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CLINICAL REVIEW

Management of toenail onychomycosis

CATHERINE M. TOM AND MICHAEL P. KANE

Abstract: The treatment of toenail onychomycosis is reviewed.

Onychomycosis contributes to 40% of all nail disorders and appears to be increasing in frequency. Mycotic nail infections are usually caused by dermatophytes, yeasts, and nondermatophyte molds. Most cases of toenail onychomycosis are caused by dermatophytes. Mycotic nail infections do not always resolve spontaneously and may have a substantial impact on the patient's quality of life.

Current treatment modalities for onychomycosis include surgery, topical antifungals, and oral antifungals. Surgery is generally not recommended as first-line therapy. Broad-spectrum topical and oral antifungal agents are the most frequently used treatments. Topical treatment is well tolerated but is usually not effective because of poor patient compliance and inadequate penetration of the nail. Oral antifungals are more successful but carry greater risks. Griseofulvin and ketoconazole have been oral antifungals traditionally used for onychomycosis, but these agents are associated with relatively low cure rates. Itraconazole and terbinafine are both safe and effective first-line agents, with reported overall cure rates of 50–90% for dermatophyte-related onychomycosis. Intermittent oral antifungal therapy may reduce the risk of systemic adverse effects and the cost of therapy; more study of this approach is needed.

Oral antifungal agents offer patients with toenail onychomycosis greater likelihood of a cure than topical antifungals, but oral therapy carries greater risks and requires closer monitoring.

Index terms: Antifungals; Clinical studies; Diagnosis; Drug administration routes; Drugs; Economics; Itraconazole; Onychomycosis; Surgery; Terbinafine hydrochloride; Topical preparations

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Onychomycosis, or fungal infection of the nail bed or nail plate, contributes to 40% of all nail disorders.[1] Although the prevalence of onychomycosis is relatively low, its frequency appears to be increasing.[2-4] Contributing to this increase are a growing elderly population, the spread of HIV infection and AIDS, the greater frequency of iatrogenic immunosuppression with the use of immunosuppressants, superinfections due to systemic antimicrobials, and lifestyle factors, such as wearing tight clothing and shoes and using communal bathing facilities, recreational facilities, and health clubs.[1,3,4] Improved detection and heightened public awareness are also contributing to the reported increase in the frequency of onychomycosis.[4]

This article reviews the diagnosis and treatment of toenail onychomycosis.

Diagnosis and patient impact

Mycotic nail infections are caused most commonly by dermatophytes (90% *Trichophyton, Microsporum,* and *Epidermophyton* species), yeasts (7% *Candida* species), and nondermatophyte molds (3% *Scytalidium, Fusarium, Acremonium, Aspergillus,* and *Scopulariopsis* species).[3,5,6] Four major types of mycotic nail infections have been identified: distal subungual onychomycosis (the most common type, initially affecting the plantar surfaces of the hands and feet), white superficial onychomycosis (which affects only the toenails), proximal subungual onychomycosis (which is often associated with immunosuppression), and candidal onychomycosis.[7] These infections vary with respect to the pattern of fungal invasion of the nail plate and the causative pathogen.[6,8] Clinical symptoms of onychomycosis include onycholysis (separation of the nail from its bed), hyperkeratosis (calluses, corns), brittleness, paronychial inflammation (inflammation due to infection of the skin fold at the nail margin), and color change (Figure 1).

Formal diagnosis of onychomycosis typically in-

CATHERINE M. TOM, PHARM.D., is Pharmacy Practice Resident, Thomas Jefferson University Hospital, Philadelphia, PA. MICHAEL P. KANE, PHARM.D., BCPS, is Associate Professor, Division of Pharmacy Practice, Albany College of Pharmacy, Albany, NY.

Address reprint requests to Dr. Kane at the Division of Pharmacy Practice, Albany College of Pharmacy, 106 New Scotland Avenue, Albany, NY 12208, or to kanem@panther.acp.edu.

volves preparation of nail scrapings in a potassium hydroxide solution and examination for hyphal fragments by direct microscopy; a fungal culture grown in a suitable medium for 7–14 days is necessary for specific identification of the pathogen.[1,6,8] Depending on the pathogen suspected, a cycloheximide-containing medium can be chosen to inhibit the growth of many nondermatophytes, while a cycloheximide-free medium can be used to isolate yeasts and nondermatophytes.[1] Nail biopsies from the nail bed and nail plate are warranted when onychomycosis is clinically suspected but findings from repeated microscopy and cultures are negative. In practice, the diagnosis of onychomycosis is usually based on clinical examination, and therapy is often empirical.

Mycotic nail infections do not always resolve spontaneously and may have serious consequences, including limitation of mobility and dexterity (potentially affecting physical work ability), decrease in peripheral circulation in the area affected, self-consciousness, and avoidance of physical intimacy. Onychomycosis can worsen preexisting foot problems, such as diabetic foot.[3] Although the frequency of dermatophyte nail infections is probably not increased in diabetics, the potential for serious complications from such infections may be greater in that population.[9,10]

Lubeck et al.[11] evaluated the impact of onychomycosis on quality of life, assessed as general health, bodily pain, disease symptoms, social functioning, mental health, health concerns, social confidence, and perceived problems with physical appearance and physical activities. Compared with healthy controls, onychomycosis patients had significantly lower quality-of-life scores for all measures except social confidence. The disease's greatest impact was on onychomycosis-specific measures like problems with physical activities (e.g., problems with work activities that require being on one's feet or working with one's fingers).

Treatment

Current treatment modalities for onychomycosis include surgical measures, topical antifungals, and oral (systemic) antifungals.[4,10,12] Surgical treatment consists of nail avulsion, in which the nail plate is macerated, and nail obliteration with the carbon dioxide laser (efficacy data on the latter are limited).[4] Because of patient discomfort and the risk of complications, surgery is generally not recommended as first-line therapy, except for severe or refractory infections.

Broad-spectrum topical and oral antifungal agents are most often used in managing severe toenail onychomycosis.[13,14] Table 1 lists the desirable properties of such agents. Three main classes of topical antifungals are available: (1) polyenes (e.g., nystatin), (2) imidazoles (clotrimazole, econazole, ketoconazole, miconazole, sulconazole, and oxiconazole), and (3) allylamines–benzylamines (naftifine, terbinafine, and butenafine). Only imidazoles and allylamines–benzylamines are active against dermatophytes; all three classes are active against *Candida* species.[14] Since a majority of toenail onychomycosis cases are caused by dermatophytes, only imidazoles and allylamines–benzylamines will be discussed here.

Figure 1. Typical appearance of severe toenail onychomycosis.

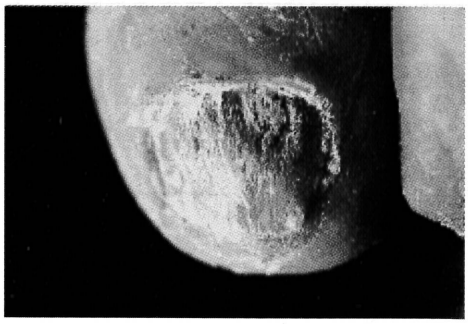

Table 1.
Properties of Ideal Antifungal Agents[13,14]

Ideal Oral Agent	Ideal Topical Agent
Incorporated into nail matrix	Efficacious at low concentrations
Diffuses through nail bed	Fungicidal
High clinical cure rate	Effective with topical application
High mycologic cure rate	High affinity for stratum corneum
Low risk of relapse	Well tolerated
Effective when used for short-term therapy	Nonsensitizing
Low risk of adverse effects	Low risk of fungal resistance
Few drug interactions	User-friendly dosage regimen
Cost-effective	

Imidazoles are relatively broad-spectrum, fungistatic antifungal agents. They cause fungal cell membrane defects by inhibiting the synthesis of ergosterol, an essential component of the cell wall. This inhibition is accomplished by interference with the conversion of lanosterol to ergosterol at the level of the cytochrome P-450 enzyme lanosterol 14-demethylase.[15] Topically applied imidazoles are generally well tolerated because mammalian cytochrome P-450 enzyme systems are not affected.[15,16] Topical administration is also advantageous in that the drug interactions and endocrine-related adverse effects (menstrual irregularities, gynecomastia, sexual dysfunction, and plasma cortisol suppression) sometimes associated with the systemic administration of imidazoles are avoided.[14,17]

Allylamines–benzylamines appear to have both fungistatic and fungicidal effects. They too interfere with the production of ergosterol, but through a different mechanism. Terbinafine, for example, inhibits the activity of squalene epoxidase, which is involved earlier

in the ergosterol metabolic pathway. Consequently, cell death occurs because of a decrease in ergosterol concentration and an accumulation of squalene in the fungal cell.[13,18] Since terbinafine appears to have a lower affinity for mammalian enzymes in vitro,[18] squalene epoxidases in mammals are spared.

Topical antifungal treatment of onychomycosis is ineffective in curing most infections. This is probably because of inadequate drug penetration of the nail—a hardened mass of tightly packed, keratinized cells.[19] Another concern with topical antifungal use is that patient compliance is likely to be suboptimal. Medication has to be applied two or three times daily for 6–12 months, if not lifelong.[4] Topical treatment may be an effective adjunct to systemic therapy, however, and adverse effects (itching, burning, and redness at the application site) are generally minor.

Overall, oral antifungal therapy is more efficacious than topical treatment in the management of toenail onychomycosis. Traditionally, griseofulvin or ketoconazole has been used. These agents are less than ideal, however. Griseofulvin is associated with low clinical and mycologic cure rates and a high relapse rate, and the duration of therapy is long (at least six months for toenail infections). Ketoconazole is only slightly more efficacious, and, as with griseofulvin, the potential for adverse effects and drug interactions is high. Fluconazole may have a role in toenail onychomycosis management, but there are limited data supporting its use for dermatophyte onychomycosis.[20,21] Although fluconazole has a favorable adverse-effect profile, up to nine months of therapy may be needed. Fluconazole cannot be recommended as first-line therapy.

Itraconazole and terbinafine

Itraconazole (Sporanox, Janssen), a triazole, and terbinafine (Lamisil, Sandoz) are two newer oral antifungal agents that offer improved safety and greater efficacy in managing toenail onychomycosis (Table 2). Both drugs are incorporated into the nail via both the nail matrix and the nail bed, thereby enhancing mycologic and clinical efficacy. They exhibit a broad spectrum of activity against dermatophytes, molds, and yeasts, although terbinafine may be less active against *Candida* species.[14] Finally, compared with other agents, the duration of treatment is much shorter.

Itraconazole accumulates slowly in the nails, and it may remain detectable for six months after it is discontinued because of its high affinity for keratinized tissues.[16] This affinity results in high nail concentrations of the drug. In a nonrandomized, nonblinded study of 39 patients with onychomycosis, nail clippings were collected during and for three months after a three-month course of itraconazole 100 or 200 mg orally daily.[22] Toenail itraconazole concentrations were 84–149 ng/g for the 100-mg group and 490–990 ng/g for the 200-mg group. Maximum mean drug concentrations (149 and 990 ng/g) were achieved after two months of therapy, and drug was detectable in the nails for six months after drug discontinuation. Itraconazole was actively incorporated into the nail matrix, as well as incorporated by passive diffusion from the nail bed into the nail plate.

In a study by Dykes et al.,[23] clippings were collected from the infected and healthy nails of 12 patients receiving a 12-week course of terbinafine hydrochloride 250 mg orally daily. Drug was detected in nail samples at week 4 (the first sampling time), but concentrations were not significantly higher at week 12. Drug concentrations in infected and uninfected nails did not differ significantly. The authors concluded that diffusion through the nail plate is the primary route by which terbinafine penetrates nails.

Itraconazole and terbinafine have both been found to be more effective than placebo in the treatment of toenail onychomycosis. Most studies defined efficacy as (1) clinical cure or response (based on a global evaluation of nails as cured or markedly improved), (2) mycologic cure or response (negative microscopy or culture results), or (3) overall cure (a combination of clinical cure and mycologic cure). The mycologic cure rate is usually used for comparing agents because of its greater objectivity.

Jones and Zaias[24] randomly assigned patients with toenail onychomycosis to 12 weeks of itraconazole 200 mg daily ($n = 36$) or placebo ($n = 37$) taken with a meal. Clinical and mycologic evaluations were made at weeks 4, 8, and 12. At week 12, clinical success was observed in 77% of patients treated with itraconazole and in 0% given placebo, while mycologic success was achieved in 69% and 6% of patients, respectively. Overall success occurred in 51% of the itraconazole-treated group and 0% of the placebo group. One year after the start of therapy, clinical relapse, mycologic relapse, and overall relapse rates of 30%, 46%, and 28% were recorded for the itraconazole group. An explanation for the high relapse rates was not provided by the study's authors, nor is one readily apparent. Adverse events (gastritis, headache, sinusitis, rhinitis, and diarrhea) did not differ significantly in frequency between the drug and placebo groups (53% versus 57%).

In a randomized, double-blind, multicenter study of 148 patients with toenail onychomycosis, Svejgaard et al.[25] compared terbinafine hydrochloride 250 mg orally daily for three months ($n = 75$) with placebo ($n = 73$). One hundred twenty-seven patients completed the initial three months of the study (12 terbinafine recipients and 9 placebo recipients withdrew because of lack of efficacy, adverse effects, and various other reasons). Twenty-six nonresponders in the terbinafine group and 57 members of the placebo group then completed an additional three-month course of terbinafine therapy. At 12 months, clinical cure was seen in 44% of the patients who received placebo alone, 67% of those given placebo

Table 2.
Comparison of Itraconazole and Terbinafine[15,18,a]

Item	Itraconazole	Terbinafine
Class of drug	Synthetic triazole	Synthetic allylamine derivative
Mechanism of action	Inhibits cytochrome P-450-dependent synthesis of ergosterol	Inhibits squalene epoxidase
Spectrum of activity	*Cryptococcus neoformans* and species of *Microsporum, Trichophyton, Epidermophyton, Candida, Pityrosporum, Histoplasma, Blastomyces,* and *Aspergillus*	*Trichophyton rubrum, Trichophyton mentagrophytes*
Regimen for toenail onychomycosis	200 mg daily with full meal for 12 wk or three 1-wk courses of 200 mg b.i.d. (with meal), with each course separated by 3 wk without treatment (intermittent regimen not FDA approved)	250 mg daily for 12 wk
Bioavailability	55% (with meal)	70% absorption, 40% bioavailability after first-pass effect
Mean ± S.D. C_{max} (ng/mL)	239 ± 85	1000
Mean ± S.D. t_{max} (hr)	4.5 ± 1.1	2
Mean ± S.D. $t_{½}$ (hr)	21 ± 5	36
Plasma protein binding (%)	99.8	>99
Elimination	Hepatic metabolism, with 40% of dose renally eliminated as inactive metabolites	Hepatic metabolism, with 70% of dose eliminated in the urine
Renal impairment	No adjustment necessary	CL_{cr}, ≤50 mL/min: clearance decreased by 50% (use not recommended)
Hepatic impairment	Monitor plasma drug concentrations	Hepatic cirrhosis: clearance decreased by 50% (use not recommended)
Precautions	Monitor liver function if history of hepatic disease present, if duration of continuous treatment is >1 mo, or if signs or symptoms of liver dysfunction arise	Changes in ocular lens and retina have occurred (clinical significance unknown). Monitor liver function if treatment duration is >6 wk. Transient decreases in absolute lymphocyte count reported (frequency, 1.7%). Isolated cases of neutropenia
Contraindications	Coadministration of terfenadine, astemizole, or cisapride; concomitant oral midazolam or triazolam therapy; pregnancy (for treatment of onychomycosis); history of hypersensitivity	History of hypersensitivity
Adverse reactions (in treatment of onychomycosis)	Reversible hepatitis, elevated liver enzymes, nausea, vomiting, diarrhea, rash, hypertension. Rarely: orthostatic hypotension, headache, malaise, myalgia, vasculitis, vertigo	Diarrhea, dyspepsia, abdominal pain, nausea, flatulence, elevated liver enzymes, taste disturbance. Rarely: visual disturbance, serious rash, neutropenia
Interacting drugs	Warfarin, terfenadine, astemizole, cisapride, ritonavir, indinavir, midazolam, triazolam, diazepam, lovastatin, simvastatin, cyclosporine, tacrolimus, methylprednisolone, digoxin, quinidine, phenytoin, phenobarbital, carbamazepine, histamine H_2-receptor antagonists, isoniazid, rifampin, rifabutin	Cyclosporine, rifampin, cimetidine, terfenadine
Pregnancy category	C (contraindicated for treatment of onychomycosis)	B
How supplied	100-mg capsules	250-mg tablets
Cost per unit ($)[b]	5.82	5.98
Cost per 12 wk of continuous therapy ($)	977.76	502.32
Cost per regimen of intermittent therapy ($)	488.88 (three weeks' doses)	. . .
Patient information	Take with full meal. Report unusual signs of fatigue, anorexia, nausea, vomiting, jaundice, dark urine, or pale stool	May take with or without food

[a] C_{max} = maximum plasma drug concentration, t_{max} = time to reach C_{max}, $t_{½}$ = elimination half-life, CL_{cr} = creatinine clearance.
[b] Costs are average wholesale prices (Garrett HM, ed. Red book. Montvale, NJ: Medical Economics; 1997).

and then terbinafine, 63% of those given terbinafine for 3 months, and 81% of those given terbinafine for 6 months; mycologic cure rates (negative microscopy and culture results) were 33%, 49%, 40%, and 47%, respectively, and overall cure rates were 25%, 40%, 38%, and 42%. The high cure rates for placebo reflect the fact that

spontaneous cure may occur in onychomycosis. The small number of patients in each group precluded statistical evaluation of drug efficacy. Adverse effects, such as gastrointestinal symptoms, urticaria, erythema multiforme, and taste and smell disturbances, were not significantly different between the terbinafine and placebo groups (13.5% versus 5.4%).

Watson et al.[26] compared terbinafine with placebo in 118 patients with toenail onychomycosis in a randomized, double-blind, 48-week, multicenter trial. Phase 1 of the study involved a 12-week regimen of terbinafine hydrochloride 250 mg once daily versus placebo, with the groups being compared at week 24 (12 weeks after treatment was discontinued). In phase 2, nonresponders were offered a 12-week course of terbinafine hydrochloride 250 mg once daily, beginning at week 28 (when the mycology results at week 24 were available). Treatment responders were observed for an additional 24 weeks.

One hundred eleven patients (56 in the terbinafine group and 55 in the placebo group) completed phase 1. At week 24, 88% of the terbinafine recipients had negative culture results, versus 29% of the placebo group ($p < 0.001$). Eighteen of the 24 nonresponders in the terbinafine group and 48 of the 52 nonresponders in the placebo group were placed on the second 12-week terbinafine regimen. At the study's end (week 48), 84% of the responders in phase 1 and 67% of the responders in phase 2 had been effectively treated. Cultures were negative in 97% of the phase 1 terbinafine recipients, 89% of the phase 1 plus phase 2 terbinafine recipients, 33% of the phase 1 placebo recipients, and 77% of the phase 1 placebo plus phase 2 terbinafine recipients. Eighty-two percent of terbinafine-treated patients and 73% of placebo recipients reported adverse effects (central nervous system, gastrointestinal, respiratory, skin, and taste effects), but the difference was not significant.

Intermittent therapy

A recent approach to the management of toenail onychomycosis is intermittent ("pulse") administration of antifungal agents, as opposed to ongoing daily administration. A fixed dose of antifungal is given daily for the first week of the month for several consecutive months. Advantages of this regimen include a reduced risk of systemic adverse effects,[12] a lower cost of therapy, and enhanced patient compliance.

Havu et al.[27] sought to determine whether intermittent therapy with itraconazole is as effective as continuous therapy for toenail onychomycosis. In a multicenter, double-blind, placebo-controlled, parallel-group study, 64 patients were randomly assigned to receive itraconazole 400 mg daily for the first week of the month for three consecutive months, while 65 other patients received 200 mg daily for 12 consecutive weeks. Mycologic cure rates for the intermittent-therapy and continuous-therapy groups were 56% and 69%, respectively, at month 6 and 52% and 66% at month 12 (not a significant difference). Overall response rates at one year were 56% in the intermittent group and 52% in the continuous group (also not significant). The frequency of adverse events (which were mainly gastrointestinal—nausea, flatulence) was 16.9% in the continuous group and 14.1% in the intermittent group. The authors concluded that both regimens were effective and well tolerated.

DeDoncker and colleagues[28] randomly assigned 50 patients in an unblinded manner to an intermittent regimen of itraconazole 200 mg twice daily with meals for the first week of the month for three months or four months. At 12 months, 84% of the patients in the three-month group had a clinical cure, versus 76% of the patients in the four-month group (difference not significant); 64% and 72%, respectively, had negative microscopy results (difference not significant). Culture results were negative in 80% of both groups. The drug was well tolerated in each group, with no important adverse effects reported.

Intermittent therapy with terbinafine has also been explored. In an unblinded attempt to investigate the efficacy of terbinafine for treating dermatophyte-associated toenail onychomycosis, 60 patients were randomly assigned to receive 250 mg daily for three months or 250 mg twice daily for the first week of each month for three months.[29] Toenails were examined clinically and mycologically at monthly intervals. At 48 weeks, there was no significant difference in the rate of cure (defined as negative microscopy and culture results) between the continuous and intermittent groups (79.2% versus 73.9%, respectively). In addition, no significant difference was found in the time to mycologic cure (22.4 versus 19.8 weeks).

Comparative studies of terbinafine and itraconazole have also been conducted. In a double-blind, randomized trial, 372 patients with clinically diagnosed toenail onychomycosis were given 12 weeks of terbinafine hydrochloride 250 mg daily or itraconazole 200 mg daily.[30] Intention-to-treat analysis revealed that, at 48 weeks, mycologic results (microscopy and culture) were negative in 73% of the terbinafine group and 45.8% of the itraconazole group ($p < 0.0001$). The report lacks important details, however, such as study inclusion criteria, a comparison of patient characteristics at baseline, the mean duration of onychomycosis before therapy, and the rate of patient withdrawals.

In a comparative, open-label trial, Arenas et al.[31] randomized 53 otherwise healthy adults with a clinical diagnosis of toenail onychomycosis to receive terbinafine hydrochloride 250 mg ($n = 26$) or itraconazole 200 mg ($n = 27$) daily for three months. Patient age, sex, and onychomycosis history were similar in both groups, although the duration of the disease before treatment was significantly longer in the terbinafine group. Pa-

tients were examined clinically and mycologically every four weeks; photographs of each patient's baseline lesion were used as a control. Six months after drug therapy ended, the overall rate of cure (clinical plus mycologic) in the 43 evaluable patients was 60.9% in the itraconazole group and 64.7% in the terbinafine group. The difference was not significant. Terbinafine-treated patients reported more frequent adverse effects (47% versus 21%, no statistical analysis reported), which consisted primarily of dysgeusia, facial rash, and abdominal pain. The authors concluded that both antifungal agents are drugs of choice in the treatment of onychomycosis.

In an open-label, randomized study, Tosti et al.[32] compared continuous terbinafine, intermittent terbinafine, and intermittent itraconazole in 60 patients with toenail onychomycosis. Patients received terbinafine hydrochloride 250 mg daily for four months, terbinafine hydrochloride 500 mg daily for the first week of each month for four months, or itraconazole 400 mg daily for the first week of each month for four months. Six months after treatment ended, the mycologic cure rate was 94.1% in the continuous terbinafine group, 80% in the intermittent terbinafine group, and 75% in the intermittent itraconazole group. There were no significant differences in efficacy or adverse effects among the three regimens.

Cost-effectiveness of oral therapy

Marchetti and colleagues[33] performed a pharmacoeconomic analysis of oral therapy for onychomycosis by comparing drug acquisition costs; mycologic cure, failure, and relapse rates; physician visit and laboratory test costs; and costs of adverse drug reactions. Specific data derived from a literature meta-analysis were applied in a decision-tree analysis. Daily terbinafine was found to have the lowest cost per mycologic cure after one treatment regimen for both toenail and fingernail onychomycosis ($791 and $454, respectively). Daily itraconazole was the second most cost-effective therapy ($1,535 and $767), while griseofulvin ($2,385 and $837) and ketoconazole ($10,025 and $1,512) were less cost-effective. In a sensitivity analysis, intermittent itraconazole therapy for toenail onychomycosis reduced drug acquisition costs by nearly half but was still less cost-effective than daily terbinafine therapy. The major limitation of this analysis was the lack of a quality-of-life assessment. The results are in agreement with two other pharmacoeconomic analyses, however.[34,35]

Discussion

Terbinafine and itraconazole are both effective first-line agents for onychomycosis, with mycologic and overall cure rates ranging from 50% to 90%. Intermittent itraconazole therapy and continuous terbinafine therapy appear to be cost-effective regimens. The results of a 72-week multicenter study of nearly 500 patients comparing continuous terbinafine with intermittent itraconazole in the treatment of toenail onychomycosis (Sigurgeirsson B, Reykjavik City Hospital, Reykjavik, Iceland, 1998 Mar 16) should better elucidate the treatment of choice.

Selection of the appropriate drug and regimen should be individualized on the basis of underlying illnesses and the potential for drug–drug interactions. For instance, terbinafine is not recommended in patients with decreased renal function (creatinine clearance, <50 mL/min) or in patients with hepatic cirrhosis. Itraconazole is contraindicated in pregnant women and in patients receiving medications that may interact with it. Immunosuppressed patients and those with documented candidal infections may benefit from itraconazole. Intermittent itraconazole therapy may be an option for patients expected to have poorer compliance with a standard regimen, although drug interactions may limit its usefulness. Sound recommendations on the use of intermittent terbinafine therapy must await the results of additional randomized, controlled studies.

Conclusion

Oral antifungal agents offer patients with onychomycosis greater likelihood of a cure than topical antifungals, but oral therapy carries greater risks and requires closer monitoring.

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