

The Role of Naftifine HCl 2% Gel and Cream in Treating Moccasin Tinea Pedis

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ABSTRACT

In recent years, new topical antifungals have emerged for the treatment and management of tinea pedis, but all have been investigated and approved for the treatment of interdigital tinea pedis. Moccasin tinea pedis has not been recognized by governing bodies as a definable and treatable disease entity separate from interdigital tinea pedis at this time. Thus, creating randomized, controlled clinical trials to investigate moccasin tinea pedis is a challenge without an agreed upon definition of the disease state, treatment regimen, and treatment course. Considering systemic therapy issues and the lack of data from large trials demonstrating safety and efficacy in the topical management of this clinical presentation, an unmet need has been created for a topical antifungal agent that can treat moccasin tinea pedis. Naftifine 2% gel, an allylamine, was studied in a clinical trial that enrolled patients who had interdigital or both interdigital and moccasin-type tinea pedis. In the moccasin group, the primary efficacy endpoint of complete cure at week 2 (end of treatment) was 1.7% (gel) vs 0.9% (vehicle) and week 6 (four weeks post-treatment) was 19.2% (gel) vs 0.9% (vehicle). Naftifine 2% cream in combination with urea 39% also showed improvement in hyperkeratotic moccasin tinea pedis.

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INTRODUCTION

In the US, tinea pedis is the most common inflammatory fungal infection that is mostly caused by dermatophytes.[1] These are the skin, hair, and nail-preferring fungi such as Trichophyton sp, Microsporum sp, and Epidermophyton sp, of which the top pedal pathogen is Trichophyton rubrum. Dermatophytes are highly contagious and may be transferred between soil, animals, humans, and fomites.

Wearing shoes, sneakers, and boots lead to creating a warm and moist environment, which is an optimal place for fungus to thrive. Traditionally, tinea pedis occurs in the pedal interdigital areas, where prolonged moisture will cause macerated tissue to occur, but it also presents on the plantar surface of the foot as dry, scaly, and itchy skin known as the moccasin type. Populations at risk to develop tinea pedis include: those who use communal facilities (pools, dorm showers, gyms); those who wear rubber or non-breathable material shoes at work; and those who are obese, diabetic, immunocompromised, vascularly compromised, or are unable to perform regular foot hygiene.

Treatment options have consisted of both prescription and over the counter topical medications as first line agents (such as naftifine, econazole, and ciclopirox), oral medications for recalcitrant and severe presentations (off label uses for terbinafine, itraconazole, and on label for griseofulvin ultra micro-sized), and patient education on proper foot hygiene. Even after educating the patient on the basics of pedal hygiene (drying between toes, changing socks and shoes daily, disinfecting family showering areas, and wearing shower shoes in communal areas), the physician will typically continue to manage the patient for a persistent and irritating plantar infection weeks to months after treating the initial infection.

Even though interdigital tinea pedis is classically described as the most common clinical presentation, many physicians agree that the moccasin type is widely seen and a challenge to treat.[2] As described earlier, moccasin tinea pedis presents on the plantar foot commonly extending from the digital sulcus to the medial, lateral, and posterior borders of the foot where it may reach superiorly towards the junction of the dorsal and plantar skin. It can present as dry serpiginous scale, but may also be hyperkeratotic and in some cases, fissure. Scaling can be fine or coarse, and erythema may be present. Long standing moccasin tinea pedis is often asymptomatic and can predispose the patient to developing onychomycosis. It may co-present with tinea manuum where the patient exhibits bilateral tinea pedis and unilateraly tinea manuum (2 feet–1 hand syndrome).

In the last few years, new topical antifungals have emerged for the treatment and management of tinea pedis, but all have been investigated and approved for the treatment of interdigital tinea pedis. Moccasin tinea pedis has not been recognized by the FDA as a definable and treatable disease entity separate from interdigital tinea pedis at this time. Thus, creating randomized, controlled clinical trials to investigate moccasin tinea pedis is a challenge without an agreed

upon definition of the disease state, treatment regimen, and treatment course. Due to the chronicity and possible co-presentation of onychomycosis, systemic therapy is often recommended for this disease state. Oral antifungals may not be accessible for all patients due to risk vs benefit when factoring in co-morbidities and drug–drug interactions. Considering systemic therapy issues and the lack of data from large trials demonstrating safety and efficacy in the topical management of this clinical presentation, an unmet need has been created for a topical antifungal agent that can treat moccasin tinea pedis.

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In a review of the literature, the first trial to investigate moccasin-type (along with interdigital tinea pedis) is the naftifine HCl gel 2% phase III clinical study. A member of the allylamine class, naftifine exhibits fungicidal, anti-inflammatory, and anti-bacterial properties.[3-6] In vitro, naftifine exhibits fungicidal activity against the dermatophytes and many Candida species. It stops fungal growth by inhibiting squalene epoxidase in the ergosterol synthesis pathway, which ultimately increases cell membrane fragility and permeability. The mycological and clinical cure rates for naftifine in the treatment of tinea are superior or equivalent to those of terbinafine, econazole, and tolnaftate.[7] In 2011, Parish et al showed that naftifine 2% cream (Naftin 2% cream, Merz) used once daily for two weeks in the management of interdigital tinea pedis had efficacy responses equivalent to naftifine 1% cream which was traditionally used for four weeks for the same infection.[8] Naftifine 2% gel (Naftin 2% gel, Merz) was approved for the same dosing regimen as the 2% cream. The 2% gel was studied in a clinical trial that enrolled patients who had interdigital or both interdigital and moccasin-type tinea pedis.[9]

The overall study design was a two six-week, double-blind, randomized, vehicle-controlled, multi-center, parallel-group for this phase III clinical trial examining the safety and efficacy of naftifine HCl 2% gel for interdigital and moccasin tinea pedis. Subjects were placed into the interdigital-type only or the interdigital with moccasin-type infection group. In order to focus on the moccasin-type only, a post-hoc analysis was completed to evaluate the safety and efficacy of a 2-week, once daily course of naftifine gel 2% versus vehicle for this sub-type.[10]

Over 40 sites were utilized in this study that enrolled male and female subjects aged 12–70 years old. A baseline clinical presentation of moderate erythema, moderate scaling, mild pruritus, and positive KOH/mycology culture on one or both feet. Patients were not enrolled if they had uncontrolled diabetes, plantar psoriasis, incapacitating tinea pedis, or atopic dermatitis.

As this is a fungal infection that is clinically symptomatic, investigators recorded two measurements to determine efficacy: mycological analysis and clinical signs and symptoms. Mycological analysis was reported after two weeks of use and at week 6 (four weeks post-treatment). Clinical assessment measured the amount of erythema, scaling, and pruritus on a four-point scale (0=absent, 1=mild, 2=moderate, 3=marked) at those same time points. The primary efficacy endpoint of complete cure was defined as negative mycology (KOH/culture) and a "0" score of erythema, scaling, and pruritus. In addition to complete cure, mycologic cure, treatment effectiveness, clinical cure, and clinical success were also reported (Table 1). Safety assessments consisting of adverse events (AE's), laboratory testing, and physical exam, were completed at defined visits.

A total of 1715 subjects were randomized, 1174 who had interdigital tinea pedis with or without moccasin-type and positive KOH and mycology culture at baseline were analyzed for efficacy. Subjects included applied the study drug or vehicle once daily for two weeks to affected areas. The study subjects were then followed for four weeks after discontinuation of the study drug. Those in the interdigital plus moccasin group applied the product both in the interspaces and the entire plantar foot. Of the 1174 subjects, 674 had interdigital tinea only while 500 had both moccasin and interdigital-type presentation. In the 500 moccasin/interdigital group, only 380 subjects satisfied the inclusion criteria to qualify for data analysis. The 380 subjects comprise the post-hoc analysis.

TABLE 1.

Efficacy Endpoints for Naftifine Gel 2% Trial

	Mycology (KOH/Culture)	Clinical Assessment (erythema, scaling, pruritus)
Complete Cure*	negative KOH/Culture	Score of 0
Mycologic Cure#	negative KOH/Culture	N/A
Treatment Effectiveness#	negative KOH/Culture	Score of 0 or 1
Clinical Cure#	N/A	Score of 0
Clinical Success#	N/A	Score of 0 or 1

*primary efficacy variable
#secondary efficacy variable

TABLE 2.

Demographics of Moccasin Group (Table similar to reference 10)		
	Naftifine gel 2% n=253	Vehicle n=127
Male	202	101
Female	51	26
Age, Mean (SD)	44.6 (13.6)	47.7 (14.0)
Black/African American	69	37
White	176	84
Other	8	6

Demographically, white, male subjects comprised the majority in the naftifine gel 2% and vehicle arms (Table 2). The mean age for the treatment group was 44.6 and the vehicle group was 47.7.

Results of the trial showed that the 2% gel was superior to vehicle at week 6 (four weeks post-treatment) for complete cure of the subject who had both interdigital and moccasin-type presentations. It was also shown to be significantly better than vehicle in achieving mycologic cure at week 6 in those same subjects. Overall, naftifine 2% gel was designed to provide a shorter and more convenient regimen while still maintaining the efficacy that practitioners have come to expect with the drug. Specifically for the moccasin group, the primary efficacy endpoint of complete cure at week 2 (end of treatment) was 1.7% (gel) vs 0.9% (vehicle) and week 6 (four weeks post-treatment) was 19.2% (gel) vs 0.9% (vehicle). The secondary efficacy endpoints for the moccasin group are listed in Table 3. At week 6, complete cure, mycological cure, treatment effectiveness, clinical cure, and clinical success were statistically superior when compared to the matching vehicle group.

Naftifine gel 2% was well tolerated in the 14-day treatment period. Three subjects in the 2% gel group experienced treatment emergent adverse events (TEAE) related to the study drug while no subjects in the vehicle group experienced TEAE related to the study treatment. TEAEs, which were rated by the investigator, included application site pruritus, rash, vesicles, and hypersensitivity.

As moccasin tinea pedis may present with plantar hyperkeratosis, this focal hyperkeratosis presents a therapeutic challenge to both the patient and the physician both during and after antifungal therapy. Hyperkeratotic tinea pedis accounts for 2-8% of tinea cases and presents as moccasin type tinea with hyperkeratosis confined to the weight bearing areas.[11] Hyperkeratosis in the presence of moccasin tinea pedis is typically bilateral and often only treated with a topical antifungal. Often, after the tinea infection has resolved, the hyperkeratosis remains, which leads the patient to believe

TABLE 3.

Efficacy Endpoints for Moccasin Subjects (n=380) (Modified from reference 10)		
	Gel	Vehicle
Complete Cure*		
Week 2	1.7%	0.9%
Week 6	19.2	0.9
Mycologic Cure#		
Week 2	29	15.2
Week 6	65.8	7.9
Treatment Effectiveness#		
Week 2	11.7	5.3
Week 6	51.4	4.4
Clinical Cure#		
Week 2	2.9	0.9
Week 6	23.9	2.6
Clinical Success#		
Week 2	33.2	31.6
Week 6	72.1	29.3

*primary efficacy variable
#secondary efficacy variable

the infection is still present. The addition of a keratolytic to reduce stratum corneum thickening is warranted in these cases. There is no combination product targeting both the hyperkeratosis and the tinea available at this time, but Kircik et al relates a pilot study of using naftifine 2% cream along with urea 39% cream on 18 subjects.[12] Patients were evaluated for 8 weeks during which they used the naftifine 2% cream for two weeks in the morning and the urea 39% cream to the affected area nightly. Ultimately, the evaluable subjects had improvements in hyperkeratosis, the active tinea infection, and pruritus. This dual therapy ultimately proved efficacious and cosmetically pleasing for the patients to use.

Considering the chronic and refractory course of moccasin tinea pedis, naftifine gel 2% and naftifine cream 2% (in combination with urea 39% cream) have been shown to be useful agents in the management of this subtype; however both are still only approved for the interdigital type, not the moccasin type. The post-hoc data reported for naftifine HCl gel 2% is a first step in creating awareness and a possible protocol to determine the safety and efficacy for a topical antifungal in the presence of moccasin tinea pedis. A once daily dosing regimen for a shorter course of therapy (2 weeks vs the standard 4-week twice daily dosing) is advantageous in patients with this chronic superficial skin infection. And, in adding a urea product, a patient can also achieve a cosmetically and therapeutically pleasing result with their topical antifungal regimen. Overall, the naftifine gel 2%

data and cream 2% data show the possibility of managing moccasin tinea pedis in an efficacious, safe, and tolerable manner.

DISCLOSURES

The author has been a principal investigator and has served as an advisory board member for Merz, Valeant, and Pharmaderm.

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