The Successful Treatment of *Trichophyton rubrum* Nail Bed (Distal Subungual) Onychomycosis With Intermittent Pulse-Dosed Terbinafine

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**Background:** The standard treatment of *Trichophyton rubrum* nail bed onychomycosis (or distal subungual onychomycosis [DSO]) with daily terbinafine for 12 weeks involves treating for a fixed period shorter than the time required for complete replacement of the nail bed and overlying nail plate by normal growth. The same total amount of terbinafine pulse-dosed for approximately 12 months would treat the patient until normal replacement of the mycotic nail bed has occurred.

**Objectives:** To determine the effectiveness of intermittent administration of oral terbinafine (250 mg/d for 7 consecutive days every 2-4 months) to cure DSO and to determine the maximum effective treatment interval.

**Design:** A prospective, nonrandomized, open study of sequential groups of office patients.

**Setting:** A private dermatology practice.

**Methods:** A sequence of 4 groups of office patients with DSO (n = 10-20 each) were treated with pulse-dosed terbinafine for 7 consecutive days at intervals of 2, 3, and 4 months, respectively. In each group, treatment was continued until the distally advancing new nail bed and nail had completely removed the mycotic defect or failure of fungistasis was detected.

**Main Outcome Measurement:** Results were determined by monthly evaluation. Cure was noted as complete replacement of the mycotic nail bed and overlying nail plate (ascertained by monthly metric measurements of the mycosis-free nail bed and overlying nail plate distal to the proximal nail fold). Treatment failure was noted when the mycosis-free proximal portion of the nail bed failed to increase in correspondence with the distally directed movement of the nail bed and overlying nail.

**Results:** Thirty-nine (93%) of the 42 patients in the first 3 groups were cured (95% binomial confidence interval, 67%-100%) with no evidence of decrease in efficacy. However, the group of patients who received the 7-day pulse treatment every 4 months experienced significantly more failures ($P < .01$), and cures dropped to 10 of 17 cases.

**Conclusion:** Terbinafine is an effective treatment for DSO when pulse-dosed for 7 days every 3 months but not every 4 months.

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We undertook this independent, office-based, open pilot study of our patients to answer 2 questions: (1) Is pulse-dosed oral terbinafine effective in treating *Trichophyton rubrum* nail bed onychomycosis (distal subungual onychomycosis [DSO])? and (2) Under a 7-consecutive-day, 1-pulse-per-day treatment regimen, what is the maximum effective interval between treatment pulses?

**Methods**

**Subjects**

We recruited patients with DSO sequentially from our regular office practice. No attempts to randomize the patients were made, and the study groups were recruited and studied sequentially. The criterion for patient selection was culture-proven DSO invasion of 60% or more of the nail bed of the great toes.

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Oral informed consent was obtained from each patient. Signed consent forms were not used, and institutional approval of this study of human subjects was not sought. A few subjects recruited for the study did not return for their first monthly postrecruitment examination; these patients were dropped from the study and are not included in the intent-to-treat analysis.

The study population consisted of adults of both sexes. The disease studied, DSO, once acquired, is a lifelong infection with no record or incidence of spontaneous recovery and may have a familial component bearing on susceptibility and infection.
TREATMENT GROUPS

The first 20 patients in this pilot study were treated with 250 mg of terbinafine daily for 7 consecutive days per month. Following this, we treated 10 patients by administering the 7-day pulse of terbinafine every 2 months, and then 12 patients by administering the pulse every 3 months, and finally 17 patients by administering the treatment pulse every 4 months. Since the results obtained from this last group indicated that we had achieved the objective of the study, the study was terminated.

Our plan was to recruit at least 10 patients into each study group after the first until a significant increase in treatment failures indicated a loss of depot effect. Seven patients were added to the final group to verify the increased failures observed in the first 10 patients.

CLINICAL EXAMINATION AND EVALUATION OF TREATMENT EFFECT

Rationale of the Method Used

In DSO, T rubrum invades the nail bed in a proximal direction, and, because of the normal growth of the nail, the overlying nail plate moves in the contrary (distal) direction (Figure 1). An effective antifungal compound (such as terbinafine) given by mouth stops the proximally directed invasion of the mycosis in the nail bed. Because the nail bed moves distally at the same rate as the overlying nail plate, the inactive mycotic lesion will be carried distally by normal growth and is eventually desquamated at the hyponychium (Figure 2). The growing new nail and nail bed proximal to the mycotic nail bed replace the retreating inactivated mycosis and eventually occupy the entire nail bed. At this point, the DSO is totally cured. (This cure should be verified by negative findings under potassium hydroxide and culture analysis.)

While foci of lasting damage to the nail unit may remain (whether from DSO or another cause), these cannot be attributed to the antifungal treatment and do not constitute treatment failure. In the case of the toenail of the large toe, the nail plate and underlying nail bed stratum corneum advance distally at a rate of close to 1 mm per month, and, depending on the size of the toenail, the mycosis will be totally cured 8 to 14 months from the start of treatment.

Examination Strategy

The strategy we used to monitor therapeutic effect was to measure the increase in new normal (nonmycotic) nail bed monthly until it occupied the entire nail bed from the nail matrix to the hyponychium. At this point, we considered the disease cured.

Baseline Measurements

Our measurement method was first characterized by Zaias and Drachman. Before treatment, a notch was cut into the surface of the nail plate to mark the most proximal margin of the nail bed lesion as seen through the transparent nail plate (ie, to mark the most proximal edge of the visible onychomycosis or a point safely proximal to it) (Figure 1). This notch served to mark the location of the distal edge of the normal noninfected nail bed before therapy. We also measured the distance in millimeters between the reference notch and some fixed reference point such as the proximal nail fold. This measurement provided a baseline measurement of the nonmycotic nail bed at the start of treatment.

The entire nail bed distal to the reference notch was considered mycotic. Because the goal of therapy was to completely remove this area by desquamation at the hyponychium before discontinuing treatment, no attempt was made to monitor treatment effect by evaluating severity, improvement, or worsening in this mycotic area. The nail bed was therefore considered to be divided into 2 parts: the distal mycotic nail bed already invaded by the fungus and the proximal normal nail bed not yet invaded by the fungus.

The objective of treatment was to increase the nonmycotic portion to 100% of the nail bed and reduce the mycotic portion to 0% (Figure 2B) while holding the fungus in a non-growing and noninvasive state. The pulsed treatments with terbinafine were continued until this objective was accomplished, at which point potassium hydroxide and culture analyses

Figure 1 Graphic illustration of the Zaias and Drachman method of monitoring clinical effect and cure of a great toenail 12 mm long with 75% of the toenail bed invaded by Trichophyton rubrum prior to treatment with pulse-dosed terbinafine. Before treatment, a reference notch is made in the nail plate to mark the proximal border of the nail bed mycosis and the baseline measurements. Note the plot (right) of the size of normal nail bed present prior to treatment. The presence of T rubrum nail bed onychomycosis should be confirmed microscopically and by culture.
were performed to confirm the absence of fungus, and the mycosis was recorded as cured. Since this is a systemic treatment, the final evaluation included the examination of all nails to ensure that the patient was entirely free of onychomycosis before declaring cure.

Monthly Examinations and Determination of Cure

During the course of treatment, all patients were examined monthly, and at each examination the distance from the most proximal edge of the nail bed lesion (as seen through the transparent nail plate) to the proximal nail fold was noted. When treatment was effective in inactivating the mycosis, the extent of the nonmycotic nail bed (as measured from the most proximal border of the nail bed mycosis to the proximal nail fold) continued to coincide with the measurement from the reference notch to the proximal nail fold; it increased steadily at a rate of close to 1 mm per month, and its growth could be plotted as a straight line (graph insets in Figure 2).

Evidence and Determination of Treatment Failure

If, on any monthly examination, the measurement of new nonmycotic nail bed (ie, the measurement from the most proximal border of the nail bed mycosis as seen through the transparent nail plate to the proximal nail fold) failed to show an increase over the previous month (ie, measured less than the measured distance to the reference notch), the result was in-
involved. However, there is no evidence that this biased the results.

Treatment failure was also evident and confirmed by simple inspection (using the reference notch as a guide) with or without measurement.

Under these circumstances, it was assumed that the patient would not attain complete replacement of the mycotic nail bed with new nonmycotic nail bed because the fungus was still actively invading the nail bed in a proximal direction, and so the patient was removed from the study protocol. Alternative treatment, after failure, was left to the judgment of the physician and the patient.

**RESULTS**

The monthly treatment group received 11 seven-day pulses of 250-mg terbinafine (19250 mg); the 2-month-interval group received 6 pulses (10500 mg); the 3-month-interval group received 4 pulses (7000 mg); and the 4-month-interval group received 3 pulses (3250 mg). For comparison, under standard therapy, a patient with 12 mm of mycotic nail bed would require 250 mg of terbinafine per day for 12 weeks, for a total of 21000 mg of drug.

Treatment failure occurred in 2 (10%) of the 20 patients in the monthly pulse group; 1 (10%) of the patients in the every-2-months group; and 0 of the 12 patients in the every-3-months group. Taken together, this 7% failure rate (3/42) is significantly better than the 41% failure rate (7/17) that occurred in the every-4-months treatment group (P<.01; 95% confidence interval, 0%-15%).

We were also able to compare the results of the monthly treatment group in the present study with those of a group of 20 patients treated earlier with itraconazole (200-mg pulse twice daily for 7 consecutive days each month). The patients in the itraconazole group experienced 5 failures and 15 cures, as has already been reported.

Although the number of patients per group in the present study is small, statistically significant results were obtained. The depot drug effect of terbinafine, and a cure rate of at least 90% of patients treated with 250 mg of terbinafine per day for 7 consecutive days every month, was maintained when the interval between 7-day pulses was increased to 2 and even to 3 months. However, when the interval between pulses was increased to 4 months, a significant increase in failures occurred (7/17, 41%; P<.01), indicating that the interval between pulse doses had been increased beyond the limit of the depot effect in some patients (Figure 3).

Additionally, Figure 3 shows that detection of treatment failure in all treatment groups can occur at any time during the course of treatment but occurs mainly in the first 6 months. No failures occurred after the first 6 months of treatment in the present study.

**COMMENT**

The treatment of 42 patients with 250-mg, pulsedosed terbinafine for 1 week every 1 to 3 months cured 39 (93%) of 42 patients with a 95% confidence interval of 68% to 100% cured. This confidence interval is higher on the percentage scale than the interval of cure rates reported for terbinafine in the large studies that provide the research data for the regimen of 250 mg/d for 12 weeks recommended by the drug manufacturer and approved by the US Food and Drug Administration. The higher overall level of success we achieved (if verified in larger studies and clinical practice) is an advantage that we do not ascribe to pulsed therapy but rather to the abandonment of the 12-week fixed treatment period in favor of treatment continued until the mycotic portion of the nail bed is shed at the hypnchium, which is the regimen recommended by Zaias and Drachman. The advantages we see in a pulsed-dose schedule of 1 week of treatment every 3 months are reduced costs to patients and medical insurance providers and the possibility of a decreased risk of adverse drug effects. The reduced-cost benefit is the result of the reduction in total milligrams of terbinafine required to cure the initially infected nail bed.

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REFERENCES


ARCHIVES Web Quiz Winner

Congratulations to the winner of our March quiz, Laxmisha Chandrashekar, MD, DNB, senior resident, Department of Dermatology and STD, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India. The correct answer to our March challenge was mycosis fungoides. For a complete discussion of this case, see the Off-Center Fold section in the April ARCHIVES (Papadopoulos EJ, Jaffe ES, Elgart GW, Raffeld M, Turner ML. Periodic fever with dyshidrosis. Arch Dermatol. 2004;140:479-484).

Be sure to visit the Archives of Dermatology World Wide Web site (http://www.archdermatol.com) to try your hand at the Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of The Art of JAMA II.