and 13%, respectively, showing a clear benefit for terbinafine. At week 4 and at end of study, this difference was significant at the $P<.001$ level.

Mycology testing supported the clinical findings. At least 70% of patients treated with terbinafine had negative culture throughout most of the study, and no more than 44% of vehicle-treated patients had negative culture at any time (Figure 2B). Terbinafine was significantly superior at all visits. The percentage of patients treated with terbinafine with negative microscopy increased from 42% at the first visit to 100% by week 2.

Safety and Tolerability—In the tinea pedis study, the tolerabilities of terbinafine and vehicle did not differ in a significant or clinically meaningful way. Approximately 15% of the terbinafine group (16 of 105 patients) and 10% of the vehicle group (5 of 48 patients) experienced at least one adverse event during the study. Most adverse events were mild and not judged to be drug related. In this study, 7.6% of patients treated with terbinafine and 6.1% of patients treated with vehicle experienced skin or application-site adverse events. At the end of the study, terbinafine tolerability was rated *good* or *very good* by 97% of patients and investigators.

In the tinea corporis/cruris study, most adverse events were mild. Six percent of the terbinafine group and 3% of the vehicle group experienced skin or application-site adverse events that were potentially related to the study drug.

There were no deaths, serious or severe adverse events, or discontinuations resulting from adverse events during either study.

Comment

These studies indicate that one week of terbinafine 1% solution is a highly effective treatment for tinea pedis, corporis, and cruris and promotes clinical and mycologic cure. The short duration of treatment encouraged compliance. Patients with tinea pedis who were treated with terbinafine had a lower relapse rate than patients in the vehicle group. Cure rates increased during follow-up, suggesting that terbinafine continued to exert pharmacologic effects long after administration. Incidence of adverse events, which were usually mild and transient, was low and comparable between groups treated with terbinafine or vehicle.

A solution formulation may expand the utility of terbinafine. Müller et al[5] recommend that tinea cruris therapy be formulated as a powder or in a minimally occlusive cream base. This solution formulation may be useful for patients with sensitivity to cream components, for persons concerned that heavy creams may stain clothing, when a drying effect is desirable, or when large surface areas are affected. In addition, although terbinafine was applied twice daily in this tinea pedis study, another study found similar efficacy when it was applied once daily.[6] These studies indicate that terbinafine solution provides effective, safe alternative therapy for superficial fungal infections. Use of this new formulation may help promote compliance, especially when large surface areas are involved.

Acknowledgments—Supported by Novartis Pharmaceuticals Corporation, East Hanover, New Jersey. The Terbinafine 1% Solution Group (SFF-351) consists of K. Butterwick, MD, Dermatology Associates of San Diego, Encinitas, California; M. Fradin, MD, Chapel Hill Dermatology, North Carolina; J. Humeniuk, MD, Med Quest, Greer, South Carolina; S. Kang, MD, University of Michigan Medical Center, Ann Arbor; J. Leyden, MD, Hospital of the University of Pennsylvania, Philadelphia; M. Morman, MD, East Rutherford, New Jersey; J. Shavin, MD, Gwinnett Clinical Research Center, Snellville, Georgia; J. Weiss, MD, Gwinnett Dermatology, Snellville, Georgia; M. Zaiac, MD, Miami Beach, Florida; M. Hall, MD, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; S. Hilss, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey; and A. Mastropolo, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.

REFERENCES

1. Smith EB. Topical antifungal drugs in the treatment of tinea pedis, tinea cruris, and tinea corporis. *J Am Acad Dermatol.* 1993;28(5 pt 1):S24-S28.
2. Petranyi G, Meingassner JG, Mieth H. Antifungal activity of the allylamine derivative terbinafine *in vitro*. *Antimicrob Agents Chemother.* 1987;31:1365-1368.
3. Martin AG, Kobyashi GS. Superficial fungal infection: dermatophytosis, tinea nigra, piedra. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, eds. *Dermatology in General Medicine*. 4th ed. New York, NY: McGraw Hill; 1993:2421-2451.
4. Evans EGV, Seaman RAJ, James IGV. Short-duration therapy with terbinafine 1% cream in dermatophyte skin infections. *Br J Dermatol.* 1994;130:83-87.
5. Müller G, Satoh Y, Geisen K. Extrapancreatic effects of sulfonylureas—a comparison between glymepiride and conventional sulfonylureas. *Diabetes Res Clin Pract*. 1995;28 (suppl):S115-S137.
6. Grosshans E, Vermeer B, Foged EK, et al. Terbinafine 1% topical solution for 1 week in the treatment of pityriasis versicolor, tinea pedis, and tinea corporis/cruris [abstract]. In: *Proceedings of the 55th Annual Meeting of the American Academy of Dermatology*. 1997:1-3.