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Original Research Article

A prospective, post-marketing clinical study to evaluate the effectiveness of luliconazole 1% cream in treating cutaneous mycoses

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ABSTRACT

Background: Superficial (or cutaneous) mycoses are fungal infections that affect the superficial layers of the skin, hair, and nails. Luliconazole is an azole antifungal, used in the treatment of infections caused by fungus and yeast. The objective of the study is to assess the effectiveness and safety of new topical formulation of luliconazole (1% w/w luliconazole with 1% pramoxine added as excipient) in patients with cutaneous mycoses.
Methods: Patients with cutaneous mycoses aged 18 years and older were included in the post-marketing open-label, monocentric, prospective study. Effectiveness was assessed on patients prescribed with new 1% w/w luliconazole cream. The primary endpoint was a change in itch severity as assessed on 10-point Visual analogue scale score. The secondary endpoints include the number of patients who achieved all-night relief from itching and the type of adverse events during the treatment. Clinical effectiveness for itching was assessed at different time points after baseline.
Results: The mean itch severity scores at 2 min, 5 min, 10 min, 1 hour, 4 hour, and 8 hour time points were observed on 30 clinically diagnosed patients. A significant reduction of the mean±standard deviation score was observed from 6.82±0.72 at baseline to 3.37±1.68 after 8 hours. About 66.6% of patients achieved all-night relief from itching. There were no adverse events reported by any participant over the study duration.
Conclusions: This new topical formulation of luliconazole (1% w/w) containing 1% pramoxine as excipient significantly reduced itch in cutaneous mycoses with no reported adverse events. Large randomised controlled studies are required to confirm our findings.

Keywords: Cutaneous mycoses, Fungal infection, Luliconazole, Post-marketing study, Topical cream

INTRODUCTION

Superficial (or cutaneous) fungal infections confined to hair, skin, and nails are a major cause of morbidity around the world, especially in the tropics, where the heat and humidity stimulate the growth of fungi causing infections.[1,2] These are widespread with an estimated prevalence of 20-25% worldwide and their incidence is increasing year after year.[2,3] These infections are limited to the epidermis (stratum corneum) and rarely penetrate to the dermis. They are often caused by dermatophytes and yeasts. Oval or round maculae and itching at infected regions with little or no inflammation characterize the condition.[1]

Erythema, scorching, cracked skin, and skin rashes are some of the other symptoms of the disease.[4] These infections are not life-threatening but affect the quality of life of the patient.[5] Treatment with antifungal agents is the best option in the management of cutaneous mycoses. Imidazole class of drugs with antifungal activity play a vital role in thetreatment due to their high efficacy and low toxicity, as well as immunomodulatory activity.[1] The treatment is usually topical with antifungal imidazole

compounds for 2-3 weeks.[6] Luliconazole is a syntheticimidazole drug with antifungal activity that is used to treat dermatophytoses or tinea infections. Antifungal imidazoles work by preventing the synthesis of ergosterol, a key component of the fungal cell membrane.[7] They block the conversion of lanosterol to ergosterol by inhibiting the fungal cytochrome P450 14 demethylase enzyme and also affect the synthesis of triglycerides and phospholipids. This builds up toxic amounts of hydrogen peroxide inside fungal cells and leads to the degradation of subcellular organelles and cell death.[8] Luliconazole is available in the form of topical cream to treat the symptoms of tinea infections. Clinical trials have demonstrated the superiority of luliconazole over placebo in dermatophytosis. Application of luliconazole 1% cream once daily is effective even when used for short duration (one week for tinea corporis/cruris and 2 weeks for tinea pedis).[9]

Till date limited studies have assessed the efficacy of luliconazole (1% w/w) added with pramoxine as excipient, in reducing the itch severity in cutaneous mycoses. Aim of the study was to evaluate the effectiveness and safety of this new luliconazole topical formulation in patients with cutaneous mycoses.

METHODS

Study design

The study was a single-arm, open label, phase IV clinical trial conducted at dermatology clinic situated in Nashik, Maharashtra, India. The study protocol and related documents were reviewed and approved by the Institutional Ethics Committee before the start of the trial. The trial was conducted in accordance with the principles of the Declaration of Helsinki and its amendments, Indian Council of Medical Research guidelines, as well as the principles of ICH-Good Clinical Practices and New Drug and Clinical Trial Rules 2019.

Inclusion criteria

Subjects of both genders over the age of 18, who have been clinically diagnosed with cutaneous mycoses and prescribed with 1% w/w luliconazole cream with 1% pramoxine (Lucrush®) were included in the study. All the subjects signed informed consent before participation and agreed to follow protocol procedures during the course of study were included.

Exclusion criteria

Patients requiring systemic antifungal drugs, pregnant or lactating women, and patients with any significant medical illness such as diabetes, immunocompromised conditions, and other sexually transmitted diseases, etc. and patients with non-compliance/incomplete data were excluded from the study. Those who have hypersensitivity to luliconazole based formulation were excluded. The patients on multiple topical antifungal usage or topical steroid-based formulation usage or oral antihistamine usage were also excluded from the study.

Participants

The study was conducted on 30 patients, who were clinically diagnosed with cutaneous mycoses (tinea faciei, tinea cruris, and tinea corporis). Participants were recruited for the study based on the inclusion/exclusion criteria. Each enrolled participant was given an information sheet and a diary comprising information about adverse events and concurrent medications. At the screening, baseline information like age and gender was recorded. A physical examination was performed, along with vital signs. The itching was assessed by the participants themselves. The test product was subsequently distributed to the participants. They were told to apply to the affected portions of their bodies as directed once a day.

Evaluation

After completion of the application of the test product at the study center, all participants were asked to stay in the clinic for 4 hours post-application and were allowed to go home and record 8th-hour reading. The response to itch score was evaluated after application at 0 hour, 2 min, 5 min, 10 min, 1 hour, 4 hours and 8 hours. Effectiveness of the cream (reduction in pruritis) as the primary endpoint was assessed using the 10-point Visual analogue scale (VAS) score (Table 1) which is one of the most commonly used methods for pruritus severity assessment. The criteria for evaluation on the effect on itching for the onset and period of action were evaluated using a patient assessment diary.

A patient diary was given to participants to record the effect of test product on itching at specified time points and also their experience regarding all-night relief from itching. The diary was collected by study staff on the next day's visit to the clinic. The number of patients who achieved all-night relief from the itching by self-assessment questionnaire and also the number of patients experiencing any adverse events along with the type during treatment was noted as secondary endpoints. Statistical analysis was carried out by 10.0 version of statistical software SPSS. All the statistical tests were interpreted ata 5% level of significance. Data describing quantitative measures were expressed as mean, standard deviation (SD), and ranges. Qualitative variables were presented as counts and percentages. The Wilcoxon Sign Rank Test was used for analyzing mean itch severity.

RESULTS

Of the 30 patients enrolled in the study, 18 were male (60%) and 12 were female (40%) of Indian origin. None of the participants had any medical history of other diseases except cutaneous mycoses. All 30 patients

completed the study without any dropouts or protocol deviations. Data were analyzed for 30 participants.

Table 1: Visual analogue pruritis scale.

Grade	Level of pruritis
0	No pruritus
>0-<4	Mild pruritus
≥4-<7	Moderate pruritus
≥7-<9	Severe pruritus
≥9-10	Very severe pruritus

Table 2: Baseline demographics and vital signs.

Parameters	Mean±SD	Range
Demographic data		
Age (years)	39.20±11.24	22-61
Physical examination and vital signs		
Temperature (°C)	36.91±0.08	36.77-37.11
Systolic blood pressure (mmHg)	120.53±3.96	114-130
Diastolic blood pressure (mmHg)	78.47±4.78	70-88
SpO_2 (%)	97.17±0.87	95-99
Respiratory rate (per min)	17.5±0.68	16-18
Medical history		
Percentage of involvement	15.73±6.17	5-30
Duration of disease (days)	43.8±20.1	20-120

The total duration of the study was 15 days (7th to 22nd July 2021), with one follow-up visit.

The data of demographics was presented in terms of mean, SD, and range (Table 2). The mean age of patients included in the study was 39.20 years and the percentage of male patients was more than the female patients.

The physical examination and vital signs include temperature, systolic blood pressure, diastolic blood pressure, oxygen saturation (SpO2), and respiratory rate were noted (Table 2) and the averages were found to be 36.91℃, 120.53 mmHg, 78.47 mmHg, 97.17% and 17.5 per min respectively.

The mean duration of disease was 43.8 days with 15.73% as the mean percentage of involvement.

Effectiveness

Assessment of itch severity

The itch score was assessed within the range of minimum zero (0) to a maximum of ten (10) (Table 3).

Table 3: Change in itch severity.

Duration	Mean itch severity scores (mean± SD)	Mean change from baseline	P value	Reduction from baseline (%)
Baseline	6.82±0.72	-	-	-
2 min	5.88±0.75	-0.95±0.41	0.001	13.9
5 min	5.19±0.95	-1.63±0.81	0.001	23.9
10 min	4.73±1.09	-2.09±1.02	0.001	30.6
1 h	4.08±1.32	-2.75±1.16	0.001	40.3
4 h	3.74±1.42	-3.08±1.19	0.001	45.1
8 h	3.37±1.68	-3.45±1.38	0.001	50.6

Table 4: All night itching relief.

Assessment	Number of patients achieving all night relief (N=30)	
	Number	**Percentage**
Strongly disagree	-	-
Disagree	2	6.7
Neither agree nor disagree	8	26.7
Agree	16	53.3
Strongly agree	4	13.3

Immediately after application of thecream 13.9% of patients reported a reduction in itch (at 2 min) and the itch severity scores (mean±SD) reduced from 6.82±0.72 to 5.88±0.75 (p=0.001).

These improvements in itch intensity were observed in patients with time and at the end of the 8 hours, 50.6% of patients reported a reduction in itch with anitch severity score of 3.37±1.68 (p=0.001).

There was a substantial decline in the itch severity with time over 8 hours (Figure 1).

Number of patients who achieved all-night relief from itching

A self-assessment questionnaire was recorded to capture all-night relief from itching as per participant perception after the application of the test product (Table 4). Out of 30 patients, 20 (66.6%) patients agreed that they achieved all-night relief from itching (Figure 2). But 8 (26.7%) patients neither agree nor disagreed with the questionnaire.

Safety of the formulation

No adverse effects have been reported by any of the patients during the study.

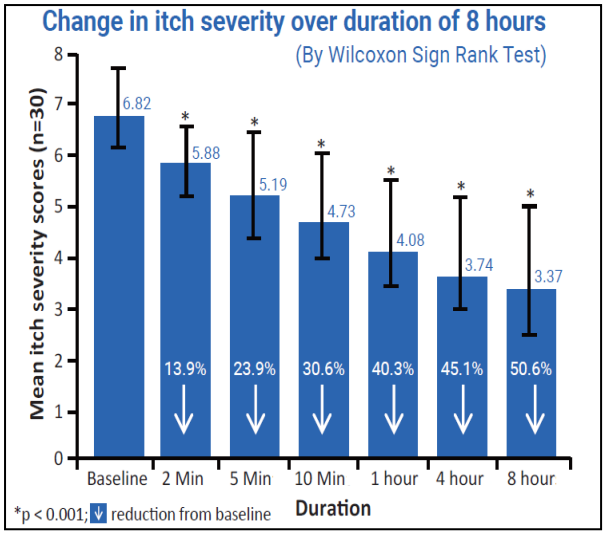

Figure 1: Results of change in itch severity.

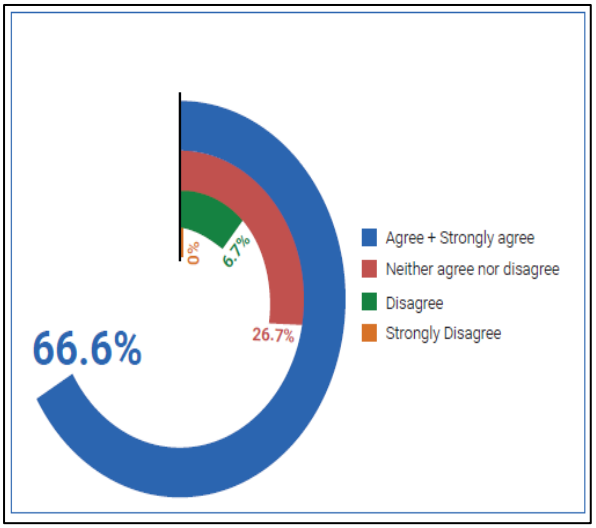

Figure 2: Percentage of patients achieved all-night itch relief.

DISCUSSION

Cutaneous mycoses mostly affect the stratum corneum of the skin.[10] They affect the quality of life of a patient creating a major public health issue. Their clinical significance lies in their morbidity, recurrence, and cosmetic disfigurement. The infections are more prevalent in tropical regions. The etiological agents vary with time and geographical location.[11]

Topical antifungals are necessary for most circumscribed infections and the duration of treatment will be around 1-4 weeks.[12] Azole group of drugs are mostly fungistatic and play a vital role in the management of localized surface infections.[13] These will be preferred for naive and recalcitrant (recurrent) tinea infections because of anti-inflammatory, antibacterial, and broad-spectrum activity.[14] Abuse and uncontrolled usage of topical corticosteroid creams to treat fungal infections has resulted in widespread resistance in India, leading to recalcitrant infections.[15] Previously treatable fungal diseases have now become resistant. So, experts recommend novel antifungals over corticosteroids.

Luliconazole, a novel azole antifungal drug, is extremely potent against dermatophytes. It is the most effective commonly prescribed drug for tinea infections.[16-18] The frequency of application (once daily) and duration of treatment (2 weeks) are also favourable when compared with other topical regimens.[9] It is currently the preferred topical drug among the antifungal agents in India because of its efficacy against dermatophytes at very low levels.[19] A study reported that luliconazole topical therapy was even cost-effective than clotrimazole topical therapy in dermatophytosis.[20]

Luliconazole 1% w/w cream applied once daily for either 2 or 4 weeks is safer and effective for the treatment of tinea pedis.[21,22] As itching is the most prevalent clinical symptom in cutaneous mycotic infections which shows a negative impact on sleep ultimately affecting the quality of life of a patient, itch reduction should be taken into account in a comprehensive treatment approach.[1,19]

A repeated exposure of azoles may be indicative of the development of resistance in dermatophytes.[23] Antifungal drugs are often prescribed with local anesthetics as adjuvants for achieving better treatment outcomes and to avoid repeated drug exposure which may lead to clinical resistance. Topical anaesthetics are excellent antipruritic drugs with few side effects and minimal systemic absorption.[24] Pramoxine, a topical anesthetic with antipruritic property act by stabilising sensory nerve membranes.[25-28] According to studies, 1% pramoxine lotion has shown a significant reduction in itch.[29-31] Pramoxine has been utilised as an excipient in this new single topical formulation (Lucrush® cream), to combat pruritis associated with cutaneous mycoses.

CONCLUSION

In this post-marketing study, 30 clinically diagnosed patients with cutaneous mycoses who are prescribed Lucrush® cream (1% w/w luliconazole with 1% pramoxine) were included and the effectiveness on itch reduction of this cream was assessed using the VAS score to predict the severity of itch after application of the cream. A significant reduction in itch severity within 8 hours of application among patients with tinea cruris, corporis, and facies was observed with no adverse events or serious adverse events were reported by any participant during the entire study duration. Thus, it was concluded that our new topical cream formulation of luliconazole (1% w/w) containing 1% pramoxine as excipient significantly reduced itch severity in cutaneous mycoses with no reported adverse events. Large randomised controlled studies are required to confirm our findings.

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Conflict of interest: Authors Anup Petare, Krishna Veligandla, Rahul Rathod, Akhila Paspulate, and Amey Mane are the employees of Dr. Reddy's Laboratories Limited
Ethical approval: The study was approved by the institutional ethics committee

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