Editorial

Onychomycosis: Current and Future Therapies

Shari Lipner, MD, PhD; Richard K. Scher, MD

Onychomycosis, a fungal infection of the nail plate by dermatophytes, yeasts, and nondermatophyte molds, is common in the United States with a prevalence of 10% to 12%.[1,2] The clinical presentation of onychomycosis is shown in the Figure. Some patients have mild asymptomatic disease and do not seek treatment. More advanced cases of onychomycosis present with pain and discomfort, secondary infection, an unattractive appearance, or problems performing everyday functions. The goal of treatment is to eliminate the fungus if possible and to restore the nail to its normal state when it fully grows out. Patients should be counseled that the treatment process generally is long (ie, ≥6 months for fingernails [growth rate, 2–3 mm per month]; 12–18 months for toenails [growth rate, 1–2 mm per month]).[3] Nails grow fastest during adolescence and slow down with advancing age.[4] Furthermore, advanced cases of onychomycosis affecting the nail matrix may cause permanent scarring of the matrix; therefore, the nail may still appear dystrophic after the causative organism is eliminated. The US Food and Drug Administration (FDA) defines complete cure as negative potassium hydroxide preparation and negative fungal culture results plus a completely normal appearance of the nail.[5]

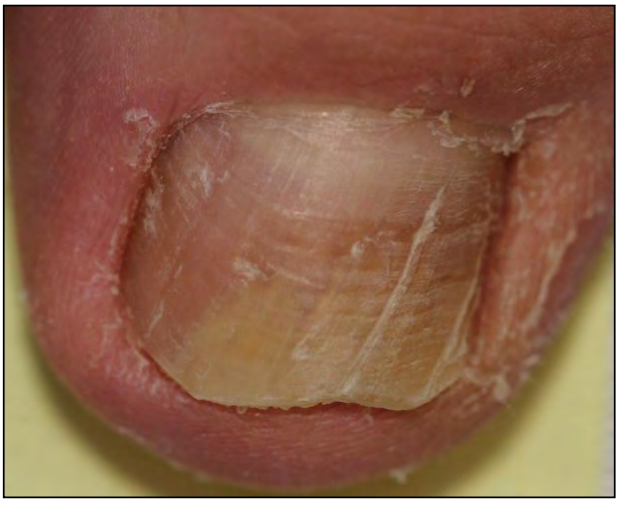
Treatment of onychomycosis poses a number of challenges for dermatologists. Hyperkeratosis and/or the fungal mass may limit delivery of topical and systemic drugs to the source of the infection. Additionally, high rates of relapse and reinfection after treatment may occur due to residual hyphae or spores.[6] The long treatment period often limits patient adherence, and many patients may be unwilling to forego wearing nail cosmetics during the treatment course. To improve patient care, dermatologists should be aware of the current therapies for onychomycosis and those awaiting FDA approval, as the newer therapies show improved efficacy with shorter treatment courses.

From Weill Cornell Medical College, New York, New York.
Dr. Lipner reports no conflict of interest. Dr. Scher is a consultant, investigator, and speaker for multiple companies that have onychomycosis products on the market.
Correspondence: Shari Lipner, MD, PhD, 1305 York Ave, 9th Floor, New York, NY 10021 (shl9032@med.cornell.edu).

Currently Available Therapies

There are 4 approved classes of antifungal drugs for the treatment of onychomycosis: allylamines, azoles, morpholines, and hydroxypyridones.[7] The allylamines (eg, terbinafine) inhibit squalene epoxidase.[8] Oral terbinafine hydrochloride (250 mg) taken once daily for 6 weeks for fingernails and 12 weeks for toenails currently is the preferred systemic treatment of onychomycosis,[9] with complete cure rates of 38%[10] and 49% in 12-week studies.[11]

The azoles inhibit lanosterol 14α-demethylase, a step in the ergosterol biosynthesis pathway.[7] Two members of this class that are widely used in treating onychomycosis are oral itraconazole[12] and oral fluconazole.[13] The approved dosage for oral itraconazole for onychomycosis of the toenails (with or without fingernail involvement) is 200 mg once daily for 3 months, with a complete cure rate of 14%.[12] The approved dosage for the fingernails is 2 treatment pulses, each consisting of 200 mg twice daily for 1 week. The pulses are separated by a 3-week period without itraconazole, with a complete cure rate of 47%. Although oral fluconazole is not FDA approved for the treatment of onychomycosis, it is used extensively in other countries and sometimes is used off label in the United States. Complete cure rates were 48% in patients who received



Distal lateral subungual onychomycosis showing onycholysis, nail bed hyperkeratosis, subungual debris, and nail plate dyschromia.

450 mg per week, 46% in those who received 300 mg per week, and 37% in those who received 150 mg per week for up to 9 months.[12] Several oral triazole antifungals, namely albaconazole,[14] posaconazole,[15] and ravuconazole,[16] have undergone phase 1 and phase 2 studies for the treatment of onychomycosis and have shown some efficacy.

The morpholines include topical amorolfine, which is approved for use in Europe but not in the United States.[17] Amorolfine inhibits D14 reductase and D7-D8 isomerase, thus depleting ergosterol.[18] In one randomized controlled study, the combination of amorolfine hydrochloride nail lacquer 5% and oral terbinafine (250 mg once daily) resulted in a higher clinical cure rate than oral terbinafine alone (59.2% vs 45.0%; complete cure rate was not reported).[17]

The hydroxypyridones include topical ciclopirox, which has a poorly understood mechanism of action but may involve iron chelation or oxidative damage.[19,20] Ciclopirox nail lacquer 8% was approved by the FDA in 1999, and complete cure rates of 5.5% to 8.5% have been reported with monthly nail debridement.[21]

On the Horizon

Based on the poor efficacy of many of the onychomycosis treatments that currently are available as well as time-consuming treatment courses, there is a clear need for alternative and novel therapies. There has been a greater emphasis on topical agents due to their more favorable side-effect profile and lower risk for drug interactions. Many new agents are in in vitro or phase 1 and phase 2 studies. Some drugs that are further along in phase 3 trials will be discussed.

Two phase 3 clinical trials have been completed for efinaconazole, a member of the azole class of drugs.[22] Patients in these 2 randomized studies were treated with either efinaconazole solution 10% or vehicle for 48 weeks followed by a 4-week washout period. For study 1 and study 2, complete cure rates were 17.8% and 15.2%, respectively, in the treated group, and 3.3% and 5.5%, respectively, in the control group. Mycologic cure rates were 55.2% and 53.4% for the treated group, respectively, and 16.8% and 16.9% for the control group, respectively. The side-effect profile was minimal with the most common being application-site dermatitis and vesiculation, with no statistically significant difference between the treated and control groups.[22]

There are some marked differences between ciclopirox and efinaconazole that may impact patient compliance. First, treatment with ciclopirox includes monthly nail debridement, which is not required with efinaconazole. Second, although ciclopirox nail lacquer must be removed weekly, efinaconazole is a solution, so no removal is necessary. Efinaconazole is currently pending FDA approval for the treatment of onychomycosis.

Terbinafine nail solution (TNS) has undergone 3 phase 3 clinical trials (2 vehicle controlled and 1 active comparator).[23] The first trial compared TNS and vehicle applied daily for 24 weeks, the second study repeated the same for 48 weeks, and the third study compared TNS to amorolfine nail lacquer 5% daily for 48 weeks. Overall, TNS showed the best complete cure rates, with a rate of 2.2% versus 0% for the vehicle in a 48-week study. The authors also concluded that TNS was not more effective than amorolfine, as complete cure rates were 1.2% versus 0.96%. The most common side effects were headaches, nasopharyngitis, and influenza.[23]

Tavaborole is member of the new benzoxaborole class, which inhibits protein synthesis by blocking aminoacyl transfer RNA synthetase.[24] Topical tavaborole solution was engineered to have improved penetration through the nail plate, and in vitro studies have shown better penetration than both ciclopirox and amorolfine.[25] Two identical phase 3, randomized, double-blind, vehicle-controlled studies evaluating tavaborole solution 5% daily compared to vehicle for 48 weeks followed by a 4-week washout period showed promising results.[26] The incidence of treatment-related side effects was comparable to the vehicle. The most common side effects were exfoliation, erythema, and dermatitis, all occurring at the application site.[26]

Laser treatment also is a developing area for onychomycosis. The appeal stems from the ability to selectively deliver energy to the target tissue, thus avoiding systemic side effects. Since 2010, the FDA has approved 5 laser devices for the temporary cosmetic improvement of onychomycosis, all Nd:YAG 1064-nm lasers.[27] It was previously thought that the mechanism of action for the fungicidal effect of lasers was achieved with heat,[28] but newer in vitro studies have shown that the amount of time and level of heat required to kill *Trichophyton rubrum* would not be tolerable to patients.[29] Although the mechanism of action is poorly understood, some clinical trials have shown success using the Nd:YAG 1064-nm laser for treatment of onychomycosis; however, in a recent study of 8 patients treated with the Nd:YAG 1064-nm laser for 5 treatment sessions, mycological or clinical cure were absent and there was only mild clinical improvement.[29] Additionally, most patients reported pain and burning during the treatments and therefore required many short breaks. Other types of lasers are being studied but are not yet FDA approved, including CO_2, near-infrared diode, and femtosecond infrared lasers.[3]

Plasma therapy is a developing area for the treatment of onychomycosis. Plasma was shown to be fungicidal to *T rubrum* in an in vitro model,[30] and a clinical trial to evaluate the safety, tolerability, and efficacy of

plasma in human subjects is ongoing (registered on March 22, 2013, at www.clinicaltrials.gov with the identifier NCT01819051).

Conclusion

Oral terbinafine currently is considered the first-line treatment of onychomycosis. The only prescription topical agent available in the United States is ciclopirox nail lacquer 8%. A new topical agent, efinaconazole (FDA approval pending), provides better efficacy without the need for nail debridement. Another topical agent, tavaborole (FDA approval pending), has shown good results in phase 3 studies to date. The Nd:YAG laser has shown some promise in earlier clinical studies but was ineffective in a recent study.

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Quick Poll Question

How often do you perform a potassium hydroxide preparation, culture, and/or periodic acid–Schiff stain before the initial treatment of onychomycosis?

a. always
b. sometimes
c. never

Go to **www.cutis.com** to answer our Quick Poll Question and see how your peers have responded