Naftifine HCl 2 % Cream for the Treatment of Tinea Pedis: A Review

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Published online: 26 June 2013
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Abstract Tinea pedis is a common skin disease that is usually managed with topical antifungal medications. Allylamines, including terbinafine and naftifine 1 % cream, have been proven efficacious and safe in the treatment of tinea pedis. The treatment duration for the majority of topical antifungal is 4 weeks, which results in poor patient compliance and frequent relapses. Recently, naftifine 2 % cream has been approved to treat tinea pedis with 2 weeks of application. We discuss the mechanism of action, adverse events, and clinical efficacy of naftifine 2 % cream.

Keywords Tinea pedis · *Trichophyton rubrum* · *Trichophyton mentagrophytes* · *Epidermophyton floccosum* · Antifungal agents · Allylamines · Naftifine · Terbinafine

Introduction

Tinea pedis is one of the most common skin diseases, affecting up to 20 % of the population of the United States [1]. It is a chronic fungal infection of the feet, most often caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. Tinea pedis may present with pruritus, erythema, white macerated areas between the third and fourth toe webs, or with scaly hyperkeratosis of the soles and heels. Some infections are complicated by severe inflammation.

The majority of tinea pedis infections are managed with topical antifungal agents. Systemic treatment should be considered when infection fails to improve with repeated topical antifungals [2]. Oral medications include itraconazole, terbinafine,

and griseofulvin. Topical antifungal treatment fails to cure approximately one-third of individuals with tinea pedis [1]. The most common cause of relapse is poor compliance.

Allylamines and azoles have been proven to be efficacious in treating tinea pedis in placebo controlled trials [3]. Comparative trials between the allylamines and azoles revealed that the allylamines cure more tinea pedis infections [3]. The allylamine class of antifungal agents includes terbinafine and naftifine. Naftifine 1 % cream (NAFT-1) is applied once daily for four weeks in the treatment of tinea pedis. The efficacy and safety of NAFT-1 have been demonstrated in several clinical trials [4••]. The clinical cure rates for NAFT-1 in the treatment of tinea pedis are equal or superior to topical terbinafine, econazole, miconazole, tolnaftate and clotrimazole [4••].

Recently, naftifine 2 % cream (NAFT-2) has been approved to treat tinea pedis. Most topical antifungal medications require 4 weeks of treatment, which makes patient compliance a challenging aspect of tinea pedis management. NAFT-2 requires once daily application for only 2 weeks for treatment of tinea pedis.

Mechanism of Action

The allylamines, including terbinafine and naftifine, contain a nitrogen atom and a neighboring double bond. Although both medications have fungicidal activity *in vitro*, the clinical significance of this finding is not known [5]. *In vitro*, naftifine has broad spectrum of activity against dermatophytes, aspergilla, *Sporothrix schenckii* and *Candida*. The efficacy of naftifine *in vitro* increases as pH increases [6].

Naftifine selectively inhibits the fungal enzyme squalene epoxidase, which is involved in the ergosterol biosynthesis pathway [7]. Ergosterol is a component of fungal cell membranes. Squalene epoxidase is also necessary for mammalian cholesterol biosynthesis, but naftifine is highly selective for fungal enzymes. Naftifine has minimal effects on mammalian cholesterol biosynthesis [8].

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Naftifine has anti-inflammatory properties similar to azole medications plus 1 % hydrocortisone [5]. It has sustained fungicidal activity following treatment cessation because the levels of naftifine remain relatively unchanged in the epidermis several weeks post-treatment [4•]. Clinical response is highest 6 to 8 weeks post-treatment with naftifine [4•].

Clinical Efficacy

A randomized, double-blind, vehicle-controlled phase 3 trial evaluated the clinical efficacy of 2 weeks of NAFT-2 in the treatment of tinea pedis [4•]. NAFT-1 for 4 weeks and a vehicle were also evaluated. Seven hundred and nine subjects were assigned to one of four treatment groups, and efficacy was analyzed in 425 randomized subjects: NAFT-2 (n=147), 2 week vehicle (n=70), NAFT-1 (n=143), and 4 week vehicle (n=65). The majority of subjects were male. The median age was 42 years with a standard deviation of 14 years.

At week 6, 18 % of NAFT-2 subjects achieved complete cure and 67 % achieved mycological cure. The response rates in vehicle-treated counterparts were 7 % and 21 %, respectively (one-sided, $P<0.001$ for both categories). Clinical cure occurred in 22 % of NAFT-2 subjects compared to 11 % of vehicle subjects (two-sided, $P=0.04$). Clinical success occurred in 78 % of NAFT-2 and 49 % of vehicle subjects (two-sided, $P<0.01$).

At week 6, complete cure occurred in 16 % of NAFT-1 subjects and mycological cure occurred in 71 % of NAFT-1 subjects. The response rates in vehicle-treated counterparts were 3 % and 22 %, respectively (both one-sided, $P<0.001$). Clinical cure occurred in 22 % of NAFT-1 subjects and 8 % of the vehicle subjects ($P=0.008$). Clinical success occurred in 84 % in NAFT-1 subjects and 44 % in the vehicle group ($P<0.001$).

Adverse Events

A randomized, double-blind, vehicle-controlled phase 3 trial evaluated the safety of 2 weeks of NAFT-2 treatment in subjects with tinea pedis [4•]. The adverse events of NAFT-2 and NAFT-1 were both similar to the vehicle. Adverse events were reported in 5 % of NAFT-2 treated subjects, 7 % of the 2 week vehicle subjects, 4 % of NAFT-1 treated subjects and 8 % of the 4 week vehicle subjects. The most common adverse events for all groups were application site irritation, pruritus and dryness [4•]. There were no clinically significant changes in laboratory findings or physical examination findings as a result of NAFT-2 treatment. Although one serious adverse event occurred during the phase 3 trial, it was determined to not be related to treatment with naftifine.

Discussion

Naftifine 2 % cream is efficacious and safe in the treatment of tinea pedis. The major cause of treatment failure of tinea pedis is poor patient compliance because treatment duration is four weeks for the majority of topical antifungal agents [9]. Most topical antifungal medications require a minimum of 4 weeks to achieve clinical cure, thus a benefit of NAFT-2 is that there is equivalent cure rates with only 2 weeks of treatment. This may result in improved patient compliance and clinical efficacy [4•]. Further studies need to elucidate the rate of patient compliance in individuals treated with NAFT-2 compared with other antifungal agents. Although there is no clinical difference between twice daily and once daily application of NAFT-1, no clinical trial has yet compared twice daily and once daily treatment with NAFT-2 [10].

Tinea pedis is sometimes complicated by inflammation, and treatment may require a medication with intrinsic anti-inflammatory properties or using the combination of an antifungal medication plus a steroid medication. Naftifine has anti-inflammatory properties that are equivalent to the combination of azole medications plus 1 % hydrocortisone [5]. Naftifine inhibits polymorphonuclear leukocyte (PMN) chemotaxis and respiratory burst activity [11]. This prevents leukocyte adherence to the endothelia and is thought to be responsible for the anti-inflammatory effects of naftifine [11].

Another advantage of topical naftifine 2 % cream is that there is fungicidal activity with highest rates of mycological cure several weeks following treatment cessation [4•]. This is consistent with previous trials that demonstrated that the levels of naftifine 1 % cream remain unchanged several weeks following treatment.

Conclusion

Naftifine 2 % cream is efficacious and safe in treatment of tinea pedis. The results of a randomized, double-blind, vehicle-controlled phase 3 trial demonstrated that 2 weeks of NAFT-2 resulted in similar cure rates of tinea pedis compared to 4 weeks of NAFT-1. The results of this study demonstrated that the adverse events of NAFT-2 were similar to the vehicle. Further studies should address whether patient compliance is improved with NAFT-2 treatment compared with other topical antifungal agents. NAFT-2 should be considered as a treatment option for tinea pedis in the appropriate clinical context.

Compliance with Ethics Guidelines

Conflict of Interest AJ Thompson declares no conflicts of interest. SK Tying has received a speaker honorarium from Merz.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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