REVIEW

Recent advances in therapies for onychomycosis and its management [version 1; peer review: 2 approved]

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Abstract

Onychomycosis is the most common affliction of the nail. It may be caused by dermatophytes, yeasts, and non-dermatophyte molds. Traditionally, oral antifungal treatments have been used to treat the fungus, although they can be accompanied by side effects and drug interactions. Topical treatments provide an alternative modality, bypassing the systemic effects of oral drugs; recent research has centered on topical drug improvement and development. Physical and laser treatments are being used in conjunction with topicals, which may help penetrate the thick nail plate. In this review, techniques from all categories are outlined: both novel experimental approaches and progress and effectiveness of recently developed treatments. More long-term studies are required to determine the efficacy of various treatments, but cure rates are improved when patients adhere to treatments and follow preventative measures to avoid disease recurrence.

Keywords

onychomycosis, tinea pedis, dermatophyte, toenail, antifungal, laser

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Introduction
Onychomycosis is a fungal infection occurring in the nails and may affect the adjacent skin. Typically, it manifests as discoloration of the nail, nail plate thickening, and onycholysis. It is the most common nail pathology and accounts for about 90% of toenail infections worldwide. This infection presents several problems for affected populations, including local pain, paresthesia, and reduced quality of life as its appearance may impair social interactions and daily activities. Most onychomycoses are caused by the dermatophytes *Trichophyton*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton*. Infections often initiate from tinea pedis, a fungal infection on the surrounding skin of the feet. Factors that contribute to disease progression are humidity, occlusive footwear, nail trauma, and genetic predisposition. Patients with diabetes, poor peripheral circulation, HIV, and immunosuppression are also more susceptible, as are elderly patients.

Owing to its chemical composition, the nail is a formidable barrier to the permeation of drugs, and diffusion into the nail is poor relative to the skin. This, coupled with slow toenail growth, requires that topicals be used for 12 months or longer, ideally until a healthy nail has regrown. Traditionally, oral therapeutic approaches have been the preferred treatment because of their accessibility and efficacy. Terbinafine and itraconazole are US Food and Drug Administration (FDA)-approved oral antifungal medications, and fluconazole is available as an off-label option in the US. Though effective, they may be accompanied by systemic side effects and drug–drug interactions, which is a concern for those already taking medications for other conditions. Patients may be hesitant to take oral antifungals. It is understandable that there is demand for non-systemic treatments. At present, there are several oral, topical, and physical therapies broadening the treatment options available to patients. Additionally, combination therapy with several drug classes/modalities can be considered.

Some research groups are studying new molecules and permeation enhancers for topicals, diversifying drug targets, and improving the effectiveness of base molecules already in use. When the efficacy of these drugs is measured, commonly used outcome measures are mycological cure and complete cure. Mycological cure is defined as eradication of the fungal pathogen from the nail, confirmed by a negative potassium hydroxide (KOH) preparation (a test to differentiate dermatophytes and yeasts from other skin disorders) and negative fungal culture. Complete cure meets the goals of the patient, physician, and regulatory bodies. Complete cure is defined as 100% clear nail (also known as clinical cure) in addition to mycological cure. This review will outline some of these recent developments in therapies for managing onychomycosis.

Building on topical therapies
Topical therapies can effectively treat onychomycosis, particularly when patients adhere to treatment instructions. Owing to the structural nature of the nail, research is focused on improving the delivery of the drug transungually to the nail bed where fungus lies. Unlike their oral counterparts, topical treatments are relatively safe and there is no potential for drug–drug interactions. Properties that influence the permeability of the drug through the nail include molecular weight, lipophilicity, affinity to keratin, ionization, pH, and the ability to sublime. It is advantageous to develop a drug delivery system that allows the drug to enter the nail plate through the transungual and subungual routes rather than just penetrating the nail plate, which is demonstrated by the application of tavaborole and efinaconazole. Phase III clinical trials have been completed for these drugs and further studies are in progress to understand long-term efficacy. Despite significant advances in the effectiveness of topical treatments, mycological and complete cure rates remain relatively lower than those of some of the oral agents (Table 1). However, clinical response rates (resulting in cosmetically clear nails) are more favorable.

Tavaborole is a novel boron-based antifungal agent that was approved by the FDA for treating onychomycosis in 2014. It penetrates the nail plate because of its small molecular weight and interferes with protein synthesis in fungal cells through its effects on cytoplasmic aminoacyl-tRNA synthetases. Phase II and III trials have demonstrated its safety and effectiveness for treating mild to moderate onychomycosis (20 to 60% nail involvement). In two phase III randomized, double-blind, vehicle-controlled trials, tavaborole 5% solution was applied once daily for 48 weeks, and efficacy was evaluated at 52 weeks. Patients ranged from 18 to 88 years of age. Mycological cure rates (negative KOH and culture) with tavaborole 5% solution for studies 1 and 2 were 31.1% and 35.9%, respectively, significantly higher than vehicle (7.2% and 12.2%, *P* < 0.001). Complete cure rates (100% clear nail and mycological cure) were significantly higher for tavaborole compared with vehicle in study 1 (6.5% and 0.5%, *P* = 0.001) and study 2 (9.1% and 1.5%, *P* < 0.001). Similarly, a pooled post-study follow-up from these two trials showed that complete cure was higher in the tavaborole-treated group compared with the vehicle control group (28.6% versus 7.7%) at week 60. Additionally, at 60 weeks, mycological cure for the tavaborole group was higher than vehicle (53.1% versus 23.1%).

Efinaconazole 10% solution was FDA-approved as a treatment around the same time in 2014. It is a triazole antifungal that inhibits the synthesis of ergosterol in the fungal cell wall. In phase III trials, patients with distal lateral subungual onychomycosis (20 to 50% nail involvement, 18 to 71 years of age)
received the solution once daily for 48 weeks and were evaluated at 52 weeks. The results were a 17.8% complete cure rate (0% clinical involvement of nail, negative KOH and culture) versus 3.3% for vehicle in study 1 and 15.2% versus 5.5% in study 2 (P <0.001). Mycological cure rates (negative KOH and culture) were significantly higher with efinaconazole (55.2% in study 1 and 53.4% in study 2) compared with vehicle (16.8% and 16.9%, P <0.001).

Luliconazole was approved in 2013 for fungal infections of the skin, including tinea pedis in the US. A 10% cream was investigated as a treatment for onychomycosis. In separate phase IIb/III clinical trials, nail samples were isolated from patients to compare the activity of 10% luliconazole with amorolfine, ciclopirox, and terbinafine against distal subungual onychomycosis. It showed a mean minimum inhibitory concentration of 0.00022 µg/mL, which was lower than that of the other three antifungals. In a Japanese multicenter, double-blind, randomized phase III study, patients 21 to 79 years of age with 20 to 50% nail involvement were placed into 2:1 groups of once-daily application of luliconazole 5% nail solution and vehicle. After 48 weeks, complete cure (0% clinical involvement of the nail and negative direct microscopy) rate was significantly higher in luliconazole groups (14.9%) compared with vehicle (5.1%, P = 0.012). Similarly, the negative direct microscopy rate was significantly higher in luliconazole (45.4%) than vehicle (31.2%, P = 0.026). It is suggested that once-daily topical application of luliconazole is clinically effective and well tolerated. Luliconazole is not approved for the treatment of onychomycosis in the US.

In Europe, ciclopirox 8% hydrolacquer (P-3051) uses a novel technology based on hydroxypropyl chitosan for the delivery of ciclopirox 8% to the nail. In a randomized, evaluator-blinded, controlled, parallel-group clinical trial, P-3051 showed statistical superiority to amorolfine after 48 weeks in complete cure (negative KOH and culture and no residual clinical involvement of the nail, 35% versus 11.7%, respectively, P <0.001) in 120 patients 18 to 75 years of age with 25 to 75% nail involvement. Similarly, mycological cure (negative direct microscopy and culture) was achieved by all patients who received P-3051 compared with 81.7% who received amorolfine (P <0.001). In a randomized, evaluator-blinded, placebo-controlled, parallel-group clinical trial comparing P-3051 with reference ciclopirox 8% and placebo, 467 patients (mean age of 49.84 ± 11.89 years) with 25 to 60% nail involvement applied the lacquers for 48 weeks, followed by a 4-week washout period and 8-week follow-up period. Complete cure (negative KOH microscopy, culture, and 100% growth of a healthy nail at week 48 and washout) was achieved in 5.7% of P-3051 users and 3.2% for reference (P = 0.6834), whereas placebo saw no cure (P = 0.0165). P-3051 complete cure rate increased at 60 weeks (12.7%) and was greater than reference (5.8%, P <0.05) and placebo (1.3%, P = 0.0029). A post-hoc analysis confirmed that severity of disease is a prognostic factor for responsiveness to P-3051 treatment and significantly affects reported efficacy data. The population subset excluded patients with more severe disease (>50% nail involvement). P-3051 was superior to placebo and reference ciclopirox in cure and response rates at 60 weeks, and efficacy rates in the P-3051 group were higher in the groups that excluded patients with more than 50% nail involvement. Ciclopirox 8% hydrolacquer (P-3051) is not approved for the treatment of onychomycosis in the US.

A study using polyurethanes (PUs) as new excipients in topical nail treatments has been conducted. A PU polymer delivered two antifungal drugs (terbinafine and ciclopirox), and a 10% PU concentration was most effective for in vitro drug release, permeation, and antifungal activity. The lacquer smooths the nail plate and reduces porosity, increasing effectiveness of the base molecule. Finally, there are ongoing clinical trials for ME-1111 and MOB-015. ME-1111 is a new agent with potent in vitro antifungal activity and small molecular weight. It targets succinate dehydrogenase of the electron transport chain, inhibiting it and blocking ATP production. MOB-015 is a topical formulation of terbinafine.

**Oral therapies**

Typically, oral therapeutics are reserved for severe infections because of their safety issues and drug–drug interactions. Recently, there has been insight about the use of ravuconazole and its produgs as new drug candidates for oral therapy. A water-soluble prodrug, mono-lysine phosphoester derivative (BFE1224), is in the advanced stages of clinical development. A phase III randomized, double-blind, placebo-controlled study of fosravuconazole (F-RVCZ) L-lysine ethanolate, the novel oral triazole, was conducted in Japan. One hundred fifty-three patients 20 to 75 years of age with at least 25% nail involvement were assigned 100 mg of F-RVCZ or placebo to take once daily for 12 weeks. Evaluation was carried out at week 48. The complete cure rates (0% nail involvement and negative KOH) for F-RVCZ and placebo were 59.4% and 5.8%, respectively (P <0.001). Mycological cure rate (negative KOH) was determined every 12 weeks and increased over time; the difference between F-RVCZ and placebo was statistically significant at 24 weeks and onward (P = 0.002 and P <0.001 at weeks 36 and 48). At week 48, mycological cure rates were 82.0% for F-RVCZ and 20.0% for placebo. Fosravuconazole (F-RVCZ) is not approved for the treatment of onychomycosis in the US.

VT-1161 is a novel, tetrazole fungal CYP51 inhibitor designed to selectively target fungal enzymes and maintains high potency for the fungal target. In a randomized, phase 2b study to evaluate the efficacy and safety of oral VT-1161 for onychomycosis, 259 patients 18 to 70 years of age with 25 to 75% nail involvement at baseline received 300 or 600 mg oral doses or matching placebo. Once-weekly VT-1161 at a dose of 300 or 600 mg was administered for 10 or 22 weeks following a 14-day once-daily loading period at the same dose (300 or 600 mg). Mycological cure (negative KOH and culture) at week 48 was shown for 61% to 72% of patients, collapsed across VT-1161 arms, whereas complete cure ranged from 32 to 40%. Phase II clinical trials have been completed.

**Physical strategies and laser therapies**

Heinlin et al. showed that repeated, daily cold atmospheric plasma treatment inhibits the in vitro growth of *T. rubrum*. Recently, a pilot study demonstrated the effects of non-thermal...
plasma in treating onychomycosis. Non-thermal plasma was created by using an electric insulator by short pulses (10 ns) of electric fields that ionize air molecules. This process creates ions, electrons, ozone, hydroxyl radicals, and nitric oxide, which are fungicidal and cytotoxic. Ultimately, 13 patients 33 to 74 years of age with 25 to 50% nail involvement completed the trial, and 15.4% achieved mycological cure (negative KOH and culture). Additional studies are required because of the small sample size and varying protocols, but it is the first clinical study to report that thermal plasma may be effective against toenail onychomycosis.

Another novel physical strategy is precise laser poration. Hollow-core photonic crystal fibers guide light from a femtosecond-pulsed laser in a focused, high-energy density beam. As it irradiates the nail, the laser creates pores (100 μm in diameter) with minimal damage to surrounding tissues. Complete poration of nails increases permeation by two to three orders of magnitude relative to an untreated nail, which in turn would increase the effectiveness of topical treatments. Flores et al. coupled poration with a nanocapsule formulation of toconazole. The nano-formulations are advantageous for topical delivery because they ensure stability of actives and act as reservoirs for extended drug delivery. Nanocapsules were composed of pullulan, a water-soluble polysaccharide that forms films. The newer film-forming formula provided the best efficiency of ex vivo delivery, and drug payload percentages were higher than those of marketed products.

Lasers are approved by the FDA because of their similarity to predicate devices. These devices improve cosmetic appearance by increasing the clarity of nail in patients with onychomycosis. The effectiveness of lasers as a standalone treatment is reported inconsistently, and cure rates for laser treatment are lower than those of oral and topical treatments. There is limited evidence that they can eradicate pathogenic fungi and this is due to incomplete reporting of randomization and lack of controls. Additionally, the inclusion criteria and definitions of efficacy outcomes between drug and devices differ, preventing meaningful comparisons. In the US, lasers are approved for the temporary increase of clear nail in onychomycosis.

Commonly used lasers include neodymium-yttrium garnet lasers and Q-switched laser systems. The smaller temporal pulse length in this laser is less than the thermal relaxation time of the fungi, which permits contained heating of the fungi in the nail plate while allowing dissipation of heat in the surrounding soft tissue of the toenail and fingernail. There is a lack of robust clinical data. Randomized, double-blind trials are required to determine whether they are actually fungicidal.

Adjunctive measures
Aside from adhering to the prescription protocol of their onychomycosis therapy, patients can perform measures to improve the effectiveness of their treatment and avoid the possibility of reinfection. They should disinfect shoes and socks, avoid walking barefoot in public places, keep feet cool and dry, and recognize the early signs of recurrence and reinfection. It is also important to treat tinea pedis, and any affected family members, early and effectively.

Conclusions
There is a diverse array of therapies for treating onychomycosis, particularly centered on topical formulas as the adverse effects are limited to the application site without systemic drug interactions. Devices are being considered as an addition to antifungal therapies, which is an important step in diversifying treatment options.

Abbreviations
FDA, US Food and Drug Administration; KOH, potassium hydroxide; PU, polyurethane.

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