

Case Letter

Onychomycosis: Current and Investigational Therapies

To the Editor:

Onychomycosis is a fungal infection of the nail plate by dermatophytes, yeasts, and nondermatophyte molds. It is a common problem with a prevalence of 10% to 12% in the United States.^{1,2} The clinical presentation of onychomycosis is shown in the Figure. Although some patients may have mild asymptomatic cases of onychomycosis and do not inquire about treatment, many will have more advanced cases, presenting with pain and discomfort, secondary infection, unattractive appearance, or problems performing everyday functions. The goal of onychomycosis treatment is to eliminate the fungus, if possible, which usually restores the nail to its normal state when it fully grows out. Patients should be counseled that it is a long process that may take 6 months or more for fingernails and 12 to 18 months for toenails. These estimates are based on a growth rate of 2 to 3 mm per month for fingernails and 1 to 2 mm per month for toenails.³ Nails grow fastest during the teenaged years and slow down with advancing age.⁴ It should be noted that advanced cases of onychomycosis affecting the nail matrix may cause permanent scarring; therefore, the nail unit may still appear dystrophic after the causative organism is eliminated. The US Food and Drug Administration (FDA) defines a complete cure as negative potassium hydroxide preparation and negative fungal culture plus a completely normal appearance of the nail.

Treatment of onychomycosis poses a number of challenges. First, hyperkeratosis and the fungal mass may limit the delivery of topical and systemic drugs to the source of the infection. In addition, high rates of

relapse and reinfection after treatment may be due to residual hyphae or spores.⁵ Furthermore, the extended length of treatment limits patient adherence and many patients are unwilling to forego wearing nail cosmetics during the course of some of the treatments.

There are 4 approved classes of antifungal drugs for the treatment of onychomycosis: allylamines, azoles, morpholines, and hydroxypyridinones.⁶ The allylamines (eg, terbinafine) inhibit squalene epoxidase.⁷ Oral terbinafine (250 mg daily) taken for 6 weeks for fingernails and 12 weeks for toenails is considered the current systemic treatment preference in onychomycosis therapy⁸ with complete cure rates in 12-week studies of approximately 38%⁹ and 49%.¹⁰

The second class of drugs is the azoles, which inhibit lanosterol 14 α -demethylase, a step in the ergosterol biosynthesis pathway.⁶ Two members of this class that are widely used in treating onychomycosis are oral itraconazole¹¹ and off-label oral fluconazole.¹² The approved dose for oral itraconazole is 200 mg daily for 3 months (or an alternative pulse regimen) with a reported complete cure rate of 14%.¹¹ Although fluconazole is not FDA approved for the treatment of onychomycosis in the United States, it is used extensively in other countries and to some



The clinical presentation of onychomycosis. The great toenail has yellow discoloration of the nail plate, ridging, and subungual hyperkeratosis.

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extent off label in the United States. In a study of 362 patients with onychomycosis treated with oral fluconazole, complete cure rates were 48% in patients who received 450 mg weekly, 46% in those who received 300 mg weekly, and 37% in those who received 150 mg weekly for up to 9 months.¹² It should be noted that several oral triazole antifungals, namely albaconazole,¹³ posaconazole,¹⁴ and ravuconazole,¹⁵ have undergone phase 1 and 2 studies for the treatment of onychomycosis and have shown some efficacy.

Another class of antifungals are the morpholines including topical amorolfine, which is approved for use in Europe but not in North America.¹⁶ Amorolfine inhibits D14 reductase and D7-D8 isomerase, thus depleting ergosterol.¹⁷ In one randomized controlled study, the combination of amorolfine nail lacquer and oral terbinafine compared to oral terbinafine alone resulted in a higher clinical cure rate with the combination (59.2% vs 46%); complete cure rate was not reported.¹⁶

Finally, the hydroxypyridinone class includes topical ciclopirox, which has a poorly understood mechanism of action but may involve iron chelation or oxidative damage.^{18,19} Ciclopirox nail lacquer 8% was approved by the FDA in 1999 and has reported complete cure rates of 5.5% to 8.5% with monthly nail debridement.²⁰

Based on the poor efficacy of many of the currently available treatments and time-consuming treatment courses, it is clear that there is a 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-drug interactions. Although there are many agents for the treatment of onychomycosis currently in development, many are in vitro studies or phase 1 and 2 studies. However, we will focus on drugs that are further along in phase 3 studies and those that were recently FDA approved.

Efinaconazole is a member of the azole class of drugs and has completed 2 phase 3 clinical trials (study 1, N=870; study 2, N=785).²¹ Patients in these 2 studies were randomized to receive either efinaconazole nail solution 10% or vehicle for 48 weeks followed by a 4-week washout period. Complete cure rates in the 2 studies were 17.8% and 15.2% in the treated group and 3.3% and 5.5% in the control group. The mycological cure rates were 55.2% and 53.4% in the treated group and 16.8% and 16.9% in the control group. The side-effect profile was minimal, with the most common adverse events being application-site dermatitis and vesiculation, which were not significantly higher in the treated group versus the control group.²¹ Efinaconazole received FDA

approval for the treatment of toenail onychomycosis in June 2014.

There are some notable differences between ciclopirox and efinaconazole that may improve patient compliance with the latter. First, treatment with ciclopirox includes monthly nail debridement, which is not required with efinaconazole. Secondly, although ciclopirox lacquer must be removed weekly, efinaconazole is a solution, so no removal is necessary.

Terbinafine nail solution (TNS) is a member of the allylamine class and has completed phase 3 clinical trials.²² Three studies—2 vehicle controlled and 1 active comparator—were performed. The first compared TNS and vehicle, both 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. The best results for complete cure were achieved with TNS for 48 weeks in the vehicle-controlled study with a rate of 2.2% versus 0%. The authors also concluded TNS was not more effective than amorolfine, as complete cure rates were 1.2% for TNS and 0.96% for amorolfine. The most common side effects were headache, nasopharyngitis, and influenza.²²

Tavaborole is a member of the new benzoxaborole class, which inhibits protein synthesis by forming an adduct with the aminoacyl-transfer RNA synthetase.²³ The topical solution was engineered to have improved penetration through the nail plate. In vitro studies showed better penetration than both ciclopirox and amorolfine.²⁴ Two identical phase 3 randomized, double-blind, vehicle-controlled studies were completed involving 1197 patients who were treated with tavaborole topical solution 5% daily compared to vehicle for 48 weeks followed by a 4-week washout period with promising results.²⁵ The incidence of treatment-related side effects was comparable to the vehicle. The most common adverse events were exfoliation, erythema, and dermatitis, all occurring at the application site.²⁵ Tavaborole was approved by the FDA for the treatment of toenail onychomycosis in July 2014.

Luliconazole is a member of the azole class and a phase 2b/3 clinical trial with a 10% solution involving 334 patients was completed in June 2013.²⁶ Results from this trial are expected in early 2015.

Lasers are a developing area for onychomycosis therapy and the appeal stems from their ability to selectively deliver energy to the target tissue, thus avoiding systemic side effects. Since 2010, the FDA has approved numerous laser devices for the temporary cosmetic improvement of onychomycosis, all of which are Nd:YAG 1064-nm lasers.^{27,28} It was previously thought that the mechanism of action for the fungicidal effect was achieved with heat,²⁹ 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.³⁰ 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 study of 8 patients treated with the Nd:YAG 1064-nm laser for 5 treatment sessions, none had a mycological or clinical cure and there was only mild clinical improvement. In addition, most patients had pain and burning during the treatments requiring many short breaks.³⁰ Although not yet FDA approved for the treatment of onychomycosis, other types of lasers are currently being studied, including CO₂, near-infrared diode, and femtosecond-infrared laser systems.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 (MOE Medical Devices, written communication, July 2012), 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).

Onychomycosis is a common problem that increases in prevalence with advancing age. Oral terbinafine is considered the first-line treatment at this point in time.³¹ Two new topical agents, efinaconazole and tavaborole, were recently FDA approved and may be used for the treatment of toenail onychomycosis without the need for nail debridement. The Nd:YAG laser has shown some promise in earlier clinical studies but was ineffective in a more recent study.

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