

Original Research Article

Real world retrospective analysis of luliconazole 1% and salicylic acid 3% as fixed dose combination in the management of hyperkeratotic dermatophytosis in India

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ABSTRACT

Background: In recent times, there is increase in prevalence of hyperkeratotic dermatophytosis in India. These hyperkeratotic lesions usually impede the absorption of topical anti-mycotic agent making infection recalcitrant to topical anti-fungal therapy alone. Hence, many times topical keratolytic are used in combination with topical anti-fungal agents which augment the shedding of scales.

Methods: To seek for short period therapy in hyperkeratotic dermatophytosis, we conducted multicentre, retrospective data analysis at 61 dermatology clinics to study effectiveness and safety of Luliconazole 1% and Salicylic acid 3% fixed dose combination (FDC) cream for 2 weeks.

Results: A data of 191 patients were included in this analysis. All patients have received some of the topicals and switched to FDC. Total symptom score of 7.19 ± 1.91 improved to 3.15 ± 1.12 in just 2 weeks ($p < 0.05$). The clinical improvement rate (percentage of 'marked improvement' plus 'moderate improvement') was 78% after 2 weeks of treatment. Moreover, 5 patients (2.61%) achieved complete clearance. This FDC was found to be safe in 51.83% ($n=99$) of the patients whereas 37.7% of the patients ($n=72$) reported it as almost safe. Minor problems with the safety was found in 9.42% of the patients ($n=18$). Two patients (1.04%) reported it as not safe and thus shifted to another drug. Irritation and burning were reported as most common adverse events (AE).

Conclusions: The short combination therapy with luliconazole and salicylic acid as FDC has been found to be effective and safe. It should be a valuable option for hyperkeratotic dermatophytosis for early achievement of clinical cure and better patient compliance.

Keywords: Hyperkeratotic dermatophytosis, Luliconazole, Salicylic acid, India, Retrospective

INTRODUCTION

In recent years, there has been startling change in dermatophytosis in India. Patients are presenting with atypical lesions requiring prolonged treatment and increasing proportion of hyperkeratotic dermatophytosis in India. These hyperkeratotic lesions usually impede the

absorption of topical anti-mycotic agent making dermatophytic infection recalcitrant to topical anti-fungal therapy alone.¹ In such cases, adjunctive oral therapy for 1 to 4 weeks is often necessary, further adding to the potential adverse effects and interactions of the drug.^{2,3}

Therefore, it is very essential to address these characteristics hyperkeratotic lesions effectively. Topical keratolytic, such as 3% salicylic acid (SA), is a practical approach to this problem. By increasing desquamation process, SA augments the shedding of scale, thus reducing fungal load. Through this keratolytic mechanism, SA may work synergistically with topical antifungal increasing its efficacy in the management of hyperkeratotic dermatophytosis. Several reports have shown the usefulness of SA in the management of hyperkeratotic dermatophytosis.^{4,6}

Recently in Indian pharmaceutical market, fixed drug combination (FDC) of luliconazole 1% and SA 3% was commercialized for the management of hyperkeratotic dermatophytosis. Hence, the objective of this study is to assess the effectiveness and safety of this FDC in the management of hyperkeratotic dermatophytosis in real world settings in India.

METHODS

This was a retrospective, multicenter, observational analysis which examined the results in patients with hyperkeratotic dermatophytosis in real-world dermatology practice at 61 centers across India. A pre-validated questionnaire was used to conduct this analysis. The questionnaire was designed to assess the effectiveness and safety of Luliconazole 1% and Salicylic acid 3% as FDC in the management of hyperkeratotic dermatophytosis patients. The study was conducted during June 2020 to September 2020. Only those patients’ records were considered who were diagnosed as hyperkeratotic dermatophytosis, were in the age group of 18-60 years and were prescribed FDC of 1% luliconazole and 3% salicylic acid once a day for 2 weeks. Patients diagnosed with recalcitrant and chronic dermatophytosis were excluded. Additionally, hyperkeratotic dermatophytosis patients treated with other anti-fungal agents in combination with this FDC were also excluded. Since this was retrospective real-world analysis, all the patients fulfilling inclusion criteria from these centres were included. This study was approved by Ethics committee (Suraksha ethics committee).

Statistical analysis

Statistical analysis was done using Statistical package for social sciences (SPSS) (IBM SPSS Inc., Chicago, IL, USA) version 15. Continuous and categorical data were expressed in terms of means and percentage, respectively. To compare changes in mean scores at baseline and 16, the Chi-square test was applied. p<0.05 was considered as statistically significant.

RESULTS

Data of 481 patients’ was analysed out of which 191 patients’ records were included in this analysis who met inclusion and exclusion criteria. Male preponderance over

female (2.1:1) was noted with mean age of 36.63±10.25 years and mean disease duration of 25.5±3.8 days. Most of the patients had presented with criteria for moderate to severe disease, based on symptom severity score. All patients had received some form of the systemic and topical treatment and were switched to FDC. Baseline demographics are described in Table 1.

Table 1: Baseline demographics.

Baseline demographics	
Total	191
Male	129
Female	62
Age (years)	36.63±10.25
Duration of disease (days)	25.5±3.8
Anatomical sites involved in hyperkeratotic tinea infections (%)	
Face	2 (1)
Hand	3 (1.6)
Groin	9 (4.7)
Trunk	16 (8.4)
Foot	36 (18.8)
Multisite	125 (65.4)
Disease severity (%)	
Mild	15 (7.9)
Moderate	25 (13.1)
Severe	151 (79.1)
Previous treatment systemic (%)	
Itraconazole	153 (80.1)
Terbinafine	27 (14.1)
Fluconazole	5 (2.6)
No treatment	6 (3.1)
Previous treatment topical (%)	
Luliconazole	106 (55.5)
Amorolfine	24 (12.6)
Ciclopirox	22 (11.5)
Sertaconazole	22 (11.5)
Ketoconazole	8 (4.2)
Terbinafine	5 (2.6)
Eberconazole	4 (2.1)
Baseline symptom score	
Erythema	2.31±0.79
Scaling	2.49±0.77
Pruritus	2.39±0.79
TSS (total symptom score)	7.19±1.91

Table 2: Effectiveness evaluation.

Marked improvement	Improvement in symptom score by >90%
Moderate improvement	Improvement in symptom score by >50% but <90%
Slight improvement	Improvement in symptoms score by <50%
No change	No change in symptom score
Worsening	Aggravation of symptom score

As per the availability of patients' clinical records, assessments were done at baseline and 2 weeks for effectiveness with 5 step scale as shown in Table 2.

Considering the adverse events (AE), we rated the safety of FDC in accordance with the following 4-step scale: 1=safe (No AE); 2=almost safe (mild AE); 3=minor problems with the safety (moderate AE); and 4=not safe (severe AE requiring discontinuation of FDC).

Binomial variables were expressed as number and percentage and continuous variables as mean (SD). Paired t-test was used for comparisons between baseline and follow-up measurements and significant difference was defined at a level of $p < 0.05$.

Mean total symptom score of 7.19 ± 1.91 improved to 3.15 ± 1.12 in just 2 weeks ($p < 0.05$) as shown in Figure 1. Additionally, there was statistical significant improvement in mean individual symptoms scores as well (Figure 2). The clinical improvement rate (percentage of 'marked improvement' plus 'moderate improvement') was 78% after 2 weeks of treatment (Table 3). Five patients (2.61%)

stopped the treatment due to complete clearance of the lesion.

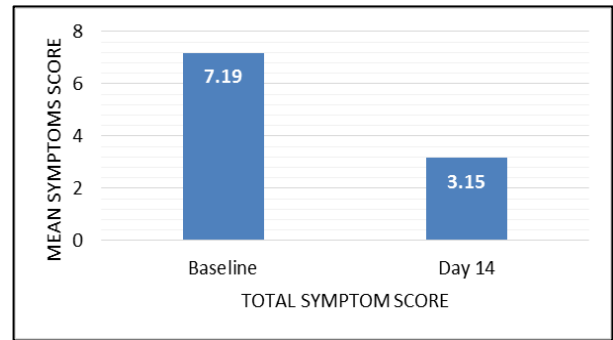


Figure 1: Reduction in mean total symptom score.

This FDC was found to be safe in 51.83% (n=99) of the patients whereas 37.7% of the patients (n=72) reported it as almost safe. Minor problems with the safety was found in 9.42% of the patients (n=18). 1.04% (n=2) reported it as not safe and thus shifted to another drug. Irritation and burning were reported as most common AE.

Table 3: Effectiveness rating of the FDC.

Effectiveness rating	Marked improvement	Moderate improvement	Slight improvement	No change	Worsening
N (%)	13 (6.8)	136 (71.2)	19 (9.94)	21 (11)	2 (1.04)

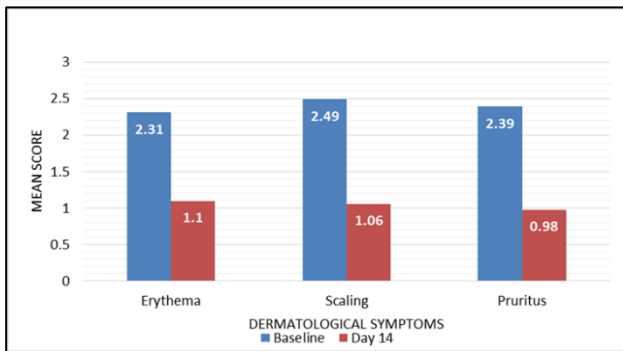


Figure 2: Reduction in mean individual symptom score.

DISCUSSION

Hyperkeratotic dermatophytosis is one the most challenging scenario to treat in office practice. Many patients do not respond to only topical anti-fungal and systemic anti-fungal have their own challenges. Treatment with only topical anti-fungal treatment may not be effective because of poor penetration of these antifungals into affected area. Hence, many times, systemic anti-fungal therapy is required. But side effects profile and drug-drug interactions profile of oral anti-fungal therapy may be one of the hurdle in management of hyperkeratotic dermatophytosis. Thus, combination therapy of anti-

fungal and keratolytic is often needed in daily practice in such scenario.

Since the keratinophilic dermatophytes reside in the stratum corneum, peeling of this superficial layer by keratolytic agents should remove the fungus. Salicylic acid is a keratolytic and 3% salicylic acid has been used in Whitfield's ointment for the management of superficial fungal infection since many years.⁶ Several reports have shown the usefulness of SA in the management of hyperkeratotic dermatophytosis.⁴⁻⁶ It helps in penetration of topical anti-fungal into the affected area through its keratolytic action. Secondly, since salicylic acid does not act directly on fungus, it is unlikely to induce resistance.⁶

Currently, there are no studies regarding combination therapy of luliconazole and SA in hyperkeratotic dermatophytosis but there are many studies suggesting usefulness of anti-fungal and keratolytic in the management of hyperkeratotic tinea pedis.⁷⁻⁹ As per one report, luliconazole was found to be one of the most potent and sensitive topical anti-fungal in current scenario.¹² In this analysis, we analysed the effectiveness and safety of luliconazole and SA as FDC in 191 patients as once daily application for 2 weeks. At the end of 2 weeks, 78% of the patients were classified as either markedly improved or moderately improved. Of this, 5 patients were completely free of symptoms after 2 weeks of therapy.

One of the most common adverse effect of SA is irritation. This is due to its strong acid action. Secondly, application of SA over the inflamed area may cause a severe burning sensation.⁶ In one report by Saoji et al, though all the patients experienced burning sensation, effectiveness was seen in 88% of the patients.⁶ There are many reports regarding safety of topical salicylic acid. In one of the report by Taylor et al, it was found that 28 g of 6% salicylic acid when applied for extensive psoriasis for 5 days neither led to any significant serum level of salicylic acid nor caused any adverse effect.¹⁰ Repeated salicylic acid 30% peeling on the face has also not resulted in any major side effects.¹¹ In this analysis also, 48.16% of the patients reported AE of which 2 patients discontinued the treatment due to severe irritation and burning.

Therefore, topical treatment with luliconazole and SA, shown in this study is an excellent addition to the arsenal in the treatment of hyperkeratotic dermatophytosis.

To the best of our knowledge, the present study is the first real world experience with use of this FDC in management hyperkeratotic dermatophytosis in India. There were a few limitations in the present analysis. Due to retrospective design, the possibility of selection bias cannot be ruled out. Second, the sample size of the present study was very less, which hampers the overviewing of results to larger population.

CONCLUSION

Hyperkeratotic dermatophytosis require combination therapy of topical and systemic anti-fungal agents but systemic drugs may add to the side effects profile, thus leading to less adherence of the patients. In such patients, FDC of Luliconazole 1% and Salicylic acid 3% is a practical approach. From this analysis, it is noteworthy to point out that clinical response of this FDC was enhanced in hyperkeratotic dermatophytosis patients with short course of therapy. This directs us to suggest that this FDC can be better placed in early part of management algorithm of hyperkeratotic dermatophytosis.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Leyden JL. Tinea pedis pathophysiology and treatment. J Am Acad Dermatol. 1994;31(2):S31-3.
2. Richardson M, Elewski B. Superficial Fungal Infections. Oxford: Health Press Limited. 2000.
3. Rupke SJ. Fungal skin disorders. Prim Care. 2000;27:407-21.
4. Rajagopalan M, Inamadar A, Mittal A, Miskeen AK, Srinivas CR, Sardana K, et al. Expert Consensus on The Management of Dermatophytosis in India (ECTODERM India). BMC Dermatol. 2018;18(1):6.
5. Sardana K, Khurana A. Overview of causes and treatment of recalcitrant dermatophytoses. In: Sardana K, editor. IADVL Manual on Management of Dermatophytoses. 1st ed. India: CBS Publishers and Distributors Pvt., Ltd. 2018;80-104.
6. Saoji V, Madke B. Efficacy of salicylic acid peel in dermatophytosis. Indian J Dermatol Venereol Leprol. 2019;10.4103.
7. Tanuma H, Tanuma M, Abe M, Kume H. Usefulness of Ianoconazole (Astat) cream in the treatment of hyperkeratotic type tinea pedis. Comparative study of monotherapy and combination therapy with 10% urea ointment (Pastaron). Mycoses. 2001;44(5):181-90.
8. Tanuma H, Doi M, Sato N, Nishiyama S, Abe M, Kume H et al. Bifonazole (Mycospor cream) in the treatment of moccasin-type tinea pedis. Comparison between combination therapy of bifonazole cream + 10% urea ointment (Urepearl) and occlusive dressing therapy with the same agents. Mycoses. 2000;43(3-4):129-37.
9. Elewski BE, Haley HR, Robbins CM. The use of 40% urea cream in the treatment of moccasin tinea pedis. Cutis. 2004;73(5):355-7.
10. Taylor JR, Halprin KM. Percutaneous absorption of salicylic acid. Arch Dermatol. 1975;111:740-3.
11. Bari AU, Iqbal Z, Rahman SB. Tolerance and safety of superficial chemical peeling with salicylic acid in various facial dermatoses. Indian J Dermatol Venereol Leprol. 2005;71:87-90.
12. Das S, De A, Saha R, Sharma N, Khemka M, Singh S, et al. The Current Indian Epidemic of Dermatophytosis: A Study on Causative Agents and Sensitivity Patterns. Indian J Dermatol. 2020;65(2):118-22.

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