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New Advances in the Topical  
Treatment of Tinea Pedis,  
Tinea Cruris, and Tinea Corporis

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## EDITORIAL

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*Leon H. Kircik MD*

## ORIGINAL ARTICLE

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- s165 **Optimizing Topical Antifungal Therapy for Superficial Cutaneous Fungal Infections: Focus on Topical Naftifine for Cutaneous Dermatophytosis**  
*James Q. Del Rosso DO FAOCD and Leon H. Kircik MD*

# Put Your Best Foot Forward: Advances in the Management of Tinea Pedis



Leon H. Kircik MD

From a nuisance itch with mild erythema to painful, fissured, inflammatory eruptions that may limit function, cutaneous dermatophyte infections present in a variety of ways, affecting a large population of patients. In fact, Americans make more than 4 million physician visits each year for dermatophytosis.<sup>1</sup> Despite intriguing research findings, such as the recent discovery of the genetic factors that predispose our patients to fungal infections,<sup>2</sup> most dermatologists are more intently focused on overcoming the day-to-day clinical challenges of treating tinea pedis, which is the most common of all the superficial dermatomycoses, and the predecessor to the development of toenail onychomycosis (tinea unguium).

Recent analysis of data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for the period from 1995 to 2004—the same analysis that documented more than 4 million physician visits for dermatophyte infections annually—found that improper treatment of tinea pedis, tinea corporis, and tinea cruris is common and expensive.<sup>1</sup> The selection of inappropriate agents is just one impediment to effective care. Therapeutic non-adherence by patients, and especially failure to continue therapy until the infectious organisms are completely eradicated, are additional challenges. Reinfection is common, especially in individuals prone to pedal carriage of *Trichophyton rubrum*.

A novel topical antifungal formulation is a welcome new option in the treatment of topical dermatophytosis. Naftifine 2% cream is a topical allylamine antifungal agent for the treatment of superficial dermatomycoses. Previously, naftifine has been available in a 1% gel. A study of naftifine 2% cream for the treatment of tinea pedis found that 2 weeks of treatment was significantly more effective than vehicle and equivalent to 4 weeks of treatment with naftifine 1% gel.<sup>3</sup> In a trial of naftifine 2% cream for tinea cruris, 25% of subjects achieved complete cure in 4 weeks. Overall, 60% of subjects treated with naftifine 2% cream achieved treatment success vs just 10% of controls.<sup>4</sup>

Naftifine is a versatile topical antifungal agent with a therapeutic reservoir in skin post-therapy. In vivo, it is fungicidal and potent against a broad spectrum of dermatophyte fungi and provides good activity against *Candida* and *Aspergillus* species. It also exhibits activity against gram-negative and gram-positive bacteria that may potentially colonize toe web spaces secondarily, but is not recommended as a primary treatment for bacterial infections.<sup>5</sup> With broad antimicrobial activity, naftifine 2% cream offers a cosmetically elegant, once-daily topical treatment option for dermatomycoses. The new 2% strength allows reduced application frequency in addition to a shorter treatment period for tinea pedis compared with other topical antifungals. This may lead to better compliance and better treatment outcome in our patients. Given the prevalence of dermatophyte infections in the United States, and the challenges of management, the availability of an effective topical therapy that permits convenient once-daily and shorter therapy duration is welcome in our daily practices.

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# Optimizing Topical Antifungal Therapy for Superficial Cutaneous Fungal Infections: Focus on Topical Naftifine for Cutaneous Dermatophytosis

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## ABSTRACT

Superficial cutaneous fungal infections (SCFIs) are commonly encountered in clinical practice in the United States, and comprise infections of the skin by dermatophytes and yeasts. The most common organisms causing SCFI are dermatophytes, especially *Trichophyton spp*. With the exception of onychomycosis and tinea capitis, most cases of SCFIs are amenable to properly selected topical antifungal therapy used over an adequate period of time.

A variety of topical antifungal agents are available for the treatment of SCFIs, and they encompass a few major chemical classes: the polyenes (ie, nystatin), imidazoles (ie, ketoconazole, econazole, oxiconazole, etc), allylamines (ie, naftifine, terbinafine), benzylamines (ie, butenafine), and hydroxypyridones (ie, ciclopirox). The 2 major classes that represent the majority of available topical antifungal agents are the azoles and the allylamines. Overall, the allylamines are superior to the azoles in activity against dermatophytes, although both are clinically effective. The reverse is true against yeasts such as *Candida spp* and *Malassezia spp*, although topical allylamines have proven to be efficacious in some cases of tinea versicolor and cutaneous candidiasis.

Naftifine, a topical allylamine, is fungicidal in vitro against a wide spectrum of dermatophyte fungi and has been shown to be highly effective against a variety of cutaneous dermatophyte infections. Rapid onset of clinical activity and favorable data on sustained clearance of infection have been documented with naftifine. The more recent addition of naftifine 2% cream has expanded the armamentarium, with data supporting a clinically relevant therapeutic reservoir effect after completion of therapy.

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## INTRODUCTION

Superficial cutaneous fungal infections (SCFIs) are commonly encountered in clinical practice in the United States.<sup>1</sup> The majority of etiologic fungal organisms associated with the common SCFIs are caused by dermatophytes, including *Trichophyton spp* (especially *Trichophyton rubrum*), *Microsporum spp*, and *Epidermophyton floccosum*.<sup>1-3</sup> Dermatophyte infections can affect both children and adults, and demonstrate an affinity for keratin with the ability to infect glabrous skin, hair-bearing skin, hair shaft, and the nail unit.<sup>3</sup> Specific dermatophyte infections will be discussed in more detail later and are a primary focus of this article. The most common SCFIs induced by yeasts are tinea versicolor, which is caused by a variety of *Malassezia spp*, and cutaneous candidiasis, most often caused by *Candida albicans*.<sup>4-9</sup>

### Overview of Superficial Cutaneous Fungal Infections

Although this article will focus on cutaneous dermatophyte infections, an overview of the common SCFIs is very relevant as there can be overlap in the differential diagnosis and available therapeutic options.

### Cutaneous Yeast Infections

#### Tinea versicolor

Tinea versicolor, also referred to as pityriasis versicolor, predominantly affects predisposed adults of either gender, who periodically experience conversion of the commensal saprophytic yeast form (*Pityrosporum spp* such as *Pityrosporum ovale*) to its mycelial (hyphal) form (*Malassezia spp*), with subsequent proliferation most commonly on the trunk, proximal extremities, and lower neck.<sup>4,5</sup> Among the more common mycelial forms identified on patients with tinea versicolor are *Malassezia globosa* (50%-60%), *Malassezia sympodialis* (3%-59%), *Malassezia furfur* (1%-10%) and *Malassezia slooffiae* (1%-10%), although the involved species may vary geographically, and the prevalence is markedly increased in tropical climates with high ambient humidity.<sup>4,5</sup> Patients presenting with tinea versicolor are generally immunocompetent, and the factors that incite initial emergence and subsequent recurrences are usually inexplicable.<sup>4,5</sup> However, immunocompromised patients, such as those with human immunodeficiency virus (HIV) infection, are predisposed to the development of tinea versicolor, tend to exhibit more widespread

**FIGURE 1.** Clinical presentation of common superficial cutaneous fungal infections.

involvement, and are often more refractory to conventional therapies and/or exhibit frequent recurrence.<sup>7</sup>

Importantly, due to the commensal nature of the causative organism, recurrences of tinea versicolor are common after a course of effective therapy in both immunocompetent and immunocompromised populations, with a recurrence developing usually within 2 years of a previously treated episode. The clinical manifestations are somewhat variable and the eruption is usually asymptomatic, with mild pruritus reported in occasional cases.<sup>5,6</sup> The common clinical presentations are multiple tan, salmon-colored, or light pink patches with fine (pityriasiform) scaling, which become hypopigmented as compared with non-affected skin when a tanning response occurs after ultraviolet light exposure, or in individuals with darker skin color (Figure 1). Patients with dark skin can present with hyperpigmented patches or with multiple small truncal macules that appear to be perifollicular.<sup>5,8</sup> A potassium hydroxide preparation (KOH) of scales obtained from affected areas demonstrates short hyphae and clusters of round spores (“ziti and meatballs”), although organism growth is not sustained on conventional fungal cultures, including a dermatophyte test medium (DTM).<sup>4,6</sup> After successful clearance of the proliferated yeast organism, it may take several weeks for the variations in skin color from previously affected and non-affected sites to match up visibly, a point that is important to communicate to patients.<sup>5</sup>

### Candidiasis

Cutaneous candidiasis (CC), which can include some forms of mucocutaneous infection, is most often caused by *Candida albicans* and includes presentations more commonly seen in office dermatology practice such as *Candida* intertrigo (Figure 1), *Candida* genital infections (balanitis, vulvovaginitis), oral candidiasis (acute and chronic), angular cheilitis (perleche), *Candida* paronychia, and in some cases diaper dermatitis.<sup>6,9,11</sup> Less common CC presentations encountered in dermatology offices are “erosio interdigitalis

blastomycetica” (usually third web space of a hand), *Candida* glossitis (atrophic; painful), congenital cutaneous candidiasis (acquired in utero; manifests first day after birth; diffuse), neonatal candidiasis (onset days after birth), acute denture stomatitis (often coexists with perleche), and *Candida* folliculitis (rare; affecting hair-bearing areas of face).<sup>9-11</sup> However, other species that are believed to behave as pathogens in some cases have been identified from skin and nails, such as *C parapsilosis* and *C tropicalis*, which were identified in 29.1% and 7.8% of cases, respectively.<sup>10</sup>

Cutaneous candidiasis usually emerges as an opportunistic infection due to local factors and/or systemic factors that promote colonization of skin or mucosa.<sup>7,9,11</sup> Involvement of naturally intertriginous areas (ie, axillae, inframammary, groin, mouth corners), other skin folds (ie, abdominal apron), and interdigital web spaces are cutaneous sites of predisposition, although sometimes other skin sites can be affected.<sup>6,9</sup> Local factors promoting colonization and infection are occlusion, accumulated moisture, maceration, structural compromise of the epidermal barrier, and other aberrations of epidermal barrier function such as alkaline skin pH (ie, in newborns), alterations in cutaneous microbial flora, and impairments of the antimicrobial and immune response barriers of the epidermis.<sup>9</sup>

**"The more recent addition of naftifine 2% cream has expanded the armamentarium, with data supporting a clinically relevant therapeutic reservoir effect after completion of therapy."**

Systemic factors that may predispose a patient to colonization and infection with *Candida spp* are recent exposure to antibiotic or corticosteroid therapy, diabetes (especially when poorly controlled), or immunosuppression by underlying disease states or specific therapies.<sup>7,9,12</sup> The multiple clinical presentations of CC, which also include chronic mucocutaneous types of infection, are beyond the scope of this article and are well described elsewhere.<sup>6,9</sup> Nevertheless, the common clinical presentation of *Candida* infection involving the skin, *Candida* intertrigo, is described as briskly erythematous patches/plaques that are often tender, painful, and/or pruritic, can be denuded and exudative in some cases due to friction, may exhibit some scaling toward the edges, and typically exhibit “satellite lesions,” which are erythematous papules and pustules (Figure 1).<sup>6,9</sup> When *Candida* intertrigo affects the groin region of males, the scrotum may be affected, which differs from dermatophyte infection (tinea cruris) where scrotal involvement is very rarely seen.

### Cutaneous Dermatophyte Infections

Other than tinea capitis, cutaneous dermatophyte infections (CDIs) are relatively uncommon in children; hence this article



**FIGURE 2.** Variations in appearance of cutaneous dermatophyte infections.

will focus on CDIs in adult patients. These are caused by *Trichophyton spp*, *Microsporum spp*, and *Epidermophyton floccosum*, and they most often involve non-scalp skin and nails. Scalp infection (tinea capitis) is far less common in adults, but has been reported. Onychomycosis caused by a dermatophyte (tinea unguium) affecting the nail bed and nail plate, and sometimes also the nail matrix, is a very common SCFI that increases with age in adulthood, most often affects toenails with or without fingernail involvement, and is more refractory to therapy than CDIs involving glabrous or hair-bearing skin. Dermatophyte-induced onychomycosis frequently necessitates use of an oral antifungal agent to achieve clearance, is not fully responsive to therapy in many cases, is often recurrent even after complete clearance with antifungal therapy, and is rare in children and adolescents, including those presenting with nail dystrophy that is clinically suggestive of a fungal infection.<sup>13-15</sup>

A given CDI, which hereafter refers to those not involving scalp (skin, hair follicles, hair shaft) or nails, is categorized by the anatomic location affected, with the most common being tinea pedis (feet), tinea corporis (body except for scalp, face, hands, feet, and nails), and tinea cruris.<sup>16-19</sup> Other CDIs include tinea faciei (face), tinea barbae (male beard area), tinea manus (hands), tinea profunda (deeper dermatophyte infection with follicular involvement), and tinea incognito.<sup>16,18,20</sup> The latter refers to a CDI that is altered in appearance by application of a topical corticosteroid (TCS). Tinea profunda often presents as tinea incognito because of "local immunosuppression" from TCS application, or systemic immunosuppression, which leads to unchecked fungal proliferation with deeper skin penetration of organisms, including follicular involvement.<sup>21</sup>

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.<sup>6,16,17</sup> The classic presentation is an annular patch or thin plaque with

**FIGURE 3.** Three major clinical presentations of tinea pedis (interdigital, vesicular, dry plantar).

an accentuated scaly edge and a tendency for central clearing that corresponds to the magnitude of erythema intensity and is reflective of the host inflammatory response (Figure 2).<sup>6,16,17</sup> Host-related factors include genetic predisposition, general health status, and immune status. Exogenous factors include topically applied agents (ie, antifungal agents, TCS, calcineurin inhibitors, barrier repair) and/or systemic medications (ie, corticosteroids, immunosuppressants) that can alter appearance, disease progression, or therapeutic response. Even the application of barrier repair/moisturizer agents to tinea corporis, pedis, or cruris can reduce scaling and create a more homogenous rather than "annular edge" appearance. The altered appearance may cause the clinician to not consider a dermatophyte infection, leading to misdiagnosis and improper treatment. Similarly, moisture accumulation and maceration of the groin folds can alter the appearance of tinea cruris, thus simulating frictional intertrigo, again resulting in incorrect diagnosis and treatment. Three major presentations of tinea pedis are well recognized (Figure 3).<sup>6,16,18,19</sup>

In some cases, specific fungal organisms tend to produce certain clinical presentations such as the common association of *T rubrum* and dry plantar ("moccasin") tinea pedis, or *Trichophyton mentagrophytes* and vesicular tinea pedis (Figure 3).<sup>6,16,18,19,22-24</sup> Many adults with dermatophyte infections exhibit an "immunologic blind spot" against dermatophytes, especially *T rubrum*, which predisposes them to chronic dermatophytosis, presenting primarily as dry plantar tinea pedis and toenail +/- fingernail tinea unguium as the "pedal source," with more diffuse involvement manifesting at other skin sites over time in some patients (Figure 4).<sup>23,24</sup> These patients are prone to recurrence of dermatophyte infections after successful clearance with treatment. Children with tinea pedis and/or tinea unguium are almost always from families that are affected by the genetic predisposition of chronic dermatophytosis.<sup>14,15,23</sup>

In adults or children with tinea corporis and/or tinea faciei, with or without tinea capitis, especially with erythematous

**FIGURE 4.** Chronic dermatophytosis (*Trichophyton rubrum*). Forty-seven-year-old male with multiple sites of involvement.**FIGURE 5.** Extensive cutaneous dermatophyte infection caused by direct skin contact with infected cat (*Microsporum canis*). Clinical involvement of neck, chest, and shoulders with brisk inflammatory plaques.

patches or with multiple plaques, consideration needs to be given to *Microsporum canis* as the pathogen, most often from an infected cat.<sup>16,25</sup> Affected patients often have lesions on the face, arms, neck, and /or thighs, and possibly other skin sites, where inoculation has occurred due to contact with the infected feline source while holding it. In cases caused by *M canis* or other zoophilic fungi, the lesions are often more briskly inflammatory and do not always present with the classic picture of annular patches that are typically anticipated when considering tinea corporis in the differential diagnosis (Figure 5). A fungal culture should be obtained that allows for organism identification, and animal contact sources should be considered in such cases. Also, a DTM can be obtained as an inexpensive “screening culture medium” to initially support fungal colony growth (Figure 5).<sup>16</sup> Once characteristic dermatophyte colonies grow on a DTM, this

can then be sent to a qualified mycology laboratory to identify the dermatophyte genus and species.

### Topical Antifungal Therapy

Most SCFIs and CDIs are amenable to topical antifungal therapy, especially in immunocompetent patients.<sup>3,6,9,16,17</sup> Although a review of all available agents is beyond the scope of this article, the imidazoles, allylamines, and ciclopirox (a hydroxypyridone) are the most commonly used prescription agents in dermatology.<sup>3,5,6,17,19,26-28</sup> The following is a focused review on topical naftifine for the treatment of SCFIs, especially DCIs.

#### *Topical Naftifine: What Did We Learn From The Development of 1% Formulations?*

Naftifine is an allylamine derivative formulated as a hydrochloride salt for topical administration in a 1% cream or gel, and more recently a 2% cream. Naftifine 1% gel (Naftin® Gel) is approved by the United States Food and Drug Administration (FDA), and it is indicated for twice-daily topical application for the treatment of tinea pedis, tinea cruris, and tinea corporis caused by *T rubrum*, *T mentagrophytes*, *T tonsurans*, and *E floccosum* (recommended duration 3-4 weeks).<sup>29</sup> Naftifine 2% cream (Naftin® Cream 2%) is FDA-approved with indication for once-daily treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *T rubrum* in adult patients ≥18 years of age (2 weeks treatment duration).<sup>30</sup> Much of the clinical data collected on topical naftifine evaluated the 1% formulations once or twice daily, with once-daily shown overall to be equivalent in efficacy to twice-daily application for CDIs.<sup>28-32</sup> Additional studies are also available with the 2% cream formulation and are discussed later.

The following properties of naftifine have been reported and appear to be clinically relevant:

- Naftifine exhibits in vitro fungicidal activity against a broad spectrum of organisms, including *T rubrum*, *T mentagrophytes*, *T tonsurans*, *E floccosum*, *M canis*, *M audouini*, and *M gypseum*, and also fungistatic activity against many *Candida spp.*<sup>29-31</sup> Naftifine clinical activity against staphylococcal and streptococcal pyoderms (n=30) has been demonstrated; however, it is not recommended that topical naftifine be used for the treatment of bacterial infections and such use is not FDA-approved.<sup>33</sup>
- The primary mechanism of action of topical naftifine is the arrest of fungal growth, increase in cell membrane fragility and permeability, accumulation of squalene, and disruption of the cell membrane. This occurs due to suppression of ergosterol biosynthesis via inhibition of squalene epoxidase, which differs from imidazole agents in being fungal sterol selective.<sup>28-31</sup> The observation of a more rapid onset of clinical improvement for CDIs, with topical naftifine vs imidazole antifungal agents, are likely related to the fungicidal effects of the former. However, reported anti-inflammatory properties may possibly be



clinically relevant, such as inhibition of chemotaxis, reduction in inflammation-associated skin temperature, markedly reduced erythema-wheel formation (intracutaneous histamine test), and inhibition of UV-induced erythema.<sup>26-28,31</sup>

- Naftifine is highly lipophilic, allowing for efficient penetration into the epidermis and hair follicles that are important target sites for treatment of CDIs and other SCFIs.<sup>31,32</sup> In an animal model of hair root trichophytosis, naftifine 1% cream produced complete organism eradication in 3 days, and was superior to econazole, which produced 80% mycological clearance in 7 days.<sup>34</sup>
- Systemic absorption of topically administered naftifine is minimal (2%-6%) and no major systemic side effects have been reported.<sup>28,31,32</sup> It is not known whether naftifine is excreted in human milk, and topical naftifine is rated Pregnancy Category B.<sup>30</sup>
- During clinical trials with naftifine 1% cream, the incidence of adverse reactions was as follows: burning/stinging (6%), dryness (3%), erythema (2%), itching (2%), and local irritation (2%).<sup>29</sup> Other studies have reported that application site reactions (ie, burning, stinging, itching) are relatively uncommon with topical antifungal agents overall, and were reported in 2% of naftifine-treated patients (n=185) compared with 5% for topical clotrimazole (n=194).<sup>28,35</sup> Allergic contact dermatitis has been reported with topical naftifine, with the risk of sensitization estimated to be 1:100,000.<sup>28,31,36</sup>
- Multiple efficacy studies and comparative studies support the safe and effective use of topical naftifine 1% formulations for CDIs (non-scalp, non-nail) with a usual duration of use of 3 to 4 weeks, which are consistent with studies that have gained FDA-approval with both the 1% gel and 1% cream.<sup>28-32</sup>
- Many tinea pedis studies with all available topical antifungal agents primarily evaluate interdigital tinea pedis, with fewer patients studied overall for dry plantar (moccasin) tinea pedis.<sup>27</sup> Importantly, 1-week duration studies with agents such as topical terbinafine only enrolled subjects treated for interdigital tinea pedis. In contrast, dry plantar tinea pedis is likely to warrant a longer course of topical antifungal therapy to achieve clearance due to the thicker stratum corneum (SC) on plantar skin, wider area of involvement, and a host-related immunologic blind spot against *T rubrum* in many cases.<sup>16,18,19,23,27,28</sup>
- In patients treated for specific CDIs, based on comparative studies and meta-analyses, allylamines including naftifine 1% (primarily cream) demonstrated superior efficacy regarding faster onset of clinical improvement and symptom reduction, and better sustained cure outcomes, when compared with several imidazole agents, such as econazole, oxiconazole, clotrimazole, and ketoconazole.<sup>26-28,31</sup> The superior sustained cure outcomes with CDIs treated with topical allylamines such as naftifine may be explained by their lipophilicity, keratinophilic properties, fungicidal activity, and persistence of drug levels within the skin after discontinuation of application.<sup>26,37</sup>

- An in vitro assessment evaluating the possible development of antifungal resistance showed that strains of *T rubrum* and *T mentagrophytes* developed no tendency to become resistant to naftifine following repeated exposures.<sup>38</sup>
- Although not FDA-approved for cutaneous yeast infections, topical naftifine has demonstrated clinical efficacy in controlled studies of patients with cutaneous candidiasis and an uncontrolled study of patients with tinea versicolor.<sup>31</sup>

#### *The Addition of Naftifine 2% Cream: What Does it Bring to the Table?*

As discussed above, naftifine exhibits fungicidal activity against dermatophytes, with time-kill studies showing dose-dependent activity against *T rubrum*, *T mentagrophytes*, and *E floccosum*.<sup>39</sup> This supported the concept of developing formulations with a higher concentration of naftifine. Naftifine hydrochloride 2% cream gained FDA-approval in adult patients ≥18 years of age for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *T rubrum* using once-daily application for 2 weeks.<sup>30</sup> In these trials, multiple endpoints were evaluated. Mycological cure was defined as a negative KOH and dermatophyte culture.<sup>30,40,41</sup> Treatment effectiveness was defined as a negative KOH preparation, a negative dermatophyte culture, and erythema, scaling, and pruritus grades of 0 or 1 (absent or nearly absent).<sup>30,40,41</sup>

#### **Tinea pedis**

A randomized, double-blind, vehicle-controlled study of naftifine 2% cream applied once daily for 2 weeks vs naftifine 1% cream applied for 4 weeks vs vehicle for interdigital tinea pedis evaluated efficacy and safety at end of treatment, and at weeks 2 and 4 post-treatment.<sup>40</sup> Continuous post-treatment improvement was observed in actively treated subjects, suggesting the potential for a "therapeutic reservoir effect" of persistent naftifine in the skin after its application is stopped. At week 6 (4 weeks post-treatment), naftifine-treated subjects achieved 67% mycological cure rate and 57% treatment effectiveness, compared with 21% ( $P<.001$ ) and 20% ( $P<.001$ ) in the vehicle group, respectively. The outcomes with naftifine 2% cream used for 2 weeks and naftifine 1% cream used for 4 weeks were equivalent.<sup>40</sup> Tolerability and safety were favorable in all study arms.

#### **Tinea cruris**

A randomized, double-blind, vehicle-controlled study of naftifine 2% cream applied once daily for 2 weeks vs vehicle for tinea cruris evaluated efficacy and safety at end of treatment, and at 2 weeks post-treatment.<sup>41</sup> At week 4 (2 weeks post-treatment), naftifine-treated subjects achieved 72% mycological cure rate and 60% treatment effectiveness, compared with 16% ( $P<.001$ , one-sided) and 10% ( $P<.001$ , one-sided) in the vehicle group, respectively. Tolerability and safety were favorable in both study arms.<sup>41</sup>

**TABLE 1.****Detection and Relevance of Persistence of Naftifine in the Stratum Corneum up to 4 Weeks After the Last Application of Naftifine 2% Cream**

		Day	Naftifine 2% Cream Mean ± SD N=6 (ng/cm²)		Naftifine 2% Cream Median N=6 (ng/cm²)	
Total Amount of Naftifine 2% Cream Recovered from the Tape Strip Samples (ng/cm²)		1 (initiation of treatment)	0.097 ± 0.212		0.006	
		15 (end of treatment)	321.63 ± 245.90		349.00	
		29 (2 weeks post-treatment)	66.60 ± 157.38		1.65	
		43 (4 weeks post-treatment)	2.87 ± 3.39		2.07	
	Day	Tape Strips 1-5 Mean (SD)	Tape Strips 6-10 Mean (SD)	Tape Strips 11-15 Mean (SD)	Tape Strips 16-20 Mean (SD)	Tape Strips 21-25 Mean (SD)
Mean and Standard Deviation (SD) of the Amount of Naftifine 2% Cream Recovered from Sequential Tape Strip Sets (ng/cm²) (N=6)	15	189.0 (142.3)	58.6 (54/2)	30.4 (32.5)	21.9 (24.1)	20.9 (17.6)
	29	45.0 (160.9)	9.1 (21.2)	6.1 (14.4)	4.2 (9.8)	2.2 (5.1)
	43	1.4 (1.9)	0.65 (0.76)	0.28 (0.27)	0.28 (0.31)	0.22 (0.24)

Naftifine 2% cream was present on all sample collection days. The highest amount of drug was stripped at the end of treatment and potentially clinically relevant presence of naftifine 2% cream was present in the skin up to 4 weeks post-treatment. The best reflection of the stratum corneum tissue content are represented by the innermost tape strips (strips 21-25).

**Therapeutic reservoir effect**

The observation that topical allylamines exhibit a tendency to produce greater sustained cure outcomes after treatment of CDIs appears to relate at least partially to persistence of a cutaneous therapeutic reservoir of the drug after its application is stopped.<sup>26</sup> Figure 6 outlines the objectives and methodology of a tape-stripping study that evaluated the detection and relevance of naftifine levels in the SC up to 4 weeks after the last application of naftifine 2% cream.<sup>42</sup> Table 1 depicts the results, including results with inner strips, which provide a better assessment of SC levels of naftifine that may correlate with therapeutic reservoir effect, with results suggesting that naftifine persists in the SC for several weeks after its application is stopped. With repeated application, the epidermal levels of naftifine remain relatively unchanged at the sites of application and persist for several weeks post-treatment, which is consistent with a bioavailable depot or reservoir of naftifine. The detection of naftifine in the SC up to 4 weeks post-treatment provides a possible explanation for the observed progressive improvements in efficacy rates during the treatment period and up to 4 weeks post-treatment in clinical trials using naftifine 2% cream.<sup>42</sup>

**CONCLUSION**

Superficial cutaneous fungal infections, especially CDIs, are commonly seen in clinical practice and can exhibit a variety of presentations. In many cases, a topical antifungal agent can effectively eradicate CDIs as long as an adequate duration of therapy is completed. Overall, the topical allylamine agents have been shown to provide faster onset and greater sustained clearance than imidazole agents for CDIs. Topical naftifine is an allylamine antifungal agent with a long track record of efficacy and safety.

**FIGURE 6.****Is There a Clinically Relevant Reservoir Effect? Detection and Relevance of the Persistence of Naftifine in the Stratum Corneum up to 4 Weeks After the Last Application of Naftifine 2% Cream****Study Objectives and Methodology**

The primary objective is to present the results of the tape-stripping study in order to assess the amount of naftifine HCl 2% cream available in the stratum corneum (SC) over a 28-day period following the last dose after 2 weeks of application.

The secondary objective is to briefly present the two phase 3 clinical trial results in order to show continuous post-treatment efficacy improvement rates. These results justify the rationale for conducting a tape-stripping study.

Note: The tape-stripping study and the two phase 3 clinical trials were conducted independently, and the objective is not to directly correlate the results but rather to discuss the tape-stripping results in order to provide one possible explanation of continuous post-treatment improvement rates seen in the trials.

**Overall Tape-Stripping Study Design and Plan**

This was an open-label, intra-subject, single-exposure study comparing the amounts of drug that were absorbed into the SC following topical application of naftifine HCl 2% cream.

Six subjects were dosed with naftifine HCl 2% cream.

All subjects had a total of 12 8 cm<sup>2</sup> test application sites demarcated on the upper back (randomly assigned and as 2 rows of 3 on each side of the spine.)

A total of 25 individual sequential strips (strip sets 1-5, 6-10, 11-15, 16-20, and 21-25) were applied to each test site.

Eleven sites were dosed once daily with naftifine HCl 2% cream (5.0  $\mu$ L/cm<sup>2</sup>) for 14 days and the final site was left untreated to serve as the control site.

On days 1, 15, 29, and 43, a selected test site was stripped to collect the SC in order to process the amount of drug present over 28 days following the last dose application.

The recent introduction of the 2% cream has been shown to be effective for tinea pedis and tinea cruris with once-daily application over a shorter duration (2 weeks) than what has been used in most cases with the 1% formulation. Although many of the available topical antifungal agents are effective and safe for CDIs and other SCFIs, naftifine offers fungicidal activity in most cases of CDIs, a rapid onset of clinical effect, and a therapeutic reservoir effect that may correlate with sustained clearance post-treatment.

## DISCLOSURES

Dr. Del Rosso has served as a consultant, advisory board participant, clinical investigator, and/or speaker for Allergan, Bayer Healthcare (Dermatology), Dermira, Eisai, Ferndale, Galderma, Innocutis, LeoPharma, Liquidia, Merz Pharmaceuticals, Onset Dermatologics, Pharmaderm, Primus, Promius Pharma, PuraCap, Quinnova, Ranbaxy, Taro, Unilever, Valeant Pharmaceuticals (Medicis, Consumer Care), and Warner-Chilcott.

Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Allergan, Galderma, Bayer Healthcare, LeoPharma, Merz Pharmaceuticals, Promius Pharma, Quinnova, Stiefel/GSK, Taro, Valeant, and Warner Chilcott.

This article was reviewed by Merz Pharmaceuticals as required for internal review. No questions emerged regarding accuracy or explanation of content. The paper was finalized solely by the authors, who wrote the manuscript and maintained full control over all the content. After submission to the journal, only the JDD editorial staff, dermatologists involved in the official peer-review process, and authors were involved with communications related to this manuscript. All final decisions on content were determined by the authors.

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