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Original Research Article

A real-world retrospective study to determine the safety and effectiveness of naftifine 2% cream in the treatment of *Tinea cruris* and *Tinea corporis* in Indian patients

Anil Soni[1], Aditya Tripathi[2], Soumajyoti Sarkar[3], Dibyajyoti Sarkar[4], Rajendra Shinde[5], Alka Makwana[6], Ashok Jaiswal[7]*, Monika Chinda[7]

[1]Department of Dermatology, Genesis Cosmetology and Hair Transplant Centre, Indore, Madhya Pradesh, India
[2]Department of Dermatology, ASHA Derma Clinic, Gorakhpur, Uttar Pradesh, India
[3]Shantiniketan Medical College, Bolpur, West Bengal, India
[4]Department of Dermatology and Venerology, Malda Medical College and Hospital, West Bengal, India
[5]Department of Dermatology, MIMER Medical College and hospital, Pune, Maharashtra, India
[6]Arista Skin, Hair and Laser Clinic, Ahmedabad, Gujarat, India
[7]Medical and Regulatory Affairs, Zydus Healthcare Ltd, Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Ashok Jaiswal,
E-mail: AshokD.Jaiswal@zyduslife.com

ABSTRACT

Background: This real-world retrospective analysis of the case record forms (CRFs) was done to evaluate the safety, effectiveness, compliance, and tolerability of naftifine 2% cream in treating superficial infections, especially *Tinea corporis* and *Tinea cruris*, in Indian patients.
Methods: The data was collected from 158 dermatologists/physicians' outpatient department in India, on using naftifine 2% cream in patients presenting with new or recurrent *Tinea* infections. The CRFs of 1258 patients who had previously visited the dermatology outpatient department from July 2023 to May 2024 and received naftifine 2% cream as monotherapy or in combination therapy at the discretion of the treating physician were included in the study.
Results: A total of 1,258 eligible CRFs were analyzed, revealing that 81% of patients treated with naftifine 2% cream achieved clinical cure, while 99.6% achieved mycological cure. Adverse events were reported in only 2.6% (n=33) of patients, and naftifine 2% cream treatment was well tolerated.
Conclusions: This retrospective study suggests that naftifine 2% cream is safe and effective in patients with superficial fungal infections, including *Tinea corporis* and *Tinea cruris*.

Keywords: Naftifine, *Tinea* infections, *Tinea corporis*, *Tinea cruris*, Superficial fungal infections, Dermatophytosis

INTRODUCTION

The treatment of dermatophytosis, a superficial fungal infection prevalent in tropical and subtropical countries like India, varies based on the extent, site of infection, and severity and includes topical or systemic antifungal drugs or a combination of both.[1,2] Topical antifungals are broadly recognised as the first-line therapy for uncomplicated, small-area tinea infections of shorter duration owing to their high efficacy and low potential for systemic adverse effects. They readily penetrate the stratum corneum when applied to the skin surface, which leads to the killing of the fungi or inhibiting their growth, achieving clinical and mycological elimination.[3,4] An ideal antifungal agent for treating superficial fungal infections should have broad-spectrum activity, high mycological cure rate, low

incidence of side effects, and cost-effectiveness. There remains a significant need for more effective antifungal treatments that meet these criteria, emphasizing the ongoing pursuit of better topical solutions.[5]

Naftifine is an allylamine class of topical antifungal agent and has a broad spectrum of activity against dermatophytes, Aspergilla, Sporothrix, and Candida.[6] It penetrates the stratum corneum and epidermis demonstrating in-vitro fungicidal activity against various dermatophyte organisms including Trichophyton, Microsporum, and Epidermophyton, with a minimal inhibitory concentration (MIC) range of 0.1 to 0.2 mg/ml.[7] The level of naftifine in the epidermis remains relatively unchanged several weeks post treatment resulting in sustained fungicidal effect.[6] Apart from antifungal properties, Naftifine's substantial antibacterial and anti-inflammatory properties are beneficial in superficial dermatoses with superimposed bacterial infection and inflammation.[7,8] Naftifine act by selectively inhibiting the fungal enzyme squalene epoxidase, which is involved in the ergosterol biosynthesis pathway. Ergosterol is an important integral component of fungal cell membranes. Squalene epoxidase is also necessary for mammalian cholesterol biosynthesis, but naftifine is highly selective for fungal enzymes. The effect of naftifine is minimal on mammalian cholesterol biosynthesis.[6,8]

Currently, naftifine hydrochloride is globally available as both topical cream and gel formulations in 1% and 2% strengths.[7] In India, a topical cream formulation was developed by Zydus Healthcare Ltd., naftifine hydrochloride 2% w/w, which was approved by DCGI in 2022 for treating superficial fungal skin infections. And, the formulation has been available for clinical usage in the Indian market since 2023.

This retrospective study analysed clinical records of Indian patients treated with naftifine 2% cream for superficial fungal skin infections, particularly tinea corporis and tinea cruris. The goal is to corroborate the findings of a previous prospective study by providing additional real-world data on the effectiveness and safety of naftifine 2% cream in treating these conditions.

METHODS

Study design

This retrospective study aimed to evaluate the real-world safety and effectiveness of naftifine 2% cream in Indian patients with superficial fungal infections. The clinical records were collected from the 1258 patients who had been treated for superficial fungal infection with naftifine from July 2023 to May 2024 from 158 dermatologists/physicians' outpatient department. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, ensuring the protection and confidentiality of patient data.

Study population

The clinical records of the patients who met the data eligibility criteria were included in the study. This criterion includes male and non-pregnant female patients aged 18 years or older with new or recurrent tinea infections who had previously visited the dermatologists/physicians' outpatient department and received naftifine 2% cream as monotherapy or in combination therapy at the discretion of the treating physician. Patients with malignancy, renal or hepatic disease, and hypersensitivity towards naftifine were excluded from the study.

Data collection and statistical analysis

Data of patients who had previously visited the department of dermatology for superficial fungal skin infection treatment and received naftifine as monotherapy or in combination with other antifungal at the discretion of the treating physician was retrieved from the medical records of the patients.

From the clinical records, a total of 1384 case record forms (CRFs) were received, of which 1258 CRFs met the eligibility criteria and were considered for analysis. The symptom scoring was captured from case record forms for various parameters, including erythema, itching, and scaling on a 4-point scale which determined the symptom severity score at baseline and subsequent follow up visits (Table 1).

Table 1: Criteria of grading symptom severity score.

Grade	Criteria		
	Erythema	**Scaling**	**Itching**
0 – None	No evidence of erythema present	No scaling	No itching
1 – Mild	Slight pink coloration	Barely perceptible, fine scales present	Slight itching, not bothersome
2 – Moderate	Definite redness	Fine-scale generalized to all affected areas	Definite itching that is somewhat bothersome
3 – Severe	Marked erythema, bright red to dusky dark red in colour	Scaling and peeling of skin	Intense itching that may interrupt daily activities and/or sleep

The clinical cure was defined as total symptom score of 2 or less than 2 with itching score of 0, and erythema and scaling score should not be more than 1 at follow up. The microscopical data for detecting fungal hyphae [KOH mount] was also captured from baseline and follow up visit to analyse the mycological cure. The absence of fungal hyphae at follow up visit was considered as mycological cure in patients who presented with positive KOH at baseline. Any incidence of adverse events and tolerability was also evaluated. Data was also extracted for demographics and vital signs of patients.

Statistical analysis

The data collected from the CRF were analyzed for tolerability, safety, efficacy, and demographics using descriptive statistical methods. The results are presented as numbers (percentages) or as mean±SD, with a p value of <0.05 considered statistically significant.

RESULTS

This retrospective study includes 1258 patients, with mean (SD) age of 39.66 (12.41) years. The basic demographic details of the patients are described in Table 2. Of the total patients, 17.25% presented with underlying medical conditions, with diabetes mellitus being the most common (49.62%), followed by hypertension (35.88%) and thyroid disorders (8.78%).

Table 2: Patients' demographic details.

Parameters	Frequency	Percentage
Total patients	1258	100
Male	686	54.5
Female	572	45.5
Age (years) (mean±SD)	39.66±12.41	
Weight(kg) (mean±SD)	68.68±13.24	
Height (cm) (mean±SD)	157.75±11.46	
Presence of any medical history		
Yes	717	17.25
No	1041	82.75
Type of infection		
T. corporis	778	61.84
T. cruris	397	31.56
Both	83	6.6%
Type of *Tinea* infection		
New *Tinea*	720	57.23
Recurrent *Tinea*	590	46.98

Out of 1258 patients, 1165 patients were on various combination therapy (Table 3). Naftifine 2% cream was advised to be applied twice daily in 68.3% and once daily in 31.7% patients. The mean duration of naftifine treatment was 4.78±2.19 weeks.

Out of 1258 CRFs analyzed for safety, only 33 patients (2.6%) reported the adverse events indicating the safety of naftifine in patients with superficial fungal infections. The most common adverse event was irritation, followed by rash and burning sensation, erythema, and itching. All the reported adverse events are mild to moderate in nature.

Of the 1258 patients, 81% of patients achieved clinical cure and 99.6% of patients achieved mycological cure. When investigator was asked to rate the clinical response of naftifine 2% cream then 53.5% investigators rated the clinical response as good, followed by excellent from 43%, and fair by 3.4%. The tolerability of naftifine was rated by the physicians as excellent in 43.6% of the patients, good in 53.3%, and fair in 2.9% at the end of the treatment. A significant improvement was observed in the follow up and baseline between the mean score for erythema, scaling, pruritus, and itching at all follow ups, with a 95% CI tested by analysis of variance (ANOVA) test ($p<0.0001$).

Drug compliance of >80% was seen among 97.8% of the patients treated with naftifine 2% cream. This showed that the drug is both tolerable and clinically effective for patients with superficial fungal infections.

Table 3: Concomitant medication along with naftifine.

Drug class	Frequency	Percentage
Oral antifungal		
Itraconazole	881	75.60
Terbinafine	159	13.60
Fluconazole	82	7.00
Griseofulvin	28	2.40
Susp. itraconazole	1	0.09
Voriconazole	1	0.09
Topical antifungal		
Luliconazole cream	7	0.60
Ketoconazole	1	0.09
Immunosuppressant		
Cyclosporine	4	0.30
Corticosteroid		
Clobetasol	1	0.09
Total	1165	100.00

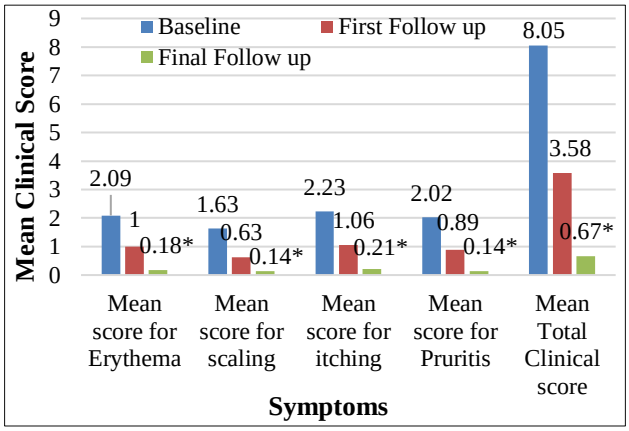

Figure 1: Comparison of mean clinical score at different follow-ups.

*P values <0.0001 (baseline versus final follow-up)

DISCUSSION

The management of superficial infections, especially those caused by dermatophytes that invade keratinized tissues such as the skin, hair, and nails, can be quite difficult.[8] The majority of imidazole antifungals are fungistatic, they prevent fungal growth and alleviate symptoms temporarily, leading to premature discontinuation of treatment by patients who frequently stop their treatments too soon. This may result in spore production, relapse of symptoms, and fungal revival, ultimately resulting in chronic/recalcitrant tinea infections.[9] Allylamines, have enhanced penetration and strong binding to keratin, are recommended for complete cures. The lipophilic property of allylamines allows them to penetrate deeply into the stratum corneum and exhibit fungicidal activity.[10] Naftifine HCl, an allylamine derivative, has demonstrated effectiveness in treating tinea pedis, corporis, and cruris when used as a gel or cream. Increased clinical and mycological cure rates have also been reported in tinea corporis and tinea cruris from past research on Indian patients.[11,12]

The findings of the present retrospective analysis revealed a significant improvement in the clinical symptoms at the end of the treatment. Among the 1,258 patients with a positive microscopic KOH test, 99.6% tested negative after treatment, indicating a substantial reduction in fungal infection ($p<0.0001$). These outcomes are higher compared to the 82.07% clinical cure rate observed by Godse et al in patients with tinea cruris and tinea corporis infections treated with naftifine 2% cream, with or without oral antifungals.[13] This outcome highlights the naftifine 2% cream's effectiveness and supports its use in the management of dermatophytosis within this population. Additionally, only 2.6% of the total patients reported adverse events, which were mild to moderate in nature, aligning with the 5% adverse event rate reported in a U.S. safety assessment by Thompson et al.[6] Evidence from various populations consistently demonstrates that naftifine is safe and effective for treating tinea infections, which are frequent in India, despite the paucity of specialized clinical research on Indian patients.[6,13-16] Excellent tolerability of naftifine 2% cream, as exhibited in this real-world study, helps in improving patient compliance and satisfaction. It can be a viable treatment choice for treating tinea corporis and tinea cruris in Indian patients due to its positive safety profile and real-world effectiveness.

The study's limitations included that the nature of the study is a retrospective study without having a comparator arm.

CONCLUSION

The findings based on retrospective real-world analysis of naftifine 2% cream demonstrate its safety and effectiveness in treating tinea cruris and tinea corporis in Indian patients. It offers a potential option as a combination therapy with oral anti-fungal in the management of dermatophytosis.

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