SUPPORTED BY AN EDUCATIONAL GRANT FROM PFIZER INC

Onychomycosis: therapeutic update

Richard K. Scher, MD *New York, New York*

Onychomycosis is a common disease of the nail unit caused by dermatophytes, yeasts, and molds. In more than 80% of cases, onychomycosis is caused by the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes.* The prevalence of onychomycosis in the world's population is 2% to 18% or higher and accounts for approximately 50% of all nail disorders. Until recently, available therapies were inadequate because of low cure rates, high relapse rates, and often dangerous side effects. An increased understanding of nail pharmacokinetics has led to the development of safer, more effective systemic therapies for onychomycosis, such as itraconazole, fluconazole, and terbinafine. These new oral antifungal agents allow shorter periods of treatment, provide rapid efficacy, and may improve patient compliance and attitudes regarding therapy. Treatment selection will depend on several factors, including appropriate spectrum of activity, adverse effects, and potential drug interactions plus patient preferences for specific dosing regimens. (J Am Acad Dermatol 1999;40:S21-6.)

Onychomycosis is a common fungal infection of 1 or more components of the nail unit.[1] Although the exact prevalence is unknown, onychomycosis accounts for up to 50% of all nail disease and affects 2% to 18% or more of the world's population.[2-4] The incidence of onychomycosis increases with age, and some studies suggest that up to 48% of the population may be affected by age 70 years.[1] Toenail infection is several times more common than fingernail infection and is generally more difficult to treat because of the slow rate of toenail growth.[1]

In the United States and other developed countries, the incidence of onychomycosis may have increased dramatically in recent years. This is likely the result of such factors as the aging of the population, possible higher incidence of diabetes mellitus, greater use of immunosuppressive and antibiotic agents, increased exposure to infecting organisms, and the acquired immunodeficiency syndrome epidemic.[1,2]

From the Department of Dermatology, Columbia-Presbyterian Medical Center, New York, New York.

This work was supported by a research grant from Pfizer Inc. The author has also served as an investigator, consultant, and a speaker for Novartis, Pfizer, and Janssen. CMD, Inc. assisted in the writing of this article.

Reprint requests: Richard K. Scher, MD, Department of Dermatology, Columbia-Presbyterian Medical Center, 161 Fort Washington Ave, Room 750, New York, NY 10032.

0190-9622/99/$8.00 + 0 **16/0/98108**

Table I. Principal causes of onychomycosis

Dermatophytes
T rubrum
T mentagrophytes
Epidermophyton floccosum
Nondermatophytes
Acremonium
Aspergillus
Onychocola canadensis
S brevicaulis
Scytalidium dimidiatum
S hyalinum
Yeasts
C albicans

From Elewski BE, Charif MA, Daniel CR III. Onychomycosis. In: Scher RK, Daniel CR III, editors. Nails: diagnosis, treatment, surgery. 2nd ed. Philadelphia: WB Saunders, 1997. p. 151-62. By permission.

In more than 80% of cases, onychomycosis is caused by the dermatophytes *Trichophyton rubrum* and *T mentagrophytes* and is then referred to as tinea unguium.[2] Yeasts are responsible for between 5% and 17% of cases of onychomycosis, and in over 70% of these cases *Candida albicans* is the infecting organism. The nondermatophyte molds *Scopulariopsis*, *Scytalidium*, *Acremonium*, *Aspergillus*, and *Fusarium* cause approximately 3% to 5% of fungal nail disease (Table I).[1-3]

Far from being merely a cosmetic issue, onychomycosis may have serious emotional and physical consequences for the patient.[2,5] The condition

Table II. Treatment selection criteria in onychomycosis

Causative pathogen
Potential adverse effects
Potential drug interactions
Dosage schedule
Patient compliance
Age and health of patient
Allergic history
Prior antifungal therapy
Cost

From Elewski BE, Charif MA, Daniel CR III. Onychomycosis. In: Scher RK, Daniel CR III, editors. Nails: diagnosis, treatment, surgery. 2nd ed. Philadelphia: WB Saunders, 1997. p. 151-62.

may be associated with significant pain and discomfort; in severe cases, onychomycosis could lead to disfigurement and loss of dexterity and mobility.

As a recent quality-of-life study by Lubeck et al[6] has demonstrated, onychomycosis can impose significant psychologic and social limitations.[7] In this study, supported by Sandoz Research Institute, patients with fungal nail disease reported avoiding intimate and social situations for fear of exposing their disfigured nails and experienced difficulties with work-related activities requiring them to use their fingers or to be on their feet for long periods of time.

Treatment of onychomycosis has traditionally been difficult, in part because of the unique absorption properties of the nail unit. To be effective, antifungal drugs must penetrate the affected nail tissue and remain in high concentrations until the pathogen is eradicated.[8] Topical antifungal drugs, which poorly penetrate the nail plate, have only limited use in onychomycosis treatment.[4]

The early systemic treatments, griseofulvin and ketoconazole, have also proved unsatisfactory.[4,8] Griseofulvin has a narrow spectrum of activity and requires prolonged courses of treatment; low cure rates and high relapse rates further limit its usefulness in onychomycosis.[4,8] Although ketoconazole has demonstrated higher cure rates than griseofulvin, prolonged therapy (12 to 18 months for toenails) is required, and relapse rates have been high. In addition, ketoconazole carries a risk of drug interactions and serious adverse effects, such as hepatotoxicity.[8]

NEW TREATMENT OPTIONS

The newer agents itraconazole, fluconazole, and terbinafine show great promise in the treatment of fungal nail disease. Pharmacokinetic studies indicate that these drugs reach the distal end of the nail shortly after therapy begins.[2] When selecting among these agents, however, several factors need to be considered, including efficacy against the causative pathogen, potential adverse effects and drug interactions, dosage regimens, cost, and compliance issues (Table II).[1]

Itraconazole

Itraconazole, like fluconazole, is a triazole antifungal agent. The 3 nitrogen atoms in the 5-member triazole ring may be responsible for itraconazole's broad spectrum of activity, which includes dermatophytes, yeasts, and nondermatophyte molds; improved tissue penetration; and lower toxicity compared with ketoconazole. Unlike ketoconazole, an imidazole derivative, the triazoles have increased specificity for fungal rather than mammalian cytochrome P-450 enzymes at therapeutic levels, which significantly decreases the risk of drug interactions.[9]

Mechanism of action. Itraconazole is fungistatic in vitro; it impairs ergosterol synthesis in fungal cells by blocking the cytochrome P-450–dependent enzyme lanosterol cl4-α-demethylase. This results in decreased ergosterol and increased lanosterol in the fungal cell membrane, which alters its function and permeability. This mechanism of action is common to all azoles.[9]

Pharmacokinetics. Itraconazole is well absorbed when administered orally with food but is erratically absorbed with changing gastric pH. However, it achieves excellent tissue distribution. The pharmacokinetic properties of itraconazole are related to its pronounced lipophilicity.[3] The plasma half-life varies between 15 and 25 hours; the peak plasma concentration is reached within 2 to 4 hours after a single 100-mg dose. Itraconazole also binds firmly to protein and has a marked affinity for lipids.[3] The slow elimination of itraconazole from tissues may explain its continued therapeutic efficacy after treatment is discontinued.[3] Itraconazole also has a strong affinity for keratinized tissue, which results in high drug concentrations in the nails and explains the drug's efficacy in onychomycosis.[3] The concentration of itraconazole in nails, 90 days after a 7-day course of medication, greatly exceeds the minimum inhibitory concentration (MIC) of common dermatophytes.[10]

Dosing. Two dosing schedules have been inves-

tigated: continuous and intermittent (pulse) therapy. The fixed dosage of itraconazole is 200 mg daily for 12 weeks in onychomycosis of the toenail and for 8 weeks in fingernail disease. Studies demonstrate that although the nail is not yet normal when therapy ends, the new nail will grow free of fungus because of the continued presence of itraconazole in the nail.[1] Pulse or intermittent therapy is based on the rationale that the drug reaches the nail within 7 days of therapy and remains there for 6 to 9 months, although serum levels of the drug are no longer detectable 1 week after discontinuation of therapy.[1] The Food and Drug Administration recently approved 2 pulse doses of itraconazole for onychomycosis of the fingernails, but no pulse therapy has been approved for toenails at present. Intermittent cycles of 400 mg daily for 1 week per month can be continued for 2 months for fingernail infection and 3 months for toenail infection.[1] Cure rates approaching 80% have been reported in European studies with these regimens,[11] although cure rates have been lower in other studies.[12]

Efficacy. Results of US studies of itraconazole effectiveness in the toenail have shown a mycologic cure rate of 54%, a clinical success rate of 65%, and an overall success rate (clinical success and mycologic cure) of 35%.[1] Investigators using itraconazole in toenail infections at doses of 200 mg/day for 3 months have reported mycologic cure rates of 86% at 9 months and 79% at 12 months.[2] At 18-month follow-up, mycologic cure rates decreased to 67%. Relapse rates in toenail infections at 9 and 12 months after treatment with this regimen have been reported to be 9% to 11%.[2]

Safety. The principal safety concern regarding itraconazole relates to its potential for serious drug interactions. Elevated liver function tests have been reported in 0.3% to 5% of patients receiving itraconazole therapy, but symptomatic hepatic injury has rarely been reported. In general, liver function tests return to normal 4 to 10 weeks after therapy is discontinued. Itraconazole should be avoided during pregnancy (Food and Drug Administration Pregnancy Category C), and women of childbearing age should be advised to take adequate contraceptive precautions during therapy.[2]

Adverse effects. The adverse effects reported for itraconazole by more than 1% of patients in clinical trials for the treatment of onychomycosis of the fingernail are as follows: headache (5%), pruritus (5%), nausea (5%), rhinitis (5%), rash (3%), and dyspepsia (3%).[13] Other side effects reported include dizziness, fatigue, fever, somnolence, impotence, decreased libido, and malaise.[2]

Drug interactions and contraindications. Itraconazole and its major metabolite are potent inhibitors of the cytochrome P-450 3A4 enzyme system. Concomitant use of itraconazole with drugs metabolized by this enzyme system may result in increased plasma concentrations of these drugs, leading to potentially serious or life-threatening events. Coadministration of itraconazole and drugs such as terfenadine, astemizole, simvastatin, lovastatin, midazolam, triazolam, and cisapride are specifically contraindicated. Coadministration of itraconazole with drugs such as digoxin, cyclosporine, and phenytoin requires close monitoring. When oral warfarin or hypoglycemic agents are coadministered with itraconazole, prothrombin time and blood glucose levels may also require monitoring.[2,3,13] Food increases the gastrointestinal absorption of itraconazole, whereas antacids and gastric acid secretion suppressors that lower gastric acidity decrease absorption of itraconazole.[2]

Fluconazole

Fluconazole is an oral antifungal agent with activity against dermatophytes, *Candida,* and some nondermatophyte molds. It has only recently been studied as a potential therapy for onychomycosis. Fluconazole has a distinct chemical structure and unique pharmacologic and pharmacokinetic properties.

Fluconazole is a bis-triazole, having 2 triazole groups with each containing 3 nitrogen atoms. Fluorine atoms in the 2 and 4 positions of the phenyl ring contribute to fluconazole's decreased lipophilicity and protein binding (approximately 12%), resistance to metabolism, increased specificity, and higher potency compared with other azole antifungal agents.[9] A hydroxyl group and low molecular weight also make fluconazole more water-soluble than the other azoles, which results in rapid absorption, high bioavailability (>90%), and wide tissue distribution. Fluconazole has a volume of distribution similar to that of water in the body, a long half-life (30 hours), and dose-proportional serum concentrations.[9]

Mechanism of action. The mechanism of action is similar to the other azoles. As with itraconazole, fluconazole is fungistatic in vitro. The

triazoles have a high affinity for fungal cytochrome P-450 enzymes but a very weak affinity for mammalian P-450 enzymes. In *C albicans*, the azoles inhibit transformation of blastospores into the invasive mycelium form.[9]

Pharmacokinetics. Studies have demonstrated that fluconazole penetrates nails rapidly. In a small pilot study, Hay[14] found that fluconazole was detectable in nails within 2 hours after a single 50-mg oral dose. Fluconazole accumulates well in or on the stratum corneum of nails, reaching levels up to 50 times those found in plasma, and remains there even after the drug is no longer detectable in plasma. This factor is believed to contribute to the continued improvement observed in some patients even after the end of active treatment.[4] Recent studies have demonstrated that concentrations of fluconazole are found 2 weeks after the onset of treatment and throughout the treatment and post-treatment period were well above the MIC for dermatophytes and nondermatophytes.[8] Unlike ketoconazole and itraconazole, food intake and gastric pH do not affect fluconazole absorption or bioavailability.[4]

Dosing. The most common dosage regimen of fluconazole prescribed for skin and nail infections world-wide is 150 to 300 mg once weekly.[15] However, depending on the clinical situation, dosages may vary. The duration of treatment is usually 2 weeks for tinea corporis, 4 to 6 weeks for tinea pedis, and 6 to 12 months for toenails until regrown.[16] Different doses of fluconazole have been investigated in the treatment of onychomycosis but none have yet been FDA approved. Doses of 50 to 100 mg daily or on alternate days until the normal nail has grown out have been shown to be effective.[2] In a study of 11 patients with onychomycosis of the toenail and fingernail, 8 patients received fluconazole 300 mg once weekly, 1 patient received 200 mg once weekly, and 2 patients received alternate-day therapy with 100 mg or 200 mg of fluconazole. Eight of the patients also received a topical antimycotic treatment. All 6 patients with toenail involvement were clinically cured after a mean duration of 6 months. All 5 patients with fingernail involvement were cured after 3.7 months. No adverse laboratory or clinical adverse events were recorded.[17]

The use of chemical urea nail avulsion with fluconazole therapy has also been demonstrated to improve cure rates.[1] In patients who do not respond to treatment, the dose of fluconazole can be increased to 300 or 450 mg once weekly.[1] This once-weekly regimen may be especially useful for patients who are receiving multiple medications and for whom compliance may be an issue.[1]

Efficacy. The efficacy of fluconazole in onychomycosis is well studied. Montero-Gei et al[18] demonstrated that fluconazole 150 mg once weekly for 3 to 12 months for dermatophyte infections of the fingernails and toenails produced a favorable clinical response in 97% of patients at the end of treatment and in 87% at follow-up. A multicenter trial by Fräki et al[19] in Finland reported similar results. Treatment with 150 mg of fluconazole once weekly for 5 to 12 months was effective and well tolerated and produced a favorable clinical response in 77% of patients at follow-up.

In a recent study by Scher et al,[15] treatment of onychomycosis of the toenail with dosages of fluconazole ranging between 150 and 450 mg once weekly for a mean period of 6 to 7 months resulted in a clinical success rate greater than 86% with a low relapse rate.

Safety. More than 50 million adult and pediatric patients worldwide have taken fluconazole for fungal infections (including vaginal candidiasis, oropharyngeal and esophageal candidiasis), skin and nail infections, systemic candidiasis, and cryptococcal meningitis. The use of doses of 400 mg/day in severely ill, immunocompromised patients confirms the safety and tolerability of fluconazole.[4] Fluconazole is well tolerated, and hepatotoxicity is rare. Daily doses as high as 1600 to 2000 mg have been shown to be effective and well tolerated in severely ill patients, although these higher doses are not yet approved for use in most countries. Thus doses used in skin and nail infections are well below the maximum doses in this wide dosage-safety margin.

Adverse effects. Most researchers acknowledge that analyzing the adverse reactions associated with fluconazole is difficult because the drug has been used primarily in patients with severe underlying disease.[2] In studies involving 4000 patients receiving fluconazole therapy for 7 days or more for various indications, the incidence of side effects was 16%.[2,4] Treatment was discontinued in 1.3% of patients because of laboratory test abnormalities and in 1.5% of patients because of adverse clinical effects. These were mainly gastrointestinal disturbances. Other reported side

effects included headaches, rash (such as urticaria or papulomacular or morbilliform eruptions), exfoliative skin eruptions, abnormal liver function tests, and, in some instances, hepatotoxicity.[16]

Drug interactions and contraindications. Rifampin enhances fluconazole metabolism, whereas fluconazole increases the prothrombin time of coumarin-type anticoagulants and increases the plasma concentrations of phenytoin and cyclosporine.[16] In addition, fluconazole increases serum theophylline concentrations and may increase the bioavailability of oral hypoglycemic agents. As with other azole antifungal drugs, coadministration of fluconazole with terfenadine, astemizole, or cisapride is contraindicated.[2,3,16] Unlike itraconazole, absorption of fluconazole is not affected by antacids or by drugs that increase gastric pH.[16]

Terbinafine

Terbinafine is a member of the allylamine class of antifungal agents. It exerts its antifungal effects at an earlier phase in fungal-cell membrane development than do the azoles.[14]

Mechanism of action. Terbinafine's mechanism of action is different than the azoles. It blocks ergosterol synthesis by inhibiting squalene epoxidase. This inhibition results in an increase in squalene, which is toxic to fungal cells. In vitro, terbinafine is primarily fungicidal against dermatophytes, *Aspergillus* species, *Scopulariopsis brevicaulis*, *Sporothrix schenckii*, and the dimorphic fungi *Blastomyces dermatitidis* and *Histoplasma capsulatum.* Activity against yeasts is variable. Terbinafine is more active against *C parapsilosis* than C albicans.[2]

Pharmacokinetics. Oral terbinafine reaches the nail plate by diffusion from both the nail bed and nail matrix.[9] When 250 mg/day of terbinafine was administered to healthy volunteers, the drug was detected in peripheral nail clippings after 7 days.[9] The concentration of terbinafine in nails 90 days after a 7-day course of medication greatly exceeded the MIC of common dermatophytes.[9]

Dosing. A 6-week course of 250 mg/day of terbinafine is effective in fingernail disease; a 12-week course at the same dose is generally effective in toenail disease.[1,9]

Efficacy. In standard long-term treatment (6 months for fingernails, 12 months for toenails), 250 mg/day of terbinafine demonstrated mycologic cure rates of 95% for fingernail and 80% for toenail infections. At 250 mg/day for 3 months, 82% of patients achieved mycologic cure at 1 year after treatment. When treatment regimens of 250 mg/day for 6, 12, and 24 weeks were compared, it was shown that for onychomycosis of the toenail, a 12-week course of treatment was comparable to 24 weeks of therapy. A regimen of 250 mg/day for 6 weeks in fingernail infection and 12 weeks in toenail infections achieved 90% and 80% cure rates, respectively. At 12 months, relapse rates were between 6% and 12% for fingernails and toenails, respectively.[2]

Safety. Terbinafine is generally safe and well tolerated, and there are few significant drug interactions. Although hepatotoxic reactions are rare, many experts believe that periodic monitoring of liver function and hematopoietic parameters is reasonable, as for itraconazole and fluconazole.[1]

Adverse effects. The most common adverse effect reported with terbinafine in 3 US/Canadian clinical trials was headache, occurring in 12.9% of patients. Gastrointestinal disturbances and skin reactions accounted for most other adverse effects: diarrhea (5.8%), dyspepsia (4.3%), and nausea (2.6%); and rash, including urticaria (6.7%), and pruritus (2.8%).[20] Less common side effects reported included fatigue, inability to concentrate, pain (back, leg, and flank), taste disturbances, erectile dysfunction, transient hypoglycemia, and elevated liver function tests. No specific mutagenic effects have been reported with terbinafine, and animal studies reveal no evidence of embryonic or fetal toxicity or teratogenicity.[2]

Drug interactions and contraindications. Terbinafine does not significantly induce or inhibit the clearance of drugs metabolized by the cytochrome P-450 enzyme system; therefore at therapeutic levels, the potential for drug interactions is much lower for terbinafine than for the azoles. However, drugs that induce these enzymes, such as rifampin or phenobarbital, will increase plasma clearance of terbinafine, whereas drugs that inhibit these enzymes, such as cimetidine, will reduce terbinafine clearance. Bioavailability of terbinafine is not affected by the presence of food.[2,20] The only contraindication is hypersensitivity to terbinafine.[20]

CONCLUSIONS

Systemic treatment of onychomycosis has improved dramatically with the availability of the

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.