

Original Research Article

The role of topical tacrolimus in adherence to antifungal therapy in recalcitrant tinea incognito: a preliminary non randomised controlled study

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ABSTRACT

Background: The dropout of outpatients on antifungal therapy for recalcitrant tinea incognito is attributable to the flare on withdrawal of topical corticosteroids and the virulence of pathogens. The objective of the study was to evaluate the role of topical tacrolimus in adherence to antifungal therapy in recalcitrant tinea incognito.

Methods: 28 cases of topical corticosteroid induced tinea incognito of more than 6 months duration were enrolled and topical and systemic antifungal therapy instituted for 8 weeks. Topical tacrolimus was also instituted in the test cohort. The end point for resolution was the absence of raised margins, erythema, induration and scaling.

Results: 17 patients were male while 11 were female and their age ranged from 16-45 years (mean 26.5). Two patients were from upper-middle; 5 from lower-middle and 21 from upper-lower socioeconomic class. Their occupations included shop assistants, security guards, drivers and labourers and the duration of illness ranged from 7-36 months. Topical corticosteroids were obtained on prescription by 5 and over the counter by 23 patients. Out of the test cohort of 14, all lesions had resolved in 10 patients who had adhered to therapy and were reviewed at the end of 8 and 10 weeks. While 5 reported burning on application of tacrolimus 1 developed folliculitis. Out of the control cohort of 14, though 5 had adhered to therapy all lesions had resolved only in 3 patients at the end of 8 and 10 weeks.

Conclusions: Topical tacrolimus facilitates adherence to antifungal therapy in recalcitrant tinea incognito.

Keywords: Recalcitrant tinea incognito, Adherence, Topical tacrolimus

INTRODUCTION

The term tinea incognito was introduced by Ive and Marks in 1968 to denote any superficial mycosis caused by dermatophytes that has been rendered unrecognisable by the use of topical corticosteroids either causing masking or unusually extensive or bizarre lesions.¹ The suppression of the local immune response may result in occurrence of lesions at unusual sites and inflammatory lesions such as kerion caused by non-zoophilic species.

The growth, integrity of cell wall and drug resistance of fungal pathogens has been linked to the calcineurin signalling pathway.² Tacrolimus a macrolide derived from streptomyces tsukubaensis is a calcineurin inhibitor used topically for its anti-inflammatory effect in atopic dermatitis and other dermatological disorders.³

The increase in prevalence of superficial dermatophyte infections is attributable to the high rate of dropout of patients from antifungal therapy. The objective of our preliminary study is to evaluate the role of topical

tacrolimus in adherence to antifungal therapy in patients with topical corticosteroid induced tinea incognito.

METHODS

28 clinically diagnosed patients of topical corticosteroid induced recalcitrant tinea incognito attending the outpatient clinics of Dr D Y Patil Medical College, Hospital and Research Centre, Pune, India – a tertiary care teaching hospital in southern India - were included in this preliminary non randomised controlled study spanning 9 months (March 2017 to December 2017). Approval of the institutional ethics committee was obtained and written informed consent taken from patients or guardians. Patients of tinea incognito with inflammatory lesions of more than 6 months duration with a history or clinical findings suggestive of misuse of topical corticosteroids were included. Antifungal therapy was instituted with topical 2% miconazole cream and cap itraconazole 100 mg twice daily for 8 weeks. Topical 0.1% tacrolimus ointment at bed time was instituted in the test cohort of 14 patients but not in the control group. The absence of erythematous plaques with raised margins, induration and scaling were the end points for resolution of lesions. The patients were reviewed at the end of 8 and 10 weeks.

RESULTS

Out of 28 patients 17 (60.7%) were male and 11 (39.3%) female and their age ranged from 16-45 years (mean 26.5). They had an urban or suburban background and their occupations included shop assistants 5 (17.9%); students 5 (17.9%); drivers 4 (14.3%); labourers 4 (14.3%); clerical workers 3 (10.7%); housekeepers 3 (10.7%); security guards 3 (10.7%); and teachers 1 (3.6%). Based on educational and occupational status and monthly income, 2 (7.1%) belonged to the upper-middle; 5 (17.9%) to the lower-middle while the majority 21 (75%) were from the upper-lower class (Table 1) vide the Revised Kuppaswamy socioeconomic status scale.⁴ Two patients (7.1%) used topical corticosteroids on prescription from medical practitioners registered under the Medical Council of India, 3 (10.7%) from AYUSH practitioners registered under the Central Council of Indian Medicine, while 23 (82.1%) had obtained these products over the counter. The duration of illness in 18 (64.3%) ranged from 7-12 months, in 6 (21.4%) from 13-18 months, in 2 (7.1%) from 19-24 months in 1 (3.6%) from 25-30 months and in 1 (3.6%) from 31-36 months (Table 2).

Adherence to antifungal therapy was observed in 10 (71.4%) out of the 14 patients in the test cohort while 4 (28.6%) were lost to follow up (Table 3). In those who had adhered to therapy the lesions had resolved by the end of 8 weeks and there was no relapse on follow up at 10 weeks. Burning or stinging on application of tacrolimus was reported by 5 (50%) out of the 10 patients who had adhered to therapy while 1 (10%) had developed

folliculitis. The patients discontinued topical tacrolimus after 2-8 weeks when the flare on withdrawal of topical steroids had subsided.

Table 1: Socioeconomic status vide revised Kuppaswamy's scale.

Class	Males	Females	Total (%)
Upper-middle	1	1	2 (7.1)
Lower-middle	3	2	5 (17.9)
Upper-lower	13	8	21 (75.0)
Total (%)	17 (60.7)	11 (39.2)	28 (100)

Table 2: Duration of illness.

Duration in months	Number of patients	Percentage of patients (%)
7-12	18	64.3
13-18	6	21.4
19-24	2	7.1
25-30	1	3.6
31-36	1	3.6

Table 3: Adherence to 8-weeks antifungal therapy.

Cohort	Adherence to therapy with percentage	Lost to follow up with dropout rate	Total
Test	10 (71.4%)	4 (28.6%)	14
Control	5 (35.7%)	9 (64.3%)	14
Chi square=3.59		d.f = 1	P=0.058

Table 4: Resolution of lesions in those adhering to 8-weeks antifungal therapy.

Cohort	Number of patients adhering to therapy	Failure to resolve despite adherence to therapy	Resolution without relapse on review at 8 and 10 weeks
Test	10	0 (0%)	10 (100%)
Control	5	2 (40%)	3 (60%)
Fisher's exact test		P=0.19	

In the control group adherence to therapy was observed in 5 (35.7%) out of 14 patients while 9 (64.3%) were lost to follow up. (Table 3). However the lesions had resolved in only 3 (60%) out of the 5 who had adhered to therapy on review at the end of 8 and 10 weeks (Table 4).

DISCUSSION

An increase in prevalence and change in the clinical pattern of superficial dermatophytoses has been reported across India and South-East Asia.⁵ We attribute this to the high dropout rate of outpatients due to the duration and cost of antifungal therapy and the availability of topical corticosteroids over the counter. The rapid relief in

inflammation and the flare on discontinuation is responsible for the potential for abuse of topical corticosteroids.

Impaired Th1/Th2 response, loss of cells expressing Langerhans' cell markers and reduced production of interleukin-1, interferon- γ , tumour necrosis factor- α and granulocyte monocytes colony-stimulating factor by topical corticosteroids has been implicated in recalcitrant dermatophyte infections.⁶

In the present study 10 (71.4%) patients in the test cohort adhered to antifungal therapy as compared to 5 (35.7%) in the control cohort. We attribute the higher rate of adherence to antifungal therapy in the test cohort to the inhibition of the flare on withdrawal of topical corticosteroids by the use of topical tacrolimus. However the difference is not statistically significant (Chi square=3.59, d.f.=1, p=0.058) due to the small sample size.

The major advantage of topical calcineurin inhibitors over topical steroids is that these agents suppress inflammation without inducing cutaneous atrophy even on long term use and can be used not only in flexural areas but also on the face.⁷ Topical calcineurin inhibitors bind to FK506 binding protein preventing calcineurin from dephosphorylating the nuclear factor of activated T cells (NFAT) and the transcription of genes encoding proinflammatory cytokines.³

The pathogenicity of invasive fungal infections not only by yeasts but also by filamentous fungi including *Aspergillus* has been linked to the calcineurin signalling pathway.⁸ The inhibition of calcineurin signalling has emerged as a novel strategy to inhibit fungal virulence and thereby increase the efficacy of existing antifungal drugs.⁹ The transcriptional response to stress by calcineurin activation in *Candida* and *Aspergillus* species is mediated by CRZ-1, the ortholog of the mammalian NFAT in eukaryotic fungal cells.¹⁰

Synergistic antifungal activity of tacrolimus combined with itraconazole against five strains of Trichophyton mentagrophytes has also been demonstrated in vitro by minimal inhibitory concentration (MIC) testing and measuring cell growth.¹¹

Out of the 10 in the test cohort who had adhered to antifungal therapy along with tacrolimus clinical resolution was observed in all (100%) patients as compared to only 3 (60%) out of the 5 patients in the control cohort who had adhered to therapy. We attribute this to the inhibition of pathogenicity and the synergistic action of tacrolimus and itraconazole against dermatophytes in the test cohort. However due to the small sample size the difference is not statistically significant (Fisher's exact test p=0.19).

The adverse effects of topical tacrolimus include transient local irritation at the site of application that decreases over a few weeks. The hypothetical risk of infections and neoplasia because of local immunosuppression by topical calcineurin inhibitors has not been substantiated.⁷

In the present study 5 (50%) had complained of burning after application while 1 (10%) developed folliculitis due to topical tacrolimus out of the 10 patients in the test cohort who had adhered to antifungal therapy.

It is pertinent to mention that there have been several case reports of tinea incognito caused by topical calcineurin inhibitors. Siddaiah et al, reported a case of widespread tinea incognito caused by topical tacrolimus.¹² A solitary scaly plaque of tinea corporis in a 6-year old boy was clinically diagnosed as eczema resulting in the development of multiple scaly plaques of pimecrolimus induced tinea incognito.¹³ A 58-year old male who had used pimecrolimus for a pruritic eruption of the groin was found to have tinea incognito.¹⁴

Despite these isolated reports implicating them as a cause of tinea incognito, topical calcineurin inhibitors may be the 'lesser evil' as compared to topical corticosteroids in reducing inflammation thereby enhancing adherence to antifungal therapy in recalcitrant dermatophyte infections.

CONCLUSION

To conclude the use of topical tacrolimus in recalcitrant topical corticosteroid induced tinea incognito may improve adherence to antifungal therapy. Inhibition of calcineurin signalling may inhibit the virulence of the pathogens.

Limitations

The limitations in our study include (i) lack of randomisation to eliminate bias, (ii) small sample size undermining statistical significance of the outcome and (iii) inadequate follow up for relapse. Randomised controlled studies with larger sample size and longer duration of follow up are required to validate our results.

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

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