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NOVEL TREATMENT STRATEGIES FOR SUPERFICIAL MYCOSES

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Onychomycosis: therapeutic update

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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]

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

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

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. Common side effects reported include 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

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