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New therapies for onychomycosis

Richard B. Odom, MD *San Francisco, California*

Until recently, the treatment of onychomycosis was discouraging because of the relatively low success rate, the need for prolonged therapy, and the laboratory monitoring necessary with the traditional oral antifungal agents, griseofulvin and ketoconazole. The advent of a new generation of oral antifungal drugs, including two triazoles (itraconazole and fluconazole) and an allylamine (terbinafine), has greatly improved the outlook for patients with fungal nail infections, particularly those with toenail involvement. Recently, the broad-spectrum triazole, itraconazole, has been approved for the treatment of onychomycosis in the U.S. Numerous studies have demonstrated its efficacy when administered either continuously for 3 months or in "pulse" dosing. Preliminary findings suggest that fluconazole and terbinafine are also promising, although their spectrum of activity is not as broad as that of itraconazole. (J Am Acad Dermatol 1996;35:S26-S30.)

Broad-spectrum, oral antifungal drugs are the most effective agents available for the treatment of moderate to severe onychomycosis. However, these drugs vary considerably in their pharmacologic and clinical characteristics. Table I lists some properties of an "ideal" oral antifungal agent. The pharmacokinetics of a given drug are important, because the drug must be incorporated into the nail matrix and diffuse through the nail bed epithelium to reach the nail bed hyperkeratosis and penetrate into the ventral surface of the nail plate. Ideally, the drug should also achieve a high clinical and mycologic cure rate, together with a low relapse rate. It should be effective when used for short-term therapy and have a low incidence of side effects. Because certain oral antifungal drugs interact with other commonly used drugs, it is also important to recognize the potential drug interactions of an antimycotic agent, particularly when treating older patients. In addition, the drug should be cost-effective.

This article describes the clinical experience with a new generation of oral antifungal agents that appears to offer an advantage over traditional treatment approaches and to fulfill many of the criteria of an "ideal" drug.

From the Department of Dermatology, University of California, San Francisco.

Reprint requests: Richard B. Odom, MD, Professor of Clinical Dermatology and Interim Chairman, Department of Dermatology, A328, University of California, 400 Parnassus Avenue, San Francisco, CA 94143.

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LIMITATIONS OF TRADITIONAL ORAL ANTIMYCOTIC AGENTS

Oral antifungal agents have been used for the treatment of onychomycosis for almost half a century. One of the major limitations of treatment with either griseofulvin or ketoconazole is the long duration of therapy required.[1-3] In addition, the clinical and mycologic cure rates are low,[4, 5] and there is a greater than 75% probability that the patient will relapse within 2 years.[4]

The potential for significant side effects is another problem, particularly with ketoconazole.[6-9]

A NEW GENERATION OF ANTIFUNGAL AGENTS

The first new agent to be introduced was the triazole fluconazole, which was approved for the treatment of HIV-positive patients with the systemic fungal infections cryptococcal meningitis and oral, pharyngeal, and esophageal candidiasis. A second triazole agent, itraconazole, was subsequently approved for the treatment of blastomycosis, histoplasmosis, and aspergillosis. At present, itraconazole and allylamine terbinafine are approved for the treatment of onychomycosis in the United States.

Table I. Properties of an "ideal" oral antifungal agent used for the treatment of onychomycosis

Favorable nail kinetics
Incorporated into nail matrix
Diffuses through nail bed
High clinical cure rate
High mycologic cure rate
Low incidence of relapse
Effective when used for short-term therapy
Low incidence of side effects
Few drug interactions
Cost effective

The pharmacokinetics of the newer agents are of particular significance because the drug is incorporated via both the nail matrix and nail bed, allowing a shorter duration of therapy.

The spectrum of activity of these newer agents is of particular relevance in the treatment of fungal nail infections, because an antimycotic agent should ideally be active against the full range of pathogens (e.g., dermatophytes, molds, and yeasts) that can potentially cause onychomycosis. Itraconazole is active against dermatophytes, yeasts, and most molds.[10] Fluconazole is also active against dermatophytes, yeasts, and some molds, although there are reports of resistance in patients with HIV and infections caused by Candida sp.[11, 12] Terbinafine is primarily active against dermatophytes. Its effectiveness against yeasts and molds is being investigated, but it appears to be less active than the triazoles.

Fluconazole

Kuokkanen and Alava[13] treated 20 patients with a severe dermatophyte infection of the fingernails and toenails. Patients received fluconazole 150 mg/week for a mean duration of 9.3 months after pretreatment with 40% urea cream. All fingernails and 92% of toenails were clinically and mycologically free of infection at the end of this time, and all fingernail infections continued to be clinically cured, as did 83% of toenail infections, at the 6-month follow-up visit.

Fraki et al.[14] administered fluconazole 150 mg/week for 5 to 12 months, with and without urea cream, to 111 patients. Fluconazole in combination with urea cream resulted in a clinical cure rate of 74% and a mycologic cure rate of 80% (Table II). In the absence of urea cream, however, there was only a 65% clinical cure rate and a 60% mycologic cure rate. Thus, fluconazole appears to be a promising agent in the treatment of onychomycosis, although there is no consensus as to the optimal dosage, frequency, or duration of therapy.

Table II. Fluconazole: intermittent therapy in toenail onychomycosis[14]

150 mg/week for 5 to 12 months (n = 102)		
Results	**+Urea**	**–Urea**
Mycologic cure	80%	65%
Clinical cure or markedly improved	74%	60%

The most common side effects of fluconazole are gastrointestinal symptoms and headache. There have been several reports of Stevens-Johnson syndrome, most commonly in patients with AIDS.[15] As with other oral azoles, drug-drug interactions may occur.[16]

Itraconazole

Numerous studies have been conducted in the U.S. and Europe to investigate the effects of various doses and dosing regimens of itraconazole in the treatment of onychomycosis. Investigators in Belgium compared 3 months of therapy with itraconazole, either 100 or 200 mg/day, in 39 patients with toenail or fingernail onychomycosis.[17] The respective cure rates with these two regimens in toenail infections were 26% and 79% at the 6-month follow-up evaluation. They also found that therapeutic concentrations of the drug were still present in the nail plate 6 months after the end of treatment. However, the drug concentrations were 10-fold higher in patients who had received the 200 mg dose of itraconazole. It was concluded that itraconazole reaches the nail by incorporation into the nail matrix, as well as by diffusion from the nail bed.

Fig. 1 summarizes the results of worldwide clinical experience with itraconazole 200 mg daily for 3 months.[18] Of the 12 studies in 558 patients with toenail infections, three were placebo controlled, two were comparative, and seven were open label. The majority of study participants had distal and lateral subungual onychomycosis or total dystrophic onychomycosis. Itraconazole was administered daily for 3 months, followed by a 9-month follow-up period. The clinical cure rate was 60%; the mycologic cure

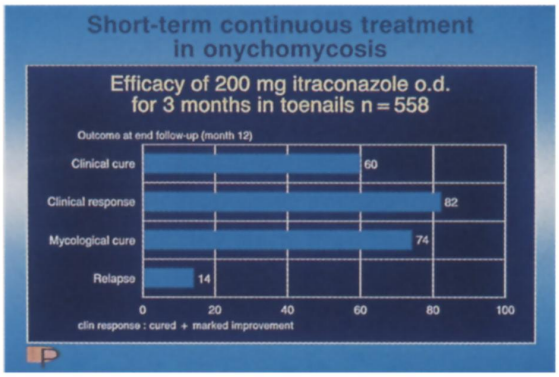

Fig. 1. Short-term continuous treatment in onychomycosis.

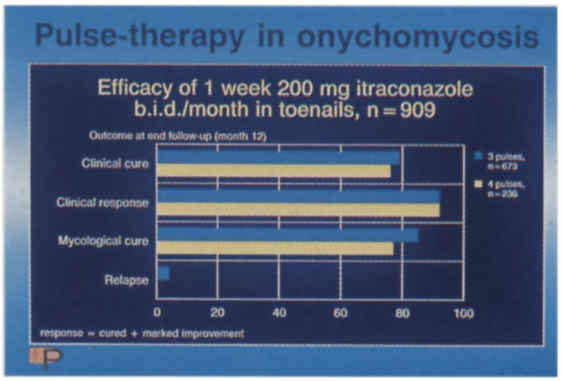

Fig. 2. Pulse therapy in onychomycosis.

rate was 74%. However, the overall clinical response (i.e., the number of patients who were cured plus those who achieved marked improvement [minimal nail involvement with significantly decreased signs]) was 82%. The relapse rate at the end of the follow-up period was 14%.

In a comparative study, 53 patients were treated with either itraconazole 200 mg/day or terbinafine 250 mg/day for 3 months, with a follow-up visit scheduled 9 months after cessation of therapy.[19] Treatment was highly effective in both groups and the clinical and mycologic cure rates for each of the two agents were not significantly different (60.9% in the itraconazole group, 64.7% in the terbinafine group). However, the incidence of adverse effects was significantly higher in the terbinafine group (47% vs only 21% in the itraconazole group). Adverse events for itraconazole included gastric upset, headache, edema, and transient transaminase elevation. Terbinafine side effects consisted of stomach upset, headache, nausea, pruritus, facial eruption, abdominal pain, menorrhalgia, and dysgeusia.

Other investigators have explored the use of itraconazole 100 or 200 mg/day for 3 or 6 months to treat Candida onychomycosis. Of the 15 patients who participated in one study, the infections were cured in 93% and improved in the remainder.[20]

More than 1.5 million patients have been treated with itraconazole for systemic and superficial infections in doses ranging from 100 to 600 mg/day. Itraconazole is well tolerated; the most common side effects are gastrointestinal disturbance and headache.[21] The drug-drug interactions with itraconazole are not well defined, but the presence of food appears to increase itraconazole's gastrointestinal absorption.[16] Itraconazole may inhibit the metabolism of both cyclosporine and digoxin, elevating blood levels of both drugs. Itraconazole may reduce plasma concentrations of phenytoin, rifampin, and H_2 antagonists. The coadministration of terfenadine, astemizole, or cisapride with itraconazole is contraindicated.[16]

One of the newest and most promising approaches to the management of onychomycosis is based on the concept of intermittent or "pulse" dosing with itraconazole. This regimen consists of administering itraconazole 200 mg twice daily with meals for only 7 consecutive days of each month. Toenail infections can generally be cured within 3 to 4 months, while fingernail infections usually require only 2 to 3 months.[18, 22, 23] There are several potential benefits associated with the use of intermittent therapy. First, the progressive accumulation of drug and persistent levels in the nail help prevent the potential development of resistance. Second, because plasma levels of drug decline in less than a week, the risk of side effects may decrease, which probably reduces the incidence of patient noncompliance.

Fig. 2 summarizes the clinical experience with pulse itraconazole in 909 patients with toenail onychomycosis.[18] The clinical outcome was similar, regardless of whether the patients received three or four pulses of therapy. The overall clinical response was identical (92%) in both groups. Less than 4% relapsed in the three-pulse group and no patients relapsed in the four-pulse group.

Fig. 3 summarizes the clinical experience with pulse itraconazole in the treatment of 328 patients with fingernail onychomycosis.[18] The clinical outcome was virtually identical, independent of whether the patients received two or three pulses of

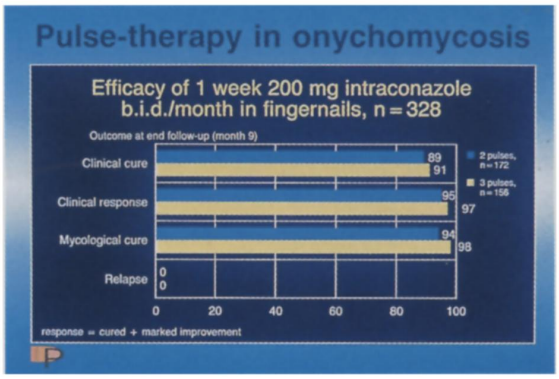

Fig. 3. Pulse therapy in onychomycosis.

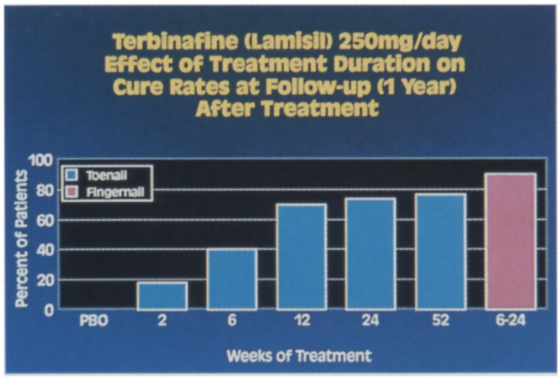

Fig. 4. Terbinafine (Lamisil®) 250/mg day. Effect of treatment duration on cure rates at follow-up, 1 year after treatment.

therapy. The clinical cure rate associated with the two-pulse regimen was 89%, as compared with 91% in the group receiving the three-pulse regimen. A total of 95% of patients receiving two cycles of therapy demonstrated a clinical response, as did 97% of patients receiving three cycles. The respective mycologic cure rates for the two regimens were 94% and 98%, and there were no relapses in either group.

From a cost perspective, it is important to note that three pulses of itraconazole appear to be as effective as four in eradicating toenail and two as effective as three in eradicating fingernail onychomycosis. Pulse dosing not only provides effective treatment, but it also reduces the patient's exposure to the drug. Reduced drug exposure, in turn, may minimize the potential for drug interactions and result in improved patient compliance.

As indicated in itraconazole's prescribing information, hepatic enzyme test values should be monitored periodically in all patients receiving continuous treatment for more than 1 month or at any time a patient develops signs or symptoms suggestive of liver dysfunction. Therefore a baseline liver function test should be done before the initiation of therapy.

Terbinafine

Terbinafine, a member of a new class of antifungals, the allylamines, has recently been approved for treatment of onychomycosis in the United States. One study in 112 patients with toenail onychomycosis showed that terbinafine 250 mg/day for 3 months produced a cure rate of approximately 70% (Fig. 4).[24] However, the overall cure rate after 24 to 52 weeks of therapy was approximately 90%. Faergemann et al.[25] conducted a study in which 85 patients with toenail onychomycosis were treated with one of two therapeutic regimens: terbinafine 250 mg/day for 16 weeks or griseofulvin 500 mg/day for 52 weeks.[25] In the terbinafine group, 84% of infections were mycologically cured and 42% were completely (both clinically and mycologically) cured at the end of 16 weeks. In contrast, only 45% of infections were mycologically cured and 2% were completely cured in the griseofulvin group. More than twice the number of patients receiving griseofulvin experienced side effects than those receiving terbinafine (29% vs. 11%, respectively).

Hofmann et al.[26] conducted a randomized, double-blind study in 195 patients with severe dermatophyte infection of the toenails. Patients were assigned to either 24 weeks of treatment with terbinafine 250 mg/day or 48 weeks of treatment with microsized griseofulvin, 1000 mg/day. At the end of 48 weeks, there was a 67% cure rate in the terbinafine group and a 56% cure rate in the griseofulvin group. At the 6-month follow-up visit, there was a 60% clinical cure rate and an 81% mycologic cure rate in the terbinafine group. The respective figures in the griseofulvin group were 39% and 62%. In another comparative study, 180 patients with dermatophyte-related fingernail infections were treated for 12 weeks with either terbinafine 250 mg/day, microsized griseofulvin 500 mg/day, or placebo.[27] At the end of the 6-month follow-up period, the cure rate in the terbinafine group was 76%, compared with 39% in the griseofulvin group. Both treatments were well tolerated.

Oral terbinafine appears to be well tolerated. The most common side effects are gastrointestinal dis-

tress and skin reactions.[28] Loss of taste, neutropenia, and pancytopenia have also been reported.[29, 30]

REFERENCES

1. Roberts DT. Oral therapeutic agents in fungal nail disease. J Am Acad Dermatol 1994;31:S78-81.
2. Piérard G, Arrese-Estrada J, Piérard-Franchimont C. Treatment of onychomycosis: traditional approaches. J Am Acad Dermatol 1993;29:S41-5.
3. Scher RK. Diseases of the nails. In: Conn H, editor. Current therapy. Philadelphia: W.B. Saunders, 1990:736.
4. Davies RR, Everall JD, Hamilton E. Mycological and clinical evaluation of griseofulvin for chronic onychomycosis. Br Med J 1967;3:464-8.
5. Frain-Bell W, Riddell RW, Stevenson CJ, et al. Chronic ringworm infection of the skin and nails treated with griseofulvin. Lancet 1960;1:1141-7.
6. Davies RR. Griseofulvin. In: Speller DCE, editor. Antifungal chemotherapy. New York: John Wiley, 1980:149-82.
7. Dollery C. Griseofulvin. In: Therapeutic drugs. Edinburgh: Churchill Livingstone, 1991:G66-9.
8. Janssen PAJ, Symoens JE. Hepatic reactions during ketoconazole treatment. Am J Med 1983;74:80-5.
9. Hay RJ. Risk/benefit ratio of modern antifungal therapy: Focus on hepatic reactions. J Am Acad Dermatol 1993;29: S50-4.
10. Odds FC. Spectrum of orally active antifungals. J Eur Acad Dermatol Venereol 1993;2(suppl 1):S12-8.
11. Powderly W, Finkelstein D, Feinberg J. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced HIV infection. N Engl J Med 1995;332:700-5.
12. Cameron ML, Schnell WA, Bruch S, et al. Correlation of in vitro fluconazole resistance of *Candida* isolates in relation to therapy and symptoms of individuals seropositive for human immunodeficiency virus type 1. Antimicrob Agents Chemother 1993;37:2449-53.
13. Kuokkanen K, Alava S. Fluconazole in the treatment of onychomycosis caused by dermatophytes. J Dermatol Treat 1992;3:115-7.
14. Fraki J, Heikkila H, Kero M, et al. Fluconazole in the treatment of onychomycosis: an open non-comparative multicenter study with oral 150-mg fluconazole once weekly. In: Future trends in the treatment of dermatomycoses. Dermatology 2000, Vienna, abstract book, poster, May 1993.
15. Osterloh IH. Safety. In: Powderly WB, Van Wout JW, editors. Fluconazole. Carnforth, United Kingdom: Marias Press, 1992:40.
16. Bickers DR. Antifungal therapy: potential interactions with other classes of drugs. J Am Acad Dermatol 1994;31:S87-90.
17. Willemsen M, De Doncker P, Willems J, et al. Posttreatment itraconazole levels in the nail. J Am Acad Dermatol 1992;26:731-5.
18. Data on file, Janssen Pharmaceutica (Beerse, Belgium).
19. Arenas R, Dominguez-Cherit J, Fernandez LM. Open randomized comparison of itraconazole versus terbinafine in onychomycosis. Int J Dermatol 1995;34:138-43.
20. Roseeuw D, De Doncker P. New approaches to the treatment of onychomycosis. J Am Acad Dermatol 1993; 29: S45-50.
21. Alcantara R, Garibay JM. Itraconazole therapy in dermatomycoses and vaginal candidiasis: effects and adverse effects profile in a large multi-center study. Adv Ther 1988; 5:326-34.
22. De Doncker P, Van Lint J, Dockx P, et al. Pulse therapy with one-week itraconazole monthly for three or four months in the treatment of onychomycosis. Cutis 1995;56: 180-3.
23. De Doncker P, Decroix J, Piérard G, et al. Antifungal pulse therapy for onychomycosis. A pharmacokinetic and pharmacodynamic investigation of monthly cycles of 1-week pulse therapy with itraconazole. Arch Dermatol 1996; 132:34-41.
24. Goodfield, MJD. Short-duration therapy with terbinafine for dermatophyte onychomycosis: a multicentre trial. Br J Dermatol 1992;126(suppl 39):33-5.
25. Faergemann J, Anderson C, Hersle K, et al. Double-blind, parallel-group comparison of terbinafine and griseofulvin in the treatment of toenail onychomycosis. J Am Acad Dermatol 1995;32:750-3.
26. Hofmann H, Bräutigam M, Wiedinger G, et al. Treatment of toenail onychomycosis. A randomized, double-blind study with terbinafine and griseofulvin. Arch Dermatol 1995;131:919-22.
27. Haneke E, Tausch I, Bräutigam M, et al. Short-duration treatment of fingernail dermatophytosis: a randomized, double-blind study with terbinafine and griseofulvin. J Am Acad Dermatol 1995;32:72-7.
28. Villars VV, Jones TC. Special features of the clinical use of oral terbinafine in the treatment of fungal diseases. Br J Dermatol 1992;126(suppl 39):61-9.
29. Stricker BH, De-Jong PA, Schreuder F, et al. Loss of taste sensation in terbinafine administration. Ned Tijdschr Geneeskd 1992;136:2438-400.
30. Kovacs MJ, Alshammari S, Guenther L, et al. Neutropenia and pancytopenia associated with oral terbinafine. J Am Acad Dermatol 1994;31:806.