

New Topical Therapeutic Options in the Management of Superficial Fungal Infections

Joshua A. Zeichner MD
Department of Dermatology, Mount Sinai Hospital, New York, NY

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.

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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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AUTHOR CORRESPONDENCE

Joshua A. Zeichner MD
E-mail:..... joshua.zeichner@mountsinai.org