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Diagnostic and Therapeutic Considerations for Onychomycosis and Cutaneous Superficial Fungal Infections

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CME

EDITORIAL

ORIGINAL ARTICLES

DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS FOR ONYCHOMYCOSIS AND CUTANEOUS SUPERFICIAL FUNGAL INFECTIONS

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Statement of Need

Superficial cutaneous fungal infections (SCFIs) are commonly encountered in clinical practice in the United States, with dermatophytosis accounting for approximately 10% to 20% of all visits to the dermatology office. The majority of SCFIs are caused by dermatophytes, may affect both children and adults, and are the most prevalent agents causing fungal infections in the U.S. Cutaneous dermatophyte infections such as tinea pedis, tinea corporis, and tinea cruris exhibit variable presentations that depend on host-related and/or exogenous factors, and sometimes the characteristics of the causative dermatophyte. Onychomycosis that is caused by a dermatophyte (tinea unguium) affecting the nail bed and plate, and sometimes the nail matrix, is a very common SCFI that increases with age in adulthood and most often affects toenails with or without fingernail involvement. It is estimated that onychomycosis affects up to 12% of the world adult population, and as many as 35 million people in the US; and currently 85% of patients with the infection are untreated. Onychomycosis constitutes an important public health problem because of its high prevalence and associated morbidity. It is therefore essential for dermatology healthcare practitioners to have increased awareness of the clinical impact of SCFIs, to have expanded knowledge of the safe and efficacious use of available treatment modalities to ensure optimal clinical outcomes, and to minimize the potential recurrence of infection.

Educational Objectives

This activity is a multi-specialty, evidence-based initiative designed to increase the knowledge and competence of dermatological practitioners by providing them with the simultaneous integration of knowledge, skills, and judgment from thought-leader testimonials, science-based research, and evidence-based data to address the difference between present patient outcomes and those considered achievable in the field of dermatology.

Upon completion of this activity, participants should be able to:

- Recognize the impact of various cutaneous superficial fungal infections presenting in the dermatology setting
- Distinguish clinical type onychomycosis
- Identify risk factors for comorbidities of onychomycosis by patient type
- Compare new topical onychomycosis treatment options with established therapies
- Evaluate methods to assess the cure rates of onychomycosis therapy
- Indicate common comorbidities of common fungal infection encountered in the dermatology practice
- Evaluate newly approved topical treatment options in the treatment of tinea corporis, tinea cruris, and tinea pedis, and compare with existing therapeutic options
- Formulate optimal topical treatment plans for onychomycosis and cutaneous superficial fungal infections
- Integrate newly acquired information from current scientific literature and expert clinical experience into evidence-based decision-making in the dermatology practice

Target Audience

This activity is intended for dermatologists, residents in dermatology, and physician assistants who need continued education in diagnostic and therapeutic considerations for onychomycosis and cutaneous superficial fungal infections.

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Improving Clinical Outcomes When Treating Dermatophyte Infections

Joshua A. Zeichner MD

Dermatophyte infections are common and, if untreated, may lead to potentially serious medical complications. The incidence of fungal infections is rising, with up to 25% of the worldwide population suffering from dermatophyte infections.[1] One study evaluating the number of office visits for fungal infections over a 10-year period found that 8.8 million Americans came to the office for tinea corporis, 7.5 million for tinea pedis, and 3.6 million for tinea cruris.[2] We commonly see these patients in our practices and must be prepared to treat them.

With several new antifungal medications on the market to choose from, it is important to understand the published efficacy and safety data for each drug and translate that data to fit our real world practices. Commonly reported study outcomes include complete clearance, mycological cure, and clinical cure, which can help quantifiably capture efficacy in a study environment. However, clinical trial efficacy does not necessarily translate to real world effectiveness. A happy patient in your office may actually be considered a treatment failure in a clinical trial. Take for example an onychomycosis patient suffering for years from moderate nail dystrophy. Even some improvement may make the patient very happy, even though it may not be enough to reach a study's efficacy endpoint. What are unfortunately not commonly published in publications are photos of the treatment "failures," which many of us dermatologists may actually consider to be real world successes.

> "A happy patient in your office may actually be considered a treatment failure in a clinical trial."

Proper drug selection is only one part of achieving a successful clinical outcome. The other, perhaps even more important, part is patient education. We must explain to patients the need to adhere to a regimen and the consequences of not treating properly. These include primary treatment failure, recurrence, or spread to other body parts or close contacts. Moreover, realistic expectations must be set to put patients in the same mindset as the practitioners.

In the following educational activity, my colleagues Dr. Ted Rosen and Dr. Boni Elewski will join me in addressing the following objectives:

- Increasing awareness of the clinical impact of common cutaneous superficial fungal infection
- Understanding the safe and efficacious use of new topical treatment options
- Optimizing clinical outcomes in the treatment of onychomycosis, tinea corporis, tinea cruris, and tinea pedis
- Minimizing the potential for recurrence of fungal infection

Most uncomplicated dermatophyte infections can be effectively treated with topical antifungal drugs. It is our job both to recognize the infections and be educated on the need to treat them.

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Onychomycosis to Fungal Superinfection: Prevention Strategies and Considerations

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ABSTRACT

Onychomycosis is the most common fungal skin infection, and it is frequently seen in the setting of other concomitant fungal infections, the most common being tinea pedis. Infected nails become a reservoir of fungal organisms that may infect the skin, and vice versa. Early, effective treatment of the nails is necessary for preventing not only permanent structural damage but also the spread and superinfection of the surrounding skin and soft tissue. Moreover, treatment of the skin is important for preventing re-infection of the nails.

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INTRODUCTION

Onychomycosis is estimated to affect 12% of the United States population and represents 50% of all nail disorders.[1,2] The incidence of skin dermatophyte infections is thought to be between 10% and 20% of the U.S. population. This translates to upwards of 59 million Americans experiencing at least one cutaneous fungal infection in any given year.[3] While male gender and increasing age have been identified as predisposing factors, an equal proportion of men and women seek care for fungal infections. Moreover, according to Intercontinental Marketing Services (IMS) data, 63% of patients who filled prescriptions for oral terbinafine for onychomyosis were younger than 55 years.[4]

Onychomycosis is a fungal infection of the nail unit, which includes the nail plate itself along with the nail bed and periungual tissue. Clinically, the nail may become thick and discolored with separation from the nail bed. Onychomycosis is a progressive disease that, if left untreated, can lead to permanent nail damage and associated discomfort. In addition, local extension or spread to other body parts or to close contacts, as well as superinfections, may develop.[5,6,7] Finally, despite the best efforts in treatment, onychomycosis patients frequently relapse, with recurrence rates estimated to be between 40% and 70%.[8,9] For these reasons, early effective therapy is important.

It is estimated that one-third of patients with onychomycosis also have tinea pedis, most commonly the inter-digital subtype.[10] The infected nails serve as a fungal reservoir that infects the skin and causes the tinea pedis infection.[11,12] Because of this, it is important for onychomycosis patients to be evaluated for concurrent tinea pedis. Moreover, treating both conditions at the same time yields the best outcome in preventing a cyclical spread of fungus between the skin and the nails.[4] The presence of tinea pedis has been shown to more than double the risk for subsequently developing onychomycosis or a recurrence once it has been cured.[13]

Predisposing Factors

Several demographic, underlying medical, lifestyle, and climatic factors influence patients' risk of developing both onychomycosis and tinea pedis. These infections have been shown to be more prevalent in men than in women, and in older compared with younger patients, as well as in smokers. Those with medical conditions such as poor peripheral circulation, diabetes, and immune deficiency are also at higher risk. Recent studies also suggest that there may be a genetic susceptibility to developing fungal infections. Finally, the incidence of dermatophyte infections has been linked to living in warmer, more humid environments as opposed to in areas that are arid and dry.[1,2,14]

Lifestyle and hygiene also come into play in predisposing patients to dermatophyte infections. Wearing occlusive shoes, along with heavy perspiration and poor foot hygiene, create a moist environment that encourages invasion of fungi into the skin and nails. Moreover, exposing the feet to fungi by walking barefoot in public facilities such as gyms and swimming pools where humidity is high and fungi are prevalent also increases risk. Finally, frequent visits to nail salons has also been identified as a risk factor, as infection may be spread from dirty instruments or infected foot-soaking basins.[1,2,14]

Prevention Strategies

While many of these factors are unavoidable, extra attention should be paid to those that can be avoided. Patients with peripheral vascular disease, diabetes, or immunodeficiencies should regularly inspect their feet and visit their dermatologists

TABLE 1.

Risks of Not Treating Onychomycosis
Nail dystrophy, which can be permanent.
Pain.
Local extension of fungal infection, eg, other toe nails.
Distant spread of fungal infection, eg, tinea pedis, tinea corporis, tinea cruris.
Bacterial superinfection and cellulitis.
Development of systemic allergic or Id reaction.

or podiatrists. Nails should be kept neatly trimmed. The cutting of cuticles should be avoided because the abrasions and lacerations serve as a portal of entry for fungal organisms. If toenails or feet are infected, hands and feet should be kept clean to prevent the infection from spreading.[9,15]

A non-hospitable environment should be created to prevent fungal growth. The feet should be kept cool and dry, with loose fitting shoes. Drying antifungal powders can be used in the socks on a regular basis, and socks that become wet from perspiration should be changed during the day. Water shoes or flip-flops should be worn in public gyms, locker rooms, and showers. Personal instruments should be brought to nail salons if no guarantees can be given regarding sterility.[9,15]

"This translates to upwards of 59 million Americans experiencing at least one cutaneous fungal infection in any given year."

Why Treat Onychomycosis?

Onychomycosis is a progressive disease. If left untreated, affected nails will worsen and the infection is likely to spread to other nails. Severe onychomycosis is associated with nail dystrophy that may be permanent, even in some cases where patients achieve a mycologic cure.[6,7] Moreover, recent data suggest that early treatment of onychomycosis is more effective than treatment of long-standing disease. Not only is the target nail more easily cured, but the spread to other nails is also prevented.[16]

In addition to the local benefit of treating fungal nail infections, there is a more global health benefit as well. The spread of fungal organisms can infect not only other nails but also the skin of the feet. This includes the interdigital web spaces, the soles of the feet, or in severe cases the entire foot.[17,18] Besides the spread of fungal infections, compromised skin provides an entry portal for bacterial superinfections that may lead to cellulitis.[19,20] Superinfections are an especially significant health issue in diabetic patients, as neuropathy and lack of sensation may prevent early detection. Ultimately, diabetics are at a higher risk for foot ulcers, bacterial cellulites, and even osteomyelitis.[21,22] Finally, fungal infections of the nails and skin are rarely associated with allergic, Id, or autoeczematization reactions. Untreated fungal infections have been associated with asthma, atopic dermatitis, urticaria, and erythema nodosum.[19,20]

"Onychomycosis is a progressive disease that, if left untreated, can lead to permanent nail damage and associated discomfort."

Onychomycosis carries a significant burden and interferes with patients' quality of life. Half of patients may experience foot pain, and an estimated 30% of patients report that the disease interferes with their ability to wear normal shoes and socks.[19,23] Moreover, patients may experience difficulty walking and be embarrassed about the appearance of the nails. In some cases, especially as reported by females, patients may be so adversely affected that the nail infection interferes with their personal relationships and self-esteem.[24]

Goals of Treatment

There are 2 primary goals in treating onychomycosis. Firstly, the therapy must eliminate the infection. Secondly, after the fungal infection has been cleared, patients must be left with a normal appearing nail.[25] The causative fungal organisms infect the nail itself, along with the skin beneath the nails. Effective therapy relies on both the ability of the drug to kill the fungus and the body's ability to restore a new, normal appearing nail. Once the nail is infected and dystrophic, it does not return to normal with treatment. Rather, a new, clean, uninfected nail is newly made in the nail matrix. As it grows out, it will replace the infected nail. This is a slow process, and even if the infection is

TABLE 2.

Onychomycosis Predisposing Factors
Gender: Men > women.
Age: Older > younger.
Cigarette Smoking.
Medical Conditions: peripheral vascular disease, diabetes, immunodeficiency.
Genetics.
Lifestyle: wearing occlusive shoes, walking barefoot in public facilities.
Frequent Pedicures at Nail Salons.

TABLE 3.

Onychomycosis Prevention Strategies
Regular inspection of the feet and nails.
Avoidance of cutting cuticles.
Changing socks and shoes during the day.
Prophylactic anti-fungal foot powders.
Use of water shoes or flip-flops in public facilities.
Use of personal instruments at the nail salon.

cured, it can take up to a year for an abnormal nail to grow out. In the event that the nail matrix itself becomes damaged, then a new nail that is produced will appear abnormal, even if the previous fungal infection has been cleared.

"Failure to treat onychomycosis can put patients at risk for nail pain, permanent deformity, potential superinfection, and quality of life impairment."

CONCLUSION

Onychomycosis is a common nail disease that carries a significant health burden. While many practitioners may overlook onychomycosis, it warrants treatment. Onychomycosis is commonly associated with concurrent tinea pedis, which should be evaluated for and treated along with the nails to prevent spread and reinfection. Failure to treat onychomycosis can put patients at risk for nail pain, permanent deformity, potential superinfection, and quality of life impairment.

DISCLOSURES

Joshua A. Zeichner MD is an advisory board member, consultant, investigator, and speaker for Valeant Pharmaceuticals; and an advisory board member for Anacor, Exeltis, and PharmaDerm.

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New Topical Therapeutic Options in the Management of Superficial Fungal Infections

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ABSTRACT

Dermatophyte infections of the skin and nails are common in the United States. These infections warrant treatment because they are symptomatic and progressive, and can predispose patients to superinfections. Topical drugs such as luliconazole, naftifine, efinaconazole, and tavaborole are newer options for treating these dermatophyte infections with proven safety, efficacy, and ease of use.

J Drugs Dermatol. 2015;14(suppl 10):s35-s41.

INTRODUCTION

Dermatophyte infections are fungal infections of keratinized tissue, including the skin, hair, and nails.[1] These infections are common, affecting an estimated 10% to 20% of people in the United States and up to 25% of the population worldwide.[2] A recent meta-analysis concluded that onychomycosis affects roughly 4% of the population in North America.[3] Visits to the doctor to treat dermatophyte infections continue to rise. One study in the U.S. reported 8.8 million visits for tinea corporis, 7.5 million visits for tinea pedis, and 3.6 million visits for tinea cruris over a 10-year period (1995-2004).[4]

Similar fungal organisms infect both the skin and the nails. While *Epidermophyton floccosum* and *Trichophyton rubrum* are common causes of tinea corporis, tinea pedis, and tinea cruris, *T. rubrum* is the most prevalent fungal pathogen worldwide.[5,6] Moreover, *T. rubrum* is responsible for 90% of cases of onychomycosis.[7]

Dermatophyte infections warrant treatment. They cause primary discomfort and pruritus, and also spread to other body parts and other people. In addition, broken skin serves as an entry site for potential bacterial superinfections.[8,9,10] Onychomycosis in particular should be treated as soon as possible because early intervention yields better outcomes[11] and progression can lead to painful nail dystrophy and significantly affect quality of life (QOL).[12,13]

The American Academy of Dermatology recommends topical therapy for the initial treatment of uncomplicated dermatophyte infections of the skin.[14] While there are many antifungal options available, proper drug selection is important because adherence to the regimen is crucial for achieving a successful therapeutic outcome.[15] Several azole and allylamine class topical antifungal agents are currently commercially available to treat dermatophyte infections. The azole class includes econazole, oxiconazole, sertaconazole, ketoconazole, sulconazole, and clotrimazole; and the allylamine class includes naftifine, butenafine, and terbinafine.

The azoles are thought to inhibit the synthesis of ergosterol, which affects the permeability of the cell membrane by binding with phospholipids to the fungal cell membrane.[16] Allylamines inhibit squalene epoxidase, an essential enzyme in the ergosterol biosynthesis pathway of fungal cell membrane formation.[16] The inhibition of squalene epoxidase results in cellular permeability and growth inhibition.[16]

For onychomycosis, topical therapies, namely ciclopirox nail lacquer, had previously been limited, as the available options yielded low efficacy and required frequent nail debridement. Recently, new topical antifungal options have been brought to the market to treat onychomycosis, including topical tavaborole and efinaconazole. New drugs for the treatment of dermatophyte infections include the azole luliconazole and the allylamine naftifine, which are indicated for the treatment of tinea pedis, tinea corporis, and tinea cruris.

Luliconazole

Background Information

Luliconazole is a new antifungal drug developed for the topical treatment of dermatophyte infections. It has been used in Japan since 2005 and received clearance by the Food and Drug Administration (FDA) in the U.S. in 2013. Its indication is for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *T. rubrum* and *E. floccosum* in adults. When treating tinea pedis, luliconazole should be administered once daily for 2 weeks. For tinea corporis and tinea cruris, it should be administered once daily for 1 week.[17]

An imidazole antifungal, luliconazole is thought to disrupt production of the fungal cell membrane. While the exact mechanism

of action is unknown, the drug appears to inhibit activity of the enzyme lanosterol 14α-demethylase, which prevents conversion of lanosterol to ergosterol, a necessary constituent of the fungal cell wall.[17]

TABLE 1.

Onychomycosis and Tinea Infection Predisposing Factors
Demographics: Male gender, increasing age, smoking.
Medical Conditions: Concurrent fungal infections (eg, onychomycosis or tinea pedis), diabetes, peripheral vascular disease, immunodeficiency, genetics.
Lifestyle Issues: Wearing occlusive shoes, frequenting public showers and gyms, frequenting nail salons.
Environment: Humid and warm climates.

Pre-clinical data demonstrated strong antifungal activity of luliconazole. In one study, the drug demonstrated potent mean inhibitory concentrations against both *T. rubrum* and *E. floccosum*.[18] While the clinical significance of this data has not been established, these organisms are the most common causes of tinea pedis, tinea corporis, and tinea cruris. In an in vivo study, luliconazole was demonstrated to be maintained at high levels in the stratum corneum over 14 days. Here, the drug was topically applied to guinea pig plantar skin, and the stratum corneum was evaluated for drug levels. After application for 3 consecutive days, high levels of luliconazole were observed and maintained over the 14-day course of the study with continued daily application.[19]

Clinical Data

Two phase 3 clinical studies have been published evaluating the safety and efficacy of luliconazole in tinea pedis and tinea cruris. In total, 324 eligible patients used luliconazole—159 in the tinea pedis study and 165 in the tinea cruris study.[20,21]

This randomized, double blind, vehicle controlled study was performed across 12 U.S. study sites to evaluate the safety and efficacy of luliconazole for interdigital tinea pedis. Three hundred and twenty-one subjects eligible for the modified intent-to-treat analysis were randomized 1:1 to receive either luliconazole 1% cream (n=159) or vehicle (n=162). They applied the study drug once daily for 2 weeks, followed by 4 weeks of follow-up. Patients were 12 years of age or older, and suffered from at least moderate disease. Baseline demographics as well as signs and symptoms of erythema, scaling, and pruritus were equally distributed in both arms of the respective studies.[21]

Tinea Pedis: Efficacy

The study's primary endpoint was complete clearance at the 4-week post-therapy time point. Complete clearance was defined as both a clinical and mycologic cure, where patients were clear of any clinical signs of erythema, scaling, and pruritus along with a negative potassium hydroxide (KOH) test and fungal culture. Statistically significant differences in complete clearance were achieved in the active vs vehicle arm ($P<.001$). 26.4% patients on luliconazole 1% cream achieved a complete clearance at day 42 (4 weeks after the 2-week treatment period), compared with 1.9% patients using the vehicle ($P<.001$).[21]

The studies met all of its secondary efficacy end points. 62.3% of patients in the luliconazole group and 17.5% in the vehicle group achieved a mycological cure (defined as both a negative KOH and fungal culture) at the 4-week post-treatment visit. Similarly, statistical significance was achieved in evaluating the clinical cure at the 4-week post-treatment visit (29.2% vs 7.8% in the luliconazole and vehicle groups, respectively, $P<.001$). Here, clinical cure was defined as the absence of any signs of erythema and scaling along with zero patient-reported pruritus.[21]

An "effective treatment" was a secondary endpoint defined as achieving both a mycologic cure along with a clinical improvement of no pruritus but at most mild erythema and/or scaling at the 4-week post-treatment visit. This hybrid endpoint represents a real-world scenario of those patients who have been cured of the infection but who have not yet fully recovered clinically. The pooled results from both studies of patients who reached this endpoint were 48.1% and 9.7% in the luliconazole cream and vehicle group respectively ($P<.001$).[21]

Tinea Cruris: Efficacy

In the phase 3 study evaluating tinea cruris, participants applied luliconazole cream once daily for a week, with follow-up for 3 weeks post-therapy (day 28). Four hundred and eighty-three patients were enrolled, and those eligible for the modified intent-to-treat analysis were randomized 2:1 to receive either luliconazole 1% cream (n=165) or vehicle (n=91). Eligible patients were at least 12 years old and had a tinea infection with signs of at least moderate erythema, mild scaling, and moderate pruritus. Baseline demographics and disease signs and symptoms were evenly matched between treatment groups.[20]

> "Dermatophyte infections warrant treatment. They cause primary discomfort and pruritus, and also spread to other body parts and other people."

The primary and secondary endpoints of the tinea cruris study mirrored those of the tinea pedis studies, and all endpoints were met. The primary endpoint of complete clearance at the 3 weeks post one-week treatment was 21.2% in the luliconazole group vs 4.4% in the vehicle group ($P<.001$). A mycological cure at that day 28 visit was achieved by 78.2% and 45.1% of

subjects in the luliconazole and vehicle groups, respectively (*P*<.001). 24.4% of patients using luliconazole achieved a clinical cure at day 28, compared with 6.6% using vehicle (*P*<.001). Finally, a statistically significant difference was observed in patients who experienced an effective treatment at the end of the study: 43% of the subjects in the luliconazole group compared with only 18.7% in the vehicle (*P*<.001).[20]

Phase 3 Safety Data

Luliconazole was safe and well tolerated in the phase 3 studies. The most common treatment-related adverse events (AEs) were application site reactions, which occurred in less than 1% of patients who received both luliconazole and vehicle. Moreover, most were mild in severity.[20,21]

TABLE 2.

Consequences of Not Treating Onychomycosis
Permanent nail damage.
Spread to other body parts, both local and distant.
Transmission to close contacts.

Naftifine

Background Information

Naftifine is a new topical allylamine class antifungal drug that exhibits broad-spectrum fungicidal activity. Naftifine hydrochloride cream is FDA-approved for the treatment of tinea pedis, tinea cruris, and tinea corporis. In 2014, a 2% gel and cream formulation was added to the previous line of 1% naftifine products. They are FDA-approved for the treatment of interdigital type tinea pedis in pediatric patients aged 12 to 17 years old.

Clinical Data

The efficacy and safety of naftifine gel 2% in the treatment of interdigital and moccasin-type tinea pedis was evaluated in two 6-week, phase 3 double-blind, randomized, vehicle-controlled, multi-center, clinical trials. Subjects were recruited from 47 clinical sites within the US. The trials ultimately randomized a total of 1715 subjects: 1144 of the subjects received naftifine gel 2% and 571 received the vehicle.[22]

Tinea Pedis: Efficacy

Subjects in the study were randomized 2:1 to apply naftifine 2% gel or vehicle and followed for 6 weeks. The medication was applied once daily for 2 weeks followed by a 4 week post-treatment follow-up period. The primary efficacy variable was a complete cure at week 6, defined as both a mycological and clinical cure. Secondary efficacy variables included a mycological cure (negative KOH and culture) and effective treatment (mycological cure plus clinical signs no worse than mild).[22] In the interdigital tinea pedis patients, naftifine showed a statistically significant (*P*=.001) complete cure rate compared with vehicle as early as week 2, and sustained until week 6. In addition, there were statistical differences between the active and vehicle arms with respect to mycological cure (*P*<.0001) and treatment effectiveness (*P*<.0001). In addition, statistical differences were observed at week 6 (*P*<.0001) for all endpoints in subjects with moccasin-type tinea pedis.[22]

Tinea Pedis: Safety

Naftifine gel was safe and well tolerated. Twenty-one subjects out of 1,143 using active drug experienced an AE, compared with 4 out of 571 on vehicle. Only 5 subjects from the naftifine group and 1 subject from the vehicle group discontinued from the study because of an AE. There were no serious AEs reported.[22]

Efinaconazole

Background Information

Efinaconazole is a new triazole antifungal indicated to treat onychomycosis caused by *T. rubrum* and *T. mentagrophytes*.[23] It received FDA approval in the U.S. in June 2014. The course of treatment for infected toenails is 48 consecutive weeks. Dispensed in an integrated flow-through brush applicator, the drug should be applied to cover completely the toenail, nail folds, and hyponychium, as well as beneath the nail plate. The drug is formulated as a non-lacquer solution. There is no buildup, nor periodic removal or debridement required.[23]

Efinaconazole is an azole class antifungal. Similar to luliconazole, while the exact action is unknown, efinaconazole is thought to block the conversion of lanosterol to egosterol by inhibiting the fungal lanosterol 14α-demethylase enzyme. This decreases the amount of available ergosterol, disrupting production of the fungal cell membrane.[23] In vitro testing demonstrated efinaconazole to have excellent anti-fungal activity against *T. rubrum* and *T. mentagrophytes*. In addition, it was active against other *trichophyton*, *microsporum*, *epidermophyton*, and *candida* species.[24] At therapeutic concentrations, efinaconazole has not been shown to affect the cytochrome P450 (CYP450) enzyme system.[23]

> "Onychomycosis is frequently found in the setting of concurrent tinea pedis, and both conditions should be treated at the same time to minimize the risk of a cyclical re-infection."

Several characteristics of efinaconazole 10% solution help explain its effectiveness in treating onychomycosis. First, it displays a low keratin binding affinity. Efinaconazole can bind to and be released from keratin, enhancing its antifungal activity.[25] Secondly, the solution has a low surface tension that enhances penetration and spreading or wicking of the drug around the

nail.[26] Efinaconazole is thought to reach the site of infection beneath the nail by 2 pathways: both transungual delivery[27] as well as spread through the subungual air space.[28] Finally, a study using cadaveric nails showed that nail polish did not interfere with penetration of efinaconazole 10% solution through the nail.[29]

Clinical Data

Two identical 52-week multi-center, randomized, double-blind, vehicle- controlled studies were performed to evaluate the safety and efficacy of efinaconazole 10% solution for the treatment of onychomycosis. In total, 1,655 patients were enrolled across the U.S., Canada, and Japan.[30]

Eligible patients were aged 18 to 70 years, and had mild to moderate distal lateral subungual onychomycosis of the great toenail, defined as 20% to 50% clinical involvement. The affected part of the nail had to be at least 3 mm from the proximal nailfold. In addition, nail thickness could be no more than 3 mm. Subjects were randomized 3:1 to receive either active drug or vehicle. Baseline demographic characteristics were evenly matched in the active vs vehicle arms. The mean patient age was 52.3 and 50.6 years in each study. The majority of enrolled patients were Caucasian males, and the mean area of the affected target toenail was 36.7% and 36.3% in the 2 studies.[29]

The study protocol required participants to apply the study medication once daily for 48 weeks. They were then followed up in the study center for another 4 weeks, for a total of 52 weeks. No nail debridement was performed at any time point in the study. The study drug was brushed on to a clean, dry nail, covering the nail plate itself, along with the lateral and proximal nailfolds, hyponychium, and underside of the nail plate.[29]

Onychomycosis Phase 3 Study: Efficacy

Efinaconazole 10% solution met all of the primary and secondary efficacy endpoints in the study. The primary efficacy variable was the complete cure at week 52, defined as a clinical cure of the target toenail (aka, 0% clinical involvement) in addition to a mycologic cure, defined as a negative KOH and negative fungal culture. At week 52, 17.8% of patients in the first study and 15.2% of patients in the second study achieved a complete cure on active drug, compared with only 3.3% and 5.5% of subjects using the vehicle ($P<.001$).[29]

Secondary efficacy endpoints included the mycologic cure, complete or almost complete cure, and clinical efficacy at week 52. The mycologic cure was defined as a negative KOH and fungal culture, independent of clinical appearance. 55.2% and 53.4% of patients in studies 1 and 2 using efinaconazole achieved a mycologic cure compared with 16.8% and 16.9% of subjects on vehicle ($P<.001$). A complete or almost complete cure was defined as clinical involvement less than or equal to 5% of the nail in addition to a mycologic cure. 26.4% of patients in study 1 and 23.4% of patients in study 2 on efinaconazole achieved a complete or almost complete cure at week 52, vs only 7% and 7.5% of vehicle-treated patients ($P<.001$).[29]

Onychomycosis Phase 3 Study: Safety

Efinaconazole was safe and well-tolerated throughout both studies. Adverse reactions that occurred during the 48 weeks of active treatment were generally mild to moderately severe, predominantly not related to study medication, and resolved without long-term effects. The discontinuation rate in the study was low. Only 2.6% and 0.2% of patients in the efinaconazole and vehicle groups, respectively, discontinued the study for any reason, the most common reason being an application site reaction to the drug.

Phase 3 Study: Post-Hoc Analyses

Since the conclusion of the phase 3 clinical trials, several post-hoc analyses have been performed re-analyzing data from the original enrolled subjects under different parameters. Onychomycosis is frequently found in the setting of concurrent tinea pedis, and both conditions should be treated at the same time to minimize the risk of a cyclical re-infection.[31] The presence and treatment of tinea pedis were not exclusion criteria from the phase 3 study program; thus, the onychomycosis patients with concurrent tinea pedis could treat the tinea pedis with topical antifungal agents during the study. When the tinea pedis was treated, the efficacy of the efinaconazole on the nails was actually found to be enhanced.[32] In addition, when comparing short vs long-term nail disease, better improvements were seen when onychomycosis was treated early.[33] This should encourage practitioners to treat nail infections when they see them, rather than brushing them off as a cosmetic issue.

In looking at diabetic vs non-diabetic patients, no differences were observed in terms of the efficacy or safety of efinaconazole.[34] Moreover, no differences in safety or efficacy were observed between subjects over and below 65 years.[23] Finally, use of efinaconazole solution in the phase 3 studies provided significant improvement in all aspects of QOL. The most significant QOL improvements were observed in patients who had improvement in the clinical appearance of the nail, with the greatest QOL improvements reported by those who had improvement in the largest percentage of their nail.[35]

Tavaborole

Background Information

Tavaborole topical solution 5% is a novel anti-fungal drug based on boron-based chemistry. This hydrophilic, small molecule is highly specific in targeting fungal cytoplasmic leucyl-transfer ribonucleic acid (tRNA) synthetase. This enzyme is important in fungal cellular

protein synthesis. In 2014, the FDA approved tavaborole 5% solution for the treatment of toenail onychomycosis.[36]

Onychomycosis Phase 3 Study: Efficacy

Two phase 3, multicenter, randomized, double-blind, vehicle-controlled trials assessed the safety and efficacy of tavaborole in adults with distal subungual onychomycosis, which affected 20% to 60% of a great toenail. The first phase 3 trial included 594 subjects, and the second phase 3 trial included 604 subjects. The subjects were randomized 2:1 to receive tavaborole or vehicle once daily for 48 weeks. The trials' primary end point was a complete cure of the affected toenail, defined as a mycological cure in addition to a clinically cured toenail at week 52.[37] In both studies, the complete cure rate in the tavaborole groups were statistically better than vehicle, 6.5% vs 1% ($P<.001$) and 9.1% vs 1.5% ($P<.001$) in studies 1 and 2, respectively.[37]

TABLE 3.

Luliconazone Efficacy Endpoint Definitions
Complete clearance = clinical and mycologic cure.
Mycological cure = negative KOH and culture.
Clinical cure = No signs or symptoms of erythema, scaling, or pruritus.
Effective treatment = Mycologic cure plus and, at most, mild erythema and/or scaling and no pruritus.

KOH, potassium hydroxide preparation.

Onychomycosis Phase 3 Study: Safety

The respective incidence of AEs with tavaborole compared with vehicle in the first trial were 64.4% vs 69.9%, and in the second trial were 57.5% vs 54.0%. The vast majority of AEs in patients receiving tavaborole (95.5%) or vehicle (93.4%) were reported as mild or moderate in severity. The most common treatment-related application site AEs with tavaborole in the 2 trials were exfoliation (2.7%), erythema (1.6%), and dermatitis (1.3%).[37]

CONCLUSION

Luliconazole was the first antifungal discussed in this article, and it is indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis. A phase 3 trial, evaluating luliconazole for the treatment of interdigital tinea pedis, randomized 321 subjects 1:1 to receive either luliconazole 1% cream or vehicle. The trial's primary endpoint was complete clearance as defined by both a clinical and mycologic cure, where patients were clear of any clinical signs of erythema, scaling, and pruritus, as well as a negative KOH test and fungal culture. In the trial, 26.4% patients receiving luliconazole 1% cream achieved a complete clearance at day 42, which was 4 weeks after the 2-week treatment period, vs 1.9% patients using the vehicle ($P<.001$).

A phase 3 trial, evaluating luliconazole 1% cream or vehicle for the treatment of tinea cruris, randomized 483 subjects 2:1 to receive luliconazole 1% cream or vehicle. The primary endpoint was complete clearance at week 3, which was one week post treatment. The primary endpoint was achieved by 21.2% of subjects in the luliconazole group compared with 4.4% in the vehicle group ($P<.001$). Additionally, 24.4% of patients using luliconazole achieved a clinical cure at day 28 vs 6.6% of patients using the vehicle ($P<.001$). Moreover, luliconazole was safe and well tolerated in the aforementioned phase 3 studies.

Naftifine hydrochloride cream is FDA-approved for the treatment of tinea pedis, tinea cruris, and tinea corporis; and a 2% gel and cream formulation has recently been FDA-approved for the treatment of interdigital type tinea pedis in pediatric patients aged 12 to 17 years old. In the 2 phase 3 trials reviewed in this article, evaluating naftifine 2% gel for the treatment of moccasin-type tinea pedis, 1,715 subjects were randomized 2:1 to receive naftifine gel 2% or the vehicle. The trials' primary efficacy variables were a negative mycology culture, which correlated with a complete cure, and scores of 0 on the clinical signs and symptoms for erythema, scaling, and pruritus at week 4 post-treatment. At week 4 post-treatment, 19.6% of the subjects receiving naftifine gel 2% achieved a complete cure vs 0.7% for vehicle-treated subjects ($P<.0001$). With regards to safety, 1.8% out of 1,143 receiving naftifine gel and 0.7% receiving the vehicle experienced one or more treatment-emergent AEs, but the majority of these subjects continued with the study and completed the trial.

TABLE 4.

Proper Application of Efinaconazole
Nail plate.
Proximal and lateral nail folds.
Hyponychium.
Nail bed beneath the nail plate.

Efinaconazole is a new triazole antifungal indicated to treat onychomycosis caused by *T. rubrum* and *T. mentagrophytes*, and it received FDA approval in 2014. Two phase 3 52-week multi-center, randomized, double-blind, vehicle-controlled studies were performed to evaluate the safety and efficacy of efinaconazole 10% solution for the treatment of onychomycosis.

The primary efficacy variable was a complete cure at week 52, which was defined by a clinical cure of the target toenail in addition to a mycologic cure, defined as a negative KOH and negative fungal culture. At week 52, 17.8% of patients in the first study and 15.2% of patients in the second study treated with efinaconazole achieved a complete cure vs 3.3% and 5.5%

of the respective subjects receiving the vehicle. Efinaconazole was also safe and well-tolerated.

"Newer antifungal agents such as luliconazole, efinaconazole, naftifine, and tavaborole augment the armamentarium of drugs available for treating these infections effectively."

The final antifungal reviewed in this article is tavaborole, a boron-based pharmaceutical approved by the FDA in 2014 for the treatment of toenail onychomycosis caused by *Trichophyton rubrum* and *T mentagrophytes*. Two phase 3, multicenter, randomized, double-blind, vehicle-controlled trials evaluated the safety and efficacy of tavaborole 5% topical solution in adults with distal subungual onychomycosis, which affected 20% to 60% of a great toenail. The first phase 3 trial included 594 subjects, and the second phase 3 trial included 604 subjects. The trials' primary end point was a complete cure of the affected toenail that was defined by a negative mycology and a fully cleared toenail at week 52. In the first trial, 6.5% of subjects achieved a complete clearance compared with 1% for placebo ($P<.001$), and in the second trial 9.1% of subjects achieved a complete clearance compared with 1.5% for placebo ($P<.001$). Tavaborole was safe and well tolerated, and the most common treatment-related application site AEs in the 2 trials were exfoliation (2.7%), erythema (1.6%), and dermatitis (1.3%).

Dermatophyte infections of the skin and nails are a common problem in the United States that warrant therapy. Newer antifungal agents such as luliconazole, efinaconazole, naftifine, and tavaborole augment the armamentarium of drugs available for treating these infections effectively. Early intervention can also lead to excellent clinical outcomes, with improvement in appearance and patient discomfort, reduction in the risk of spread or superinfection, and improvement in overall QOL.

DISCLOSURES

Joshua A. Zeichner MD is an advisory board member, consultant, investigator, and speaker for Valeant Pharmaceuticals; and an advisory board member for Anacor, Exeltis, and PharmaDerm.

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Identifying Signs of Tinea Pedis: A Key to Understanding Clinical Variables

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ABSTRACT

Tinea pedis is a frequently encountered dermatophytosis affecting the superficial skin of the feet, primarily of adults. The prevalence of tinea pedis has increased over the last several decades due to an increase in multiple risk factors. Infection from dermatophytes is most common, but infection from other fungi can also result in tinea pedis. Four distinct clinical presentations occur: interdigital, moccasin, vesicular, and acute ulcerative types. A variety of physical exam findings can help the clinician identify patients with tinea pedis.

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INTRODUCTION

Superficial cutaneous fungal infections represent a diverse group of diseases caused by dermatophytes, yeasts (*Candida albicans*), and occasionally non-dermatophyte molds. The prevalence of superficial cutaneous fungal infections has increased over the past several decades and is seen in both immunocompetent and immunosuppressed patients around the world.

Dermatophytes are a group of closely related fungi that infect the skin, hair, and nails of both humans and animals. Tinea pedis, the most common dermatophytosis, is a superficial fungal infection of the plantar surface and frequently occurs in developed countries. Although tinea pedis is caused mostly by anthropophilic dermatophytes, zoophilic infections can occasionally occur and these are usually more inflammatory.

Over the past 30 years there has been an increase in the incidence of tinea pedis due to in part to growing urbanization and changes in recreational activities; and currently up to 25% of the population may be affected at any given time in the United States.[1-4] Tinea pedis can provide a portal of entry for secondary bacterial infection, resulting in profound complications and morbidity.[5]

Pathogenesis

Only a few fungi are implicated in the vast majority of tinea pedis cases (Table 1). *Trichophyton rubrum* is by far the most common organism involved in tinea pedis, followed by specifies from within the *T. mentagrophytes* complex, *Epidermophyton floccosum*, and *T. tonsurans*.[6] Although *T. tonsurans* is an uncommon cause of tinea pedis in adults, its prevalence is increasing.[7] Of these fungi, only species from within the *T. mentagrophytes* complex have both anthropophilic and zoophilic varieties; *T. rubrum*, *E. floccosum*, and *T. tonsurans* are strictly anthrophophilic.[8] In addition to being the most common cause of tinea pedis, *T. rubrum* is also responsible for approximately 90% of onychomycosis cases.[9] Chronic untreated or undertreated tinea pedis is a predisposing risk factor for the development of onychomycosis.[9] Patients who progress from tinea pedis to develop concurrent onychomycosis have infections that are far more challenging to eradicate.

The taxonomic classification for the *T. mentagrophytes* complex has undergone multiple revisions over time as our ability to differentiate species based on molecular studies and genetic information has improved. Within the *T. mentagrophytes* complex, *T. interdigitale* (previously called *T. mentagrophytes* var. *interdigitale*) is the most commonly isolated organism. It is almost strictly anthrophilic, but can be found rarely in animals. Also within the *T. mentagrophytes* complex is the *T. mentagrophytes* species, which is primarily zoophilic and is found in association with rodents (rats, hamsters, guinea pigs), rabbits, and ferrets. In humans, the *T. mentagrophytes* species can cause a highly inflammatory form of tinea pedis. *Arthoderma benhamiae* is a third species within the *T. mentagrophytes* complex; however, this species will not be discussed here as it is primarily zoophilic and only occasionally leads to tinea corporis and tinea capitis, but not tinea pedis. Finally, *A. vanbreuseghemii* is a mating type strain within the *T. mentagrophytes* complex and will also not be discussed.

In addition to the dermatophytes mentioned above, infections from non-dermatophyte molds can also result in tinea pedis. Outside of the Western hemisphere, non-dermatophyte molds are not uncommon isolates from foot infections. For example, an outpatient epidemiology study from Thailand reported that non-dermatophyte infections account for nearly 60% of cases of tinea pedis.[10] Of these non-dermatophytes, *Neoscytalidium dimidiatum* and its hyaline mutant *N. dimidiatum* var. *hyalinum* (previously called *S. lignicola*) represent the overwhelmingly

TABLE 1.

Fungi Implicated in Tinea Pedis	
Organism	**Associated Features of Infection**
Dermatophytes	
Trichophyton rubrum	Most common species to produce tinea pedis, strictly anthrophilic.
T. mentagrophytes complex *T. interdigitale* *T. mentagrophytes*	Most common within the T. mentagrophytes complex, strictly anthrophilic. Primarily zoophilic, infection results in highly inflammatory tinea pedis.
Epidermophyton floccosum	Strictly anthrophilic.
T. tonsurans	Strictly anthrophilic, isolated from pediatric tinea pedis.
Non-Dermatophyte Molds	
Neoscytalidium dimidiatum	Geophillic organism, endemic to Africa, Asia, the Caribbean, Central and South America, and several states in the United States. Infection is indistinguishable from dermatophte tinea pedis, but is highly treatment resistant.

most common fungi.[11] *Neoscytalidium spp* are common fruit tree pathogen in the tropics, and geophilic transmission to human hosts in tropical and subtropical areas is thought to occur via contact with contaminated plants and soil.[10,12,13] *Neoscytalidium spp* are endemic to parts of Africa, Asia, the Caribbean, Central and South America, and several states in the U.S. Infection with *Neoscytalidium spp* results in chronic, treatment resistant tinea pedis, tinea manuum, and onychomycosis infection that is clinically indistinguishable from cases associated with dermatophytes.

While tinea pedis is predominantly a disease that affects adults, tinea pedis can occur in children and is associated with a distinct mycologic profile in children. *T. tonsurans* is implicated in pediatric tinea pedis cases, especially when patients have concurrent tinea capitis caused by this organism. Children can also be infected with the typical dermatophytes that affect adults via household contact with fomites.

"Chronic untreated or undertreated tinea pedis is a predisposing risk factor for the development of onychomycosis."

Infection starts when the dermatophyte arthroconidia adheres to the superficial layer of the host's epithelium, after which hyphae develop and penetrate deeper into the epithelium. *T. rubrum* can survive outside of the human host as an arthroconidia for only a short period of time, whereas *E. floccosum* can survive for years on fomites.[14] Because sebaceous glands are absent on acral skin, and their secretions are thought to have antimicrobial properties, palms and soles are the primary sites of infection. Infection is limited to the stratum corneum, which is a keratin-rich structure. Keratin is a hard, densely packed protein. Dermatophyte growth is fueled by the ability of these organisms to degrade and use keratin via specialized enzymes: keratinase, cysteine dioxygenase, and a sulfite efflux pump.[15] These enzymes represent a major virulence feature of dermatophytes.

Epidemiology

Tinea pedis is a relatively new infection in the Western world, transported through global human migration in the end of the nineteenth century. *T. rubrum*, which is the most common cause of tinea pedis, is endemic to Southeast Asia, Western Africa, and parts of Australia.[14] Interestingly, tinea pedis was not endemic in these areas at the time of its spread, probably due to the fact that people in these areas did not routinely wear occlusive footwear, which is a major risk factor for tinea pedis.

European colonization of regions with endemic *T. rubrum* is believed to be how tinea pedis was first introduced to Europe. Subsequently, *T. rubrum* infection spread throughout Europe. The first case of *T. rubrum* tinea pedis in the U.S. was documented in a World War 1 veteran in Birmingham Alabama.[16] Once a rare disease, tinea pedis is now the most common dermatophyte infection.

TABLE 2.

Risk Factors for Tinea Pedis
Uncontrollable Risk Factors
Male gender.
Medical history of immune suppression, diabetes, or peripheral vascular disease.
Dermatologic conditions, including a history of psoriasis or atopic dermatitis.
Controllable Risk Factors
Wearing occlusive footwear.
Exercising in public sports facilities, especially in community swimming pools, without wearing protective footwear.

Tinea pedis generally affects adolescent and adults. Predisposing host factors include male gender, wearing occlusive shoes, and living in a warm and humid climate (Table 2).[2] A medical history of immune suppression, diabetes mellitus, or peripheral vascular disease also place patients at an elevated risk for tinea pedis.[2] Exercising in public sports facilities, especially in community swimming pools, represent well-documented risk factors for contracting tinea pedis, particularly for men over the age of 16.[17] Patients who cohabitate with individuals affected by tinea pedis are also at risk for developing tinea pedis as transmission can occur from contact with fomites, most commonly in the bath.[8] There is also evidence to support that tinea pedis is more common in patients with certain dermatologic conditions such as psoriasis or atopic dermatitis.[18]

Clinical Presentation

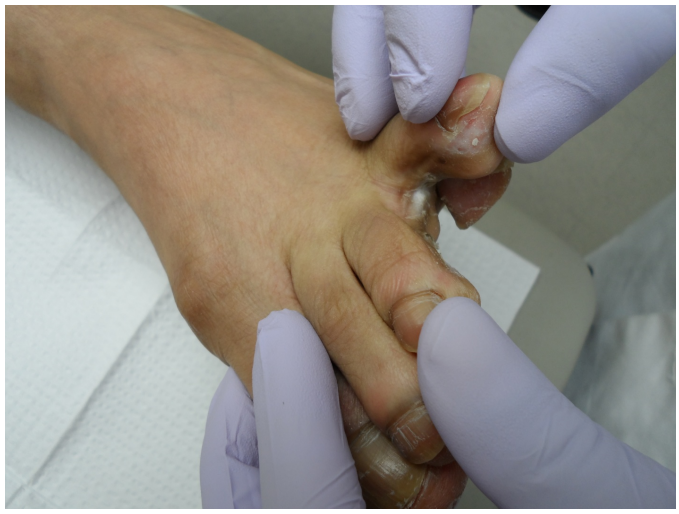
Patients with tinea pedis may present with one of 4 possible distinct clinical patterns: interdigital type, moccasin type, vesicular type, or acute ulcerative type (Table 3). Patients may complain of extensive pruritus or malodor; however, a significant proportion of patients have occult disease with an asymptomatic infection.

Patients with interdigital tinea pedis, which is the most common clinical presentation, develop macerated skin in the web spaces, most commonly in lateral 3rd and 4th interdigital web spaces (Figure 1). Contiguous skin may also be affected; however, the dorsal foot surface remains unaffected. Patients with this pattern of infection, if left untreated, develop macerated fissures and erythema. Warm and humid climates and hyperhidrosis are strong risk factors for this variety of presentation. *T. rubrum* and *E. floccosum* are commonly implicated pathogens. Highly macerated cases of interdigital tinea pedis can develop bacterial secondary infection, and this presentation has been termed dermatophytosis complex.[19] The name comes from the fact that although the dermatophyte infection is the inciting factor for this disease, secondary candida and bacterial infection may arise and complicate the clinical presentation. Overgrowth of *Micrococcus sedantarius*, *Brevibacterium epidermidis*, *Corynebacterium minutissimum*, *Pseudomonas,* or *Proteus* can produce dermatophytosis complex.[19]

TABLE 3.

Clinical Presentation of Tinea Pedis	
Clinical Pattern	**Details of Presentation**
Interdigital	Most common type of tinea pedis: patients present with macerated skin, with or without erythema and fissures, in the interdigital web spaces between the 4th and 5th toes.
Moccasin	Second most common type: patients present with dry, hyperkeratotic scales and fissures on the plantar surface of the feet. Collarets of scale can be seen along the borders of the feet. This presentation can be associated with concurrent tinea manuum, and may be asymptomatic.
Vesicular	Small vesicles over a background of erythema on the instep of the foot. This presentation can be painful or pruritic and develop rapidly; and is associated with zoophilic infection.
Acute ulcerative	This presentation results from an exacerbation of interdigital tinea pedis, and patients present with ulcers and erosions in the interdigital web spaces. Patients are at risk for secondary bacterial infections.

FIGURE 1. Interdigital type of tinea pedis. Macerated skin in the lateral 3rd interdigital web space.



> "Once a rare disease, tinea pedis is now the most common dermatophyte infection."

Moccasin type is the second most common clinical presentation of tinea pedis, and is typically caused by *T. rubrum*. Patients with the moccasin type of tinea pedis develop chronic, dry, hyperkeratotic scale and fissures on the plantar surface of one or both feet. Collarets of scale can extend superiorly along borders of the feet in a "moccasin" type distribution (Figure 2). Occasionally patients can develop profound hyperkeratosis and fissures. Patients with this type of infection are most often asymptomatic and unaware that the infection is present. The moccasin type of tinea pedis may be associated with concurrent tinea manuum infection, and so an examination of the patient's hands is prudent. These patients may present with the so-called 2 feet-1 hand syndrome, where there is bilateral tinea

FIGURE 2. Moccasin type of tinea pedis. Collarets of scale on the lateral surface of the foot.

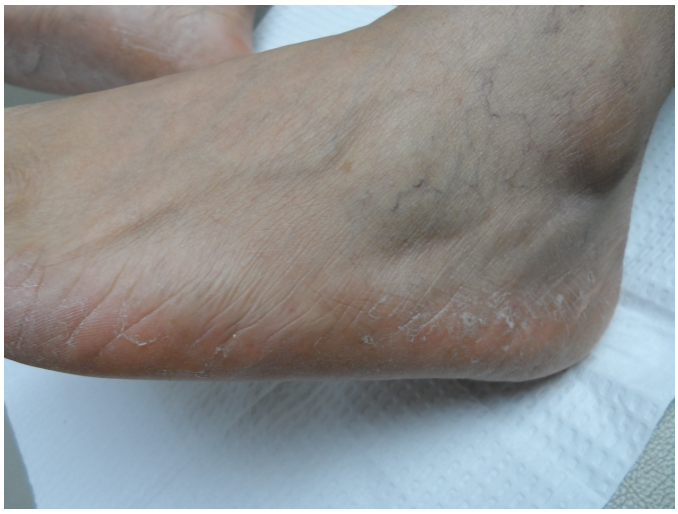
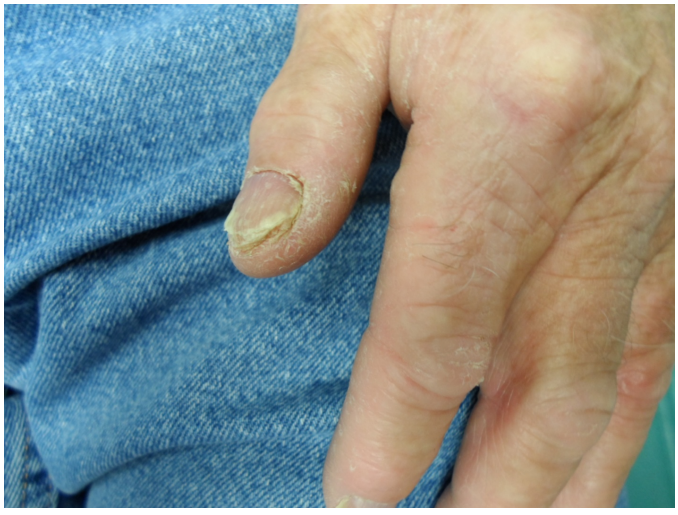


FIGURE 3. Tinea manuum and onychomycosis in a patient with tinea pedis. The presence of tinea manuum and onychomycosis increase the likelihood of concurrent tinea pedis.



pedis and a single hand with tinea manuum; or alternatively with 1 foot and 2 hands affected (Figure 3). Prolonged moccasin type of tinea pedis is a major risk factor for developing onychomycosis.

A less common presentation of tinea pedis is the vesicular type of tinea pedis where patients develop small vesicles on a background of erythema localized to the instep or medial plantar surface of their feet. These lesions are painful and pruritic, and develop far more rapidly than the other varieties of tinea pedis. Vesicular type of tinea pedis is the only subtype of tinea pedis that is exclusively associated with infection from organisms from the *T. mentagrophytes* complex infection, typically the zoophilic species.[14]

The acute ulcerative type is very rare and typically results from an exacerbation of the more common interdigital tinea pedis. Patients with acute ulcerative tinea pedis will present with ulcers and erosions in the web spaces between their toes, and these patients are at risk for secondary bacterial infection, which can be severe and debilitating. Patients may progress to develop cellulitis, lymphangitis, and fevers. The zoophilic variety of *T. interdigitale* is also implicated in this type of tinea pedis.[14] Patients presenting with this type of tinea pedis are more likely to have concurrent diabetes, immunosuppresion, or peripheral vascular disease.

In addition to the above mentioned clinical patters of infection, a noteworthy proportion of people are carriers of the dermatophytes implicated in tinea pedis. In epidemiological studies, up to 14% of patients may have occult tinea pedis as defined by "normal" appearing feet, no symptoms concerning for tinea pedis, and a positive mycologic culture from scrapings of feet.[20] Clinical findings of tinea pedis can be subtle, especially for moccasin type tinea pedis, which may have only a fine collarette of scale. Although not a distinct subtype of tinea pedis, it is still important for the clinician to be aware of the concept of occult tinea pedis because it is quite common. Patients with occult infection may be considered to have an early stage of tinea pedis and are at risk of transmitting the infection to other people.[20] In one study, the overwhelming majority of patients with occult tinea pedis had onychomycosis; thus, patients with onychomycosis without clinical signs of tinea pedis ought to be evaluated for occult tinea pedis.[20]

A variety of clinical exam findings should alert the clinician to the fact that a patient may have tinea pedis (Table 4). Patients who have either tinea manuum or tinea cruris should be examined for possible tinea pedis, as these infections often coexist. Similarly, as mentioned above, patients who have onychomycosis of either the fingernails or toenails should be evaluated for tinea pedis. Indeed, only patients with occult or clinically present tinea pedis will develop onychomycosis, so all patients with onychomycosis should be evaluated for evidence of tinea pedis.[21]

Differential Diagnosis

The differential diagnosis for tinea pedis includes both infectious and non-infectious etiologies (Table 5). Intertrigo with secondary bacterial or candidal infection can masquerade

TABLE 4.

Clinical Clues for Tinea Pedis Infection
Tinea manuum on one or both hands
Tinea cruris
Presence of onychomycosis on fingernails and/or toenails

TABLE 5.

Differential Diagnosis for Tinea Pedis	
Disease	**Distinguishing Features**
Intertrigo from bacterial or Candidal infection	Typically presents with more striking erythema when compared with tinea pedis, and is also often found concurrently in multiple intertriginous areas.
Erythrasma	Will fluoresce coral red with examination under a woods lamp, while tinea pedis will not fluoresce.
Psoriasis	Patients will typically have psoriatic lesions elsewhere. However, patients with psoriasis can also have tinea pedis, so clinicians must maintain a high level of suspicion for this infection.
Dyshidrotic eczema	Patients often have a history of dyshidrosis, and lesions will be highly pruritic.
Shoe contact dermatitis	Dorsal foot is involved for shoe dermatitis, an area which is spared in tinea pedis.

as tinea pedis. Erythrasma is also on the differential diagnosis for tinea pedis. Examination of the feet with a woods light can help differentiate between erythrasma and tinea pedis as *Corynebacterium minutissimum* fluoresces coral-red while the dermatophytes implicated in tinea pedis do not fluoresce. Non-infectious differential diagnoses include psoriasis affecting the plantar foot, as well as dyshidrotic eczema if blistering is present on the foot. Shoe contact dermatitis must also be differentiated from tinea pedis; shoe dermatitis often affects the dorsal surface of the foot, while tinea pedis primarily affects the plantar and interdigital spaces.

Clinical Evaluation and Treatment

The diagnosis of tinea pedis should be confirmed prior to initiating treatment. A scraping from the plantar surface and interdigital space should be examined microscopically with potassium hydroxide (KOH) preparation for identification of fungal elements. Fungal culture is an academic exercise and not routinely performed, as identifying the fungal species will not alter treatment decisions.

Both topical and oral agents are available. As is true for other superficial mycological infections, tinea pedis should be treated with topical antifungal medication unless the infection is extensive and treatment-resistant. Patients should also be advised to disinfect their shoes and keep their feet clean and dry, wearing fresh socks daily, as these activities will diminish the risk of re-infection and improve the chances of a cure.

CONCLUSION

Tinea pedis is a very common condition that primarily affects adults. Four presentations are possible, including interdigital type, moccasin type, vesicular type, and ulcerative type. Patients may be asymptomatic and have occult infection; so it is important for the clinician to evaluate patients' feet for evidence of infection.

Successful treatment and eradication of tinea pedis can be challenging but is an important therapeutic goal. It is imperative to treat with topical antifungals as recommended by manufacturers since inadequately treated tinea pedis is likely to return. Chronic untreated or undertreated tinea pedis greatly increases a patient's risk of progressing to developing onychomycosis, which can be even more difficult to cure. Patients often self-discontinue treatment when their symptoms of tinea pedis have resolved. Educating both patients and internists who treat tinea pedis on the importance of continuing treatment for the entire recommended treatment period will greatly facilitate successful treatment of tinea pedis and lessen the risk of a patient developing complications from their infection.

DISCLOSURES

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Assessment of Dermatophytosis Treatment Studies: Interpreting the Data

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ABSTRACT

Antifungal therapy has recently enjoyed a resurgence of interest due to the introduction of a number of new formulations of topical drugs and novel molecules. This has led to a plethora of new publications on management of cutaneous fungal disease. This paper summarizes the various clinical trial factors which may affect the published data regarding how well antifungal drugs work. Understanding these parameters allows the healthcare provider to choose more rationally between available agents based upon an assessment of the evidence.

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INTRODUCTION

While difficult to quantify precisely, dermatophyte infections are both common and widely distributed worldwide.[1-7] Estimates based upon epidemiologic data from studies done in a variety of countries and continents suggest that some 20% to 25% of the world's population will be affected by superficial cutaneous fungal infections at least once during their lifetimes. Although fungal infections of the skin, hair, and nails can include those caused by candida species, the yeasts responsible for tinea versicolor, and nondermatophyte molds, the vast majority of such infections are due to dermatophytic organisms.[3,6] Thus, it is further estimated that 10% to 15% of the world's population will acquire at least one dermatophytosis.[6] In the United States, the most recent large scale investigation disclosed that, on average, over 4 million healthcare provider (HCP) visits directly related to cutaneous fungal infection occurred annually (range 3,583,590-6,754,460), the overwhelming majority due to dermatomycoses. This represented some 0.4% of all ambulatory healthcare visits during the time period under study.[5]

It is worth suggesting that this situation will not likely abate in the near future. Well accepted predisposing factors are not likely to decrease in either incidence or prevalence. Consider that onychomycosis is more prevalent among those with diabetes, peripheral vascular disease, and immunocompromise, and amongst the elderly.[8,9] In fact, the changing demographic characteristics of the population living in industrialized countries (mirrored in nations with emerging economies) includes: an increased number of elderly, an increased prevalence of obesity, diabetes, and peripheral vascular disease, a longer survival of those with endogenous immunocompromised conditions, and the commonplace administration of iatrogenic immunosuppression (including for solid organ transplantation). These factors may well lead to even more onychomycosis.[10] Since onychomycosis is frequently associated with tinea pedis, and fungal infections of the foot are often felt to be responsible for dermatophytoses of the groin and/or trunk,[11] it is clear that such fungal infections are not going to diminish in the coming decades.

Moreover, in addition to the foregoing, social mores may lead to expansion of dermatophytoses. For example, earlier and more frequent participation in sports activities and the "workout" craze among young adults could lead to more frequent micro-trauma to the nail unit and the pedal skin; and exposure to common public sports facilities (including showers and locker rooms) are also considered to predispose to onychomycosis.[12] Finally, virtually every factor enumerated above as having the potential to lead to a persistent epidemiologic onychomycosis problem has also, independently, been implicated in the development of tinea pedis, an equally important reservoir of pathogenic fungi.[13]

At present, there is little hope of eradicating dermatophytoses, as is the case with smallpox and nearly the case with polio. Faced with the inevitability of dermatophytosis, it is no wonder that the HCP remains in search of simple, safe, convenient, and reliable therapies. That search has been further complicated by the relatively recent development, approval, and marketing of newer antifungal agents. New formulations of pre-existing molecules (1% econazole nitrate foam and 2% naftifine hydrochloride cream and gel) and novel molecules (10% efinaconazole solution, 1% luliconazole cream, 2% sertaconazole nitrate cream, and 5% tavaborole solution) have recently appeared in the marketplace and re-awakened an interest in clinical mycology.

Should not picking the "best" agent for a given disease be as simple as going to the package insert of older and newer agents

and doing a quick comparison of cure rates? The unequivocal answer to this rhetorical question is a resounding "no." Why is this so? Official product information sheets enumerate the results of clinical trials. Such trials demonstrate, to the satisfaction of the Food and Drug Administration (FDA), that an agent is safe and "effective." However, there are marked differences between trials. Limitations inherent to published studies, including those submitted as pivotal trials, include most prominently differences in study design, data collection, and data analysis. Such differences make direct comparison of efficacy across clinical trials nearly impossible, and even preclude reliable systematic reviews and meta-analysis.

"Faced with the inevitability of dermatophytosis, it is no wonder that the healthcare provider remains in search of simple, safe, convenient, and reliable therapies."

The purpose of this article is to remind the HCP of the various parameters to consider when attempting to assess the data on any of the approved agents for dermatomycoses. While emphasizing recently approved agents, a critical approach to antifungal studies is widely applicable: to new agents as well as old, oral as well as topical, and across all types of dermatophyte infection.

When and Where Study Conducted

There is a rather remarkable disparity regarding which dermatophytes are predominant in differing geographic regions of the globe; and the exact etiologic organisms have indeed undergone dramatic and significant changes during the twentieth century.[3,7] Several well-known examples of this phenomenon include the replacement of *Microsporum audouinii* by *Trichophyton tonsurans* as the leading cause of tinea capitis in the United States, as well as the replacement of *Epidermophyton floccosum* by *T. rubrum* as the leading cause of tinea cruris.

Thus, it is important to consider when and where antifungal studies were performed in order to assess the data. Studies done many years ago may not reflect currently dominant etiologic fungi and, even if comparative in nature, will not include the newer agents enumerated previously. Moreover, as the location of antifungal studies will determine which species are predominant, the results may or may not be relevant to a given clinician. For example, the results of a clinical trial involving tinea capitis done in Iran, Libya, Palestine, Spain, or Sweden would be nearly irrelevant for an American HCP because *Trichosporum violaceum* is quite common in those nations but vanishingly rare in the U.S.[7,14]

Finally, one other point is intuitively obvious. The location of a study may greatly influence the ethnicity of the participants. It may not be possible for an American practitioner, serving a community of Caucasian, Afro-American, Asian, and Hispanic individuals, to extrapolate antifungal treatment decisions based upon the results of a clinical trial done in Iceland, a land of remarkable homogeneity (Norse and Celtic ancestry). There is certainly medical evidence that some drugs have significantly different pharmacokinetic and pharmacodynamic properties in varying racial and ethnic groups.[15] To the extremely limited extent that such knowledge exists relating to antifungal agents, a HCP must consider trial subjects' race and ethnicity when assessing clinical trial data and its relevance to his/her own practice.

Study Design

There are a few critical parameters related to how a study was actually conducted which may impact reported data. These include whether the study was open label or double-blinded, prospective or retrospective, single-center or multi-center, and compared with placebo or another established active agent.

Many initial proof-of-concept and some subsequent trials are open label, especially in Phase 2 investigations. It was admirably demonstrated that, at least for onychomycosis, the efficacy rates of open label studies are substantially higher compared with randomized controlled trials, and may therefore overestimate actual cure rates.[16] This is likely due to bias engendered when both subjects and investigators "believe" that the study agent is effective (or an open label study would not be performed in the first place). A single center study is more likely to have bias (either favorable or unfavorable) than when multiple, geographically diverse centers are involved.

Finally, it has been clearly and repeatedly demonstrated that all approved antifungal drugs are superior to a placebo (including vehicle) control.[17] While this is the traditional standard for conducting antifungal studies, and is still an acceptable manner in which to obtain FDA approval, going forward most impactful antifungal studies should be done as a direct comparison between 2 active agents. In the absence of well-performed and adequately powered head-to-head treatment investigation, the real difference in efficacy between 2 agents designed to treat the same dermatomycosis may not be assessable.[17] Even when head-to-head studies ostensibly compare the same drugs for the same disease, there may be quite different results.[18-20] Such differences may relate to study design features, inherent study flaws, and the manner of efficacy data collection and reporting (discussed below).

Inclusion and Exclusion Criteria

A critical appraisal of antifungal trial data would certainly start with ascertaining who was (and who was not) allowed to enroll,

assuming an unequivocal pre-study demonstration of fungal disease (preferably with speciation to allow post-hoc efficacy data analysis). The first question should be: exactly *what disease* was being treated? Most studies of tinea pedis address only the interdigital form, and FDA approval is based upon this single morphologic type.[21-23] Nonetheless, there are other forms of tinea pedis (moccasin-type and vesiculobullous) for which FDA approval is lacking, even though some degree of efficacy was suggested during clinical trials with naftifine.[24,25] Similarly, clinical trials for oncyhomycosis are conducted on the distal and lateral subungual form of disease (DLSO).[26-32] As is true of tinea pedis, there are other types of onychomycosis aside from the most common: proximal subungual, white superficial, total dystrophic, endonyx, and mixed.[33] However, since the clinical trials address only DLSO, and FDA approval only includes DLSO, there is no way for the HCP to know how likely it is that either any of the older or newer agents will be efficacious for these less common presentations.

Another inclusion criteria of major interest, especially with reference to onychomycosis trials, is the subjects' allowable (and actual) age. Since nails grow more slowly with age, less efficacy might be perceived if a trial enrolled a substantial number of older patients compared with similar studies. As it turns out, although the tavaborole study had the oldest enrollee in any onychomycosis trial (aged 88 years),[27] virtually all the onychomycosis studies to date have had a mean age of study participants within a narrow range (43-53),[26-32] essentially negating this potentially confounding factor.

Another potential problem in the inclusion criteria in onychomycosis is the extent of involvement of the target nail(s). Interestingly, the trials involving oral agents have routinely had a higher percentage involvement (50%-75%) compared with the trials of topical antifungal agents (35%-40%). Since "complete cure" rates are reportedly higher for the oral drugs, apparently this difference in percentage of nail plate involvement does not place the oral antifungals at a major disadvantage.

Aside from inclusion criteria, reported antifungal efficacy may need to be interpreted in terms of exclusion criteria. For example, in onychomycosis studies, the HCP should take note if significant concomitant tinea pedis was sought and, if found, served as an exclusion. It is intuitive that a topical therapy (more so than a systemic one) may not work as well in treating onychomycosis if there is concurrent tinea pedis present to serve as a source of reinfection. Conversely, a pragmatic consideration might be to treat the tinea pedis concurrently with the onychomycosis in the hopes of securing a more beneficial outcome.[34]

Antifungal Studied

It goes without saying that certain studies would be of little value to select audiences. For instance, the American clinician cannot readily use data to facilitate therapeutic choices, when the agents (or one of the agents) being studied is bifonazole, tioconazole, amorolfine, fenticonazole, or flutrimazole, as these drugs are neither FDA-approved nor available over-the-counter in the U.S.

Clinical Trial Methodology

There are many methodological factors that might alter reported efficacy outcomes in antifungal studies. In fact, a classic publication reviewing the general subject of clinical studies provides a quantitative scoring system to assess the quality of randomized controlled trials.[35] It is considerably beyond the intent and scope of this article to apply this scoring system to the vast universe of antifungal studies. Moreover, this has already been done previously, in part, for both onychomycosis and other dermatophytosis clinical trials.[17,36] Suffice it to say that clinical studies involving more recently approved antifungal preparations are, according to the Jadad scale criteria,[35] acceptable, being of medium to high overall quality.[21-28,37,38] Despite the latter, there is at least one methodological feature which may confound the HCP ability to assess efficacy data, and that feature is study duration.

> "Should not picking the "best" agent for a given disease be as simple as going to the package insert of older and newer agents and doing a quick comparison of cure rates? The unequivocal answer to this rhetorical question is a resounding "no."'"

Consider that during onychomycosis treatment, visible clearance occurs as a healthy nail plate replaces a diseased one. This process requires about 12 to 18 months for a toenail.[36] All American trials involving recently approved topical treatments for toenail onychomycosis were conducted over 48 to 52 weeks.[26-28] By not taking into account the fact that it may well take over 70 weeks to grow out a toenail fully, the roughly 1 year of study may introduce uncertainty into the stated efficacy data. For example, if the drug has a reservoir effect, then the efficacy may actually be better than reported at 48 to 52 weeks because the agent continues to work as the healthy nail finally finishes growing out. Conversely, the drug's effect may be optimized by administration past 48 weeks to insure drug presence as the nail completes its full growth. In the latter case, efficacy results are actually overstated, since residual infection and/or relapse may occur in the time period between study's conclusion (48-52 weeks) and probable date of complete toenail regrowth (up to 72 weeks).

With other dermatomycoses, such as tinea pedis, tinea cruris, and tinea corporis, the longer the interval between cessation of trial drug administration and the final outcome assessment, the more meaningful the result; positive results demonstrated 14 or more days from the conclusion of therapy are considered sustained.[20] The most ambitious attempts to compare efficacy between various topical antifungal drugs, as well as between several classes of topical antifungals, found that: 1) There is no significant difference among classes of antifungal drugs in terms of short term efficacy, safety, and tolerability; and 2) The allylamine agents (and related benzylamine, butenafine) show a higher degree of sustained cure compared with classic imidazoles.[17,20] Of course, these analyses included neither newer formulations of older molecules (such as 2% nafitifine and 1% econazole nitrate foam) nor, and most importantly, new molecules (such as luliconazole); thus, while well done and comprehensive, such systematic reviews are already somewhat outmoded.

"Unless nomenclature is defined in an unequivocal manner, interpretation of trial results becomes quite precarious."

The trend in recent years has been toward shorter treatment durations for non-onychomycosis dermatophytoses. For example, whereas 4 weeks of topical treatment were once considered necessary to achieve clinically meaningful benefits in tinea pedis, newer agents (1% luliconazole and 2% naftifine) prove satisfactory after only 2 weeks of therapy.[21,24,25] Luliconazole cream has even been successfully administered once daily for only 1 week for the treatment of tinea cruris.[37]

Mycological Considerations

Participation as a study patient for all clinical trials involving dermatophytes requires clear proof of pre-treatment fungal infection. This generally requires both a positive potassium hydroxide (KOH) preparation and a positive culture. The latter also delineates which species are being treated. There is little controversy in this aspect of antifungal trials. However, the author foresees a day in the not too distant future where molecular diagnosis will be become the gold standard (eg, real time polymerase chain reaction).[40,41] This may facilitate study recruitment and re-define efficacy results due to the greater sensitivity for dermatophyte detection.

At the conclusion of the study, it is standard to report, either as a primary or secondary end point, mycological cure rates. As pointed out by Gupta and co-workers, this may also be called mycologic success, mycologic response, mycologic efficacy, or even "fungus free" or "eradication."[42] This efficacy parameter typically implies both negative KOH preparation and negative fungal culture. This definition is fairly straightforward in both tinea and onychomycosis trials. Rarely, mycological cure may be defined as negative culture or negative microscopy *alone*, a less stringent standard.[43,44]

It should also be noted clearly that mycologic cure is *not* synonymous with visually determined clinical cure. From the perspective of the patient, a normal appearing nail and lack of pain (if present pre-treatment) are the measures of successful onychomycosis treatment. Similarly, from the patient perspective, normal appearing skin (loss of erythema and scaling) and elimination of bothersome itching are the measures of successful therapy for tinea pedis, tinea cruris, and tinea corporis. From the HCP perspective, however, mycologic cure ensures that once-infected skin or nail has been successfully treated.[42] Thus, it may be advisable to counsel the patient that "successful" therapy, especially of chronic fungal infections such as onychomycosis and tinea pedis, may not result in completely normal appearing nail or skin.

There is a final, perhaps theoretical, issue worth mentioning. In order to achieve mycological cure, both KOH and culture must be negative. How many trial patients fail to achieve this goal because post-treatment specimens fail to grow (negative culture) but still possess demonstrable hyphae microscopically? While this is somewhat speculative, this author suspects that the hyphae which are visible at the end of an antifungal trial may not be viable. In other words, is it possible that the fungal structure is still there, but that the fungus can no longer propagate or cause structural damage? This would lead to lower than real mycologic and complete clinical cure rates. This possibility needs to be addressed in a coherent manner.

Clinical Efficacy Considerations

It is in this realm where assessment of trial results becomes very difficult. There is simply no standardization across antifungal trials as to what parameters are measured, nor as to the terminology used to describe what was, in fact, measured. Unless nomenclature is defined in an unequivocal manner, interpretation of trial results becomes quite precarious.

Complete cure typically means mycological cure (negative KOH and culture) and total absence of signs (onycholysis, subungual debris, discoloration). While this is the most uniform of all criteria, this may be difficult to achieve, as noted in the previous section of this paper. Thus, it is not surprising that investigators have creatively employed a dazzling and bewildering variety of terms or narrative phrases to express the fact that the patient is "better" than before therapy, if not 100% normal. Historically, for onychomycosis, the most common clinical efficacy measurements have included the items listed in Table 1. This is by no means all-inclusive. Even a cursory glance at Table 1

reveals several important items. First, the exact same terms (such as "treatment success") may be defined differently. Secondly, some investigators relied heavily on visual inspection to determine benefit from drug administration. I would submit that the best assessment of onychomycosis response to treatment includes both clinical *and* mycologic parameters, regardless of what terminology is used. Finally, almost all the assessments of the percentage of affected nail infected (both before and after therapy) are based on a subjective, visual inspection. The agreement between objective planimetry and subjective estimation is actually quite good (within 10% in 92% of cases seen by experienced investigators).[47] Nonetheless, a better practice would be routine use of computerized measurement from a photograph or digital image; this would reduce the likelihood of error and promote more accurate efficacy assessments. A final confounding factor is that efficacy assessments measurements are typically performed on a single target nail, usually the great toenail. While there is usually good correlation between the response of the target nail and response of other nails, this is not always the case.

Assessment of data for tinea pedis, tinea cruris, and tinea corporis studies is somewhat more straightforward due to the uniformity of efficacy parameters. Both older and modern studies include complete cure (sometimes called complete clearance) as the primary endpoint. This consists of negative mycology (KOH and culture) and total absence of signs (erythema, scaling) or symptoms (pruritus). Mycologic cure is virtually always shown as a secondary endpoint.

Finally, essentially all studies calculate effective treatment (also known as treatment effectiveness), which consists of negative mycology and no to mild residual signs or symptoms.[21-25,37,38] Several studies allow up to mild erythema and scale, but require no residual pruritus.[21,23,37] The latter seems optimal, since itching is often the factor driving the patient to seek medical attention. With a quick glance at the data, the HCP will note that there is not much variation in rates for these 3 measurements between drug classes. One item to note is how long after the study was the final assessment made; in other words, is there evidence of sustained benefit?

FINAL CONSIDERATIONS

Despite the HCP's careful and individualized selection of treatment options, there will be failures and recurrences of dermatomycoses. Even when the infecting fungus ostensibly has been entirely eradicated by antifungal therapy, patients remain at risk for recrudescence. This phenomenon may be due to genetic predisposition, reinfection from within the household, reinfection from shared facilities, underlying co-morbid diseases (eg, diabetes), endogenous or iatrogenic immunocompromise, or, most rarely, mycological resistance.[48-51] Obviously,

TABLE 1.

Clinical Efficacy Measurements for Onychomycosis			
Terminology	**Definition**	**Synonyms**	**Representative References**
Complete cure	Normal nail Negative mycology	Treatment cure	26-28
Almost complete cure	< 5% residual abnormality Negative mycology		26
Almost complete cure	< 10% residual abnormality Negative mycology	Treatment success	27, 28
Overall success	Clear or Markedly Improved Negative mycology	Overall response	30-32
Almost completely clear nail	< 10% residual abnormality	Treatment success	26, 27, 29
Almost completely clear nail	< 5% residual abnormality		28
Clinical success	Clear or markedly improved (no specified % residual)	Clinical response	30-32
Numerical percent reduction in affected nail	Photography with computerized planimetry		28
Numerical percent reduction in affected nail	Visual assessment		44
Descriptive degree of improvement	Cured, markedly improved, improved, same, worse		45
Number of mm of normal nail outgrowth	Measured from posterior nail fold; 4 mm or 5 mm considered response		19, 26, 46

patients must be warned about the tenacious nature of some dermatomycoses.

DISCLOSURES

Theodore Rosen MD has received honoraria from the following pharmaceutical companies with respect to participation in advisory board meetings: Anacor, Galderma, Merz, and Valeant.

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1. Azole antifungals are thought to do the following:

   a. Inhibit production of the fungal cell wall
   b. Block conversion of squalene to lanosterol
   c. Reduce the amount of available ergosterol for production of a healthy fungal cell membrane
   d. Inhibit the lanosterol 14α-demethylase that converts egosterol to lanosterol

2. The most common cause of dermatophyte infections worldwide is/are:

   a. *Epidermophyton floccosum*
   b. *Trichophytum rubrum*
   c. *Microsporum canis*
   d. *E. floccosum* and *T. rubrum*

3. Risk factors for the development of onychomycosis include:

   a. Female gender, older age, smoking
   b. Frequent washing the feet and changing socks and shoes
   c. Presence of concurrent tinea pedis
   d. Nail salons, public gyms and showers, and cool climates

4. Factors that may help explain the efficacy of efinaconazole include all except:

   a. Both transungual delivery and spread around the nail to the subungual air space
   b. Low keratin binding affinity
   c. Low surface tension
   d. Need for removal of build up and nail debridement

5. Which of the following statements is false?

   a. Treatment of tinea pedis as the same time as onychomycosis actually enhances the effect of efinaconazole on the nails
   b. Treating onychomycosis early does not offer an efficacy advantage compared with delaying treatment
   c. Efinaconazole has been shown to be as effective in treating older patients and diabetics as it is in treating younger patients and those without diabetes
   d. Failure to treat onychomycosis can predispose patients to fungal infection spread or bacterial superinfection, which may lead to cellulitis

6. True or False: When eliminating the causative fungus in tinea pedis, the nail will always return to its normal appearance as long as you wait long enough, sometimes up to one year.

   a. True
   b. False

7. Side effects of untreated tinea pedis and onychomycosis include all except:

   a. Spread to close contacts and other body parts
   b. Development of asthma, eczema, urticaria, and erythema nodosum
   c. Worsening of glycemic control in diabetic patients
   d. Significant effect on quality of life

8. When tinea pedis infection is asymptomatic, patients may be unaware of the presence of this infection. Which of the following, if present, should clue the clinician into the fact that a patient may have tinea pedis and prompt examination of the patient's feet?

   a. Hand dermatitis
   b. Tinea manuum
   c. Recent travel history
   d. Distant history of previously treated tinea pedis

9. A patient with tinea pedis fails to improve after appropriate treatment and thus a fungal culture is performed. Results from the fungal culture are notable for the presence of *Neoscytalidium dimidiatum*. How should these results be interpreted?

   a. *N. dimidiatum* is a contaminant and can be disregarded
   b. The fungal culture should be repeated
   c. *N. dimidiatum* is the causative organism and is highly resistant to treatment
   d. This can be a normal finding and is not indicative of active tinea pedis

10. A patient presents with a highly inflammatory type of tinea pedis on the instep of the foot, and a zoophilic strain of *Trichophyton mentagrophytes* is isolated from mycology culture. What is the most appropriate advice to give the patient in order to prevent recurrence of this type of tinea pedis?

    a. The patient should be advised to avoid swimming in community swimming pools
    b. Household members should be examined as this type of tinea pedis is typically spread via fomites in the bath
    c. The patient should be screened for diabetes mellitus and referred for appropriate treatment if indicated
    d. The patient's pet rodent should be evaluated by a veterinarian and treated for a tinea infection

11. Untreated or undertreated tinea pedis can place the patient at risk for complications, some of which may result in significant morbidity. All of the following are potential complications from chronic tinea pedis except:

    a. Tinea manuum
    b. Onychomycosis
    c. Secondary bacterial infection
    d. Tinea capitis

12. The most stringent of clinical antifungal trial outcomes is:

    a. Clinical response
    b. Mycologic cure
    c. Complete cure
    d. Effective treatment
    e. "Markedly improved"

13. When assessing clinical outcomes relating to antifungal drugs, factors to carefully scrutinize are:

    a. Dosing duration
    b. Open label vs double-blinded
    c. Mycologic cure includes both culture and microscopy
    d. Clear definition of primary and secondary endpoints
    e. All of the above

14. Which statement is true regarding antifungal clinical trials?

    a. Complete cure (or complete clearance) is the most common primary endpoint
    b. Effective treatment is almost never a secondary endpoint
    c. Effective treatment is defined as either positive microscopy or culture at study end
    d. Onychomycosis trials have widely accepted and standardized efficacy measures
    e. None of these statements are true

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Post-test Answer Key

1	2	3	4	5	6	7	8	9	10	11	12	13	14

☐ I certify my actual time spent to complete this educational activity to be: _____

☐ I participated in the entire activity and claim 1.5 *AMA PRA Category 1 Credit*™.

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree	*2 = Disagree*	*3 = Neutral*	*4 = Agree*	*5 = Strongly Agree*

Was timely and will influence how I practice
1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

Provided new ideas or information I expect to use
1 2 3 4 5

Addressed competencies identified by my specialty
1 2 3 4 5

Avoided commercial bias or influence
1 2 3 4 5

Impact of the Activity

Name one new strategy you learned as a result of completing this activity:

_____

Name one thing you intend to change in your practice as a result of completing this activity:

_____

Additional comments about this activity:

_____

Please list any topics you would like to see addressed in future educational activities:

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