

## ORIGINAL RESEARCH

### **A Clinico-Mycological and Therapeutic Study of Recurrent Dermatophytic Infections and Determining the Right Dose and Duration of Systemic Antifungals**

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#### **ABSTRACT**

**Aim:** To analyse clinico-mycological and therapeutic study of recurrent dermatophytic infections and determining the right dose and duration of systemic antifungals.

**Material and methods:** This randomized controlled trial was conducted at the department of DVL, Acharya Shri Chander College of Medical Sciences, Jammu from January 2021 - May 2021 among 90 patients with superficial cutaneous fungal infection coming to the dermatology OPD. Selected 90 patients were assigned to a trial group and given the standard dose of the drug i.e. Tab. Itraconazole (100mg OD), Tab. Griseofulvin (250mg BD) and Tab. Terbinafine (250mg OD). Evaluation was done by clinical assessment in terms of clinical score. The clinical signs and symptoms assessed were scaling, erythema, and pruritus.

**Results:** Tinea corporis was the principal dermatophytic lesion accounted for 93.33% of the study subjects. Pruritus, Erythema, scaling and total scores reduced significantly in all the drugs i.e. Griseofulvin, Itraconazole and Terbinafine. However reduction was reported more in Itraconazole drug in our study. Complete clinical cure was reported in 3.33%, 70% and 26.67% of the subjects in Itraconazole drug at 1st visit (3w), 2nd visit (6w) and 3rd visit (9w) respectively. No cure was reported in Griseofulvin and Terbinafine drug at 1st visit (3w). 23.33%, 76.67% and 6.67%, 43.33% of the subjects in Griseofulvin and Terbinafine drug were completely cured at 2nd visit (6w) and 3rd visit (9w) respectively.

**Conclusion:** Itraconazole was found to be the best drug for the treatment of dermatophytes among the tested antifungals.

**Keywords:** Dermatophytic Infections, Griseofulvin, Itraconazole, Terbinafine

#### **INTRODUCTION**

Dermatophytes are pathogenic fungi responsible for causing superficial mycosis known as dermatophytosis. Dermatophytosis is the most important group of superficial fungal infections caused by dermatophytes, which is a group of closely related keratinophilic fungi that are capable of growing by invading the keratin of skin, hair, and nail for obtaining

nutrients<sup>1</sup>. The severity of the disease relies on the specific strain of the infecting dermatophyte, the sensitivity of the host and the site of infection. About 20-25% of the world's populations are infected with Dermatophytic fungi and the incidence is increasing on a steady basis<sup>2</sup>.

The prevalence of dermatophytosis is attributed to environmental conditions, personal hygiene and individual susceptibility<sup>3</sup>. It is more prevalent in tropical and subtropical countries like India where the heat and humidity are high for most part of the year making dermatophytosis a very common superficial fungal skin infection<sup>4,5</sup>.

In India, it has been a common infection that was easily amenable to treatment with topical and systemic antifungals<sup>6</sup>. However superficial dermatophytosis is no longer a simple infection that is easily amenable to treatment. It has evolved into a chronic and recurrent, difficult-to-treat infection, which affects the physical and the social well-being of the affected patients.

Recurrent dermatophytosis is cutaneous dermatophytosis in which the infection recurred within 6 weeks of stopping the adequate antifungal treatment with at least two such episodes in last 6 months<sup>7,8</sup>. The current guidelines have their own inadequacies, as clinicians are experiencing recurrences, in spite of the adequate recommended therapy, with an end result of patients experiencing physical discomfort, taking incomplete treatment course and enduring financial burden. The treatment recommendations in the standard textbooks of Dermatology appear to have lost their relevance in the current clinical scenario. Thus, the management of dermatophytosis in India is in need of an evidence-based, experience-driven, practical approach from the experts in the field.

In this context, this study has been planned to know the incidence, risk factors & clinical patterns of patients with recurrent dermatophytosis and to find the current trend in the causative organisms. In addition, we intend to observe the therapeutic response in these patients to systemic agents viz. Griseofulvin, Itraconazole, Terbinafine.

## **MATERIAL AND METHOD**

This randomized controlled trial was conducted at the Department of DVL, Acharya Shri Chander College of Medical Sciences, Jammu from January 2021 - May 2021 among 90 patients with superficial cutaneous fungal infection coming to the Dermatology OPD. The study was conducted after obtaining approval from the Institutional Ethical Committee. Prior informed written consent was obtained from the patients (or guardian) before enrolment in the study.

### **INCLUSION CRITERIA**

1. Patients who had at least one episode of relapse of dermatophytosis within 6 months of stopping antifungal drugs
2. Age > 15 years

### **EXCLUSION CRITERIA**

1. Pregnancy, lactation
2. On immunosuppressants, HIV, Malignancy, other infectious diseases, Renal disease, Liver disease, Heart disease, Tuberculosis
3. Age < 15 years
4. Those who did not give consent, unwilling for follow up.

Grouping

<b>GROUP</b>	<b>DRUG</b>	<b>POPULATION</b>
A	GRISEOFULVIN	30

B	ITRACONAZOLE	30
C	TERBINAFINE	30

## METHODOLOGY

- A detailed history was taken focusing on possible risk factors for recurrent dermatophytosis such as a history of contact with pets, atopy, a family history of dermatophytosis, treatment with topical or systemic antifungals alone or in combination with corticosteroids, alcoholism, frequency of habits, type of clothes, other daily habits and familial characteristics
- Past history of similar infections was enquired
- General and systemic examinations of every patient was done.
- Baseline investigations viz. CBC, RBS, LFT, RFT, Serum electrolytes, Cardiac evaluation, HIV was done.
- Specimen to be collected: Skin scrapings from active margin of the lesion without injuring the skin. This is done by scraping with the blade kept flat on the skin surface.
- 10% KOH mount was performed to demonstrate the evidence of fungal infection in skin scrapings. If KOH mount shows positivity, fungal culture was done on Sabouraud dextrose agar to isolate the species of the dermatophyte and at last, determine any correlation between dose and duration of therapy with respect to the species isolated.

## EVALUATION

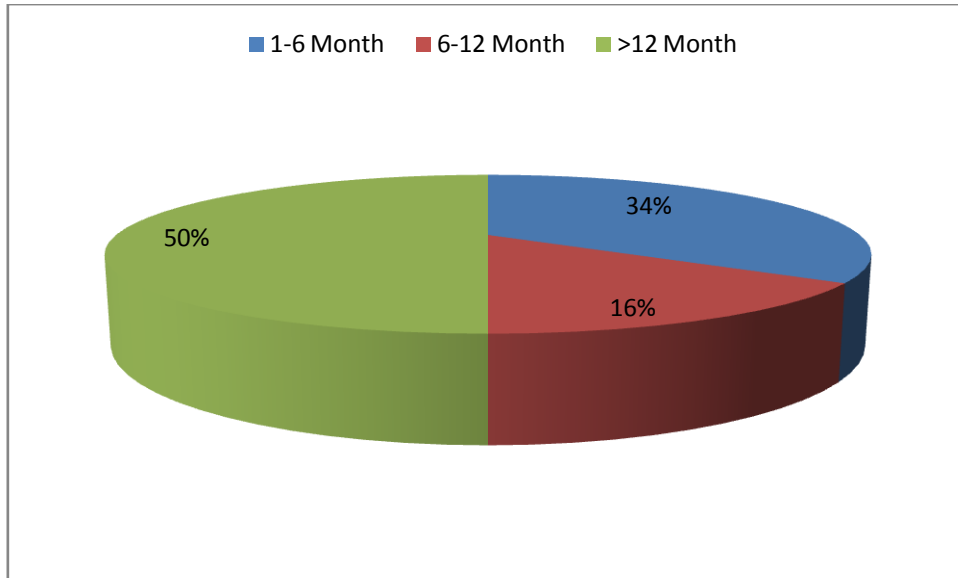
Evaluation was done by clinical assessment in terms of clinical score. The clinical signs and symptoms assessed were scaling, erythema, and pruritus. The signs and symptoms were rated as clinical score 0 to 3 (0-absent, 1-mild, 2-moderate, 3-severe). When there was a partial clinical response in association with intense itching, up dosing was considered. If there was no response or there is occurrence of new lesions, the drug was changed. After complete resolution of the lesion, KOH examination was repeated.

## STATISTICAL ANALYSIS

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). For each assessment point, data were statistically analyzed using one way ANOVA and the level of significance was set at  $p < 0.05$ .

## RESULTS

Selected 90 patients were assigned to a trial group and given the standard dose of the drug i.e. Tab. Itraconazole (100mg OD), Tab. Griseofulvin (250mg BD) and Tab. Terbinafine (250mg OD). Maximum subjects were from the age group of 21-30 followed by 31-40 and 10-20 years. Only 12 subjects were having age >50 years. There was equal distribution of subjects w.r.t. age among the study groups. In our study there were more females (63.3%) as compared to males (36.7%). There was equal distribution of male and female among the study groups. 28.9%, 24.4% and 15.6% of the subjects were housewives, students and farmers respectively. 34.44%, 15.56% and 50% of the subjects were suffering from this disease since 1-6 month, 6-12 month and >12 month respectively (graph 1).



**Graph 1: Duration of disease among the study groups**

Tinea corporis was the principal dermatophytic lesion accounted for 93.33% of the study subjects followed by T.cruris and T.faciei in 35 and 22 subjects respectively. T.corporis+T.faciei, T.cruris+T.faciei and T.corporis+T.cruris+T.faciei was seen in 12.22%, 1.11% and 6.67% of the subjects respectively (table 1).

**Table 1: Distribution of clinical types**

Type	N	%
T.corporis	84	93.33
T.cruris	35	38.89
T.faciei	22	24.44
T.corporis+ T.faciei	11	12.22
T.cruris+ T.faciei	1	1.11
T.corporis+ T.cruris+ T.faciei	6	6.67

Most common organism was Trichophyton mentagrophytes (37.78%) followed by Trichophyton rubrum (20%). Least common organism was Epidermophyton Floccosum (1.11%) followed by T.verrucosum as well as T.violaceum. Pruritus scores reduced significantly with all the drugs i.e. Griseofulvin, Itraconazole and Terbinafine. However reduction was reported more with Itraconazole drug. Erythema scores reduced significantly with all the drugs i.e. Griseofulvin, Itraconazole and Terbinafine. However reduction was reported more in Itraconazole drug followed by Griseofulvin drug. Scaling scores reduced significantly with all the drugs i.e. Griseofulvin, Itraconazole and Terbinafine. However reduction was reported more in Itraconazole drug followed by Terbinafine drug (table 2).

**Table 2: Comparison of Pruritus, erythema and scaling scores at different intervals according to type of drug**

Drug		Pruritus Scores				p value
		Baseline	1st visit (3w)	2nd visit (6w)	3rd visit (9w)	
Griseofulvin	Mean	1.87	1.30	.63	.23	<0.01*
	SD	.571	.596	.615	.43	
Itraconazole	Mean	1.83	1.10	.17	0	<0.01*
	SD	.531	.481	.461	0	
Terbinafine	Mean	2.00	1.63	1.07	.50	<0.01*
	SD	.525	.556	.583	.509	

p value		0.46	0.001*	<0.01*	<0.01*	
		<b>Erythema Scores</b>				
		<b>Baseline</b>	<b>1st visit (3w)</b>	<b>2nd visit (6w)</b>	<b>3rd visit (9w)</b>	
Griseofulvin	Mean	1.60	1.00	.40	.03	<0.01*
	SD	.563	.788	.498	.183	
Itraconazole	Mean	1.73	.77	.20	0	<0.01*
	SD	.583	.679	.407	0	
Terbinafine	Mean	1.57	1.23	.73	.20	<0.01*
	SD	.626	.626	.583	.407	
p value		0.52	0.04	<0.01*	0.007*	
		<b>Scaling Score</b>				
		<b>Baseline</b>	<b>1st visit (3w)</b>	<b>2nd visit (6w)</b>	<b>3rd visit (9w)</b>	
Griseofulvin	Mean	1.33	1.03	.43	.10	<0.01*
	SD	.547	.718	.679	.305	
Itraconazole	Mean	1.43	.70	.10	0	<0.01*
	SD	.504	.596	.305	0	
Terbinafine	Mean	1.57	1.13	.57	.07	<0.01*
	SD	.626	.681	.626	.254	
p value		0.28	0.036*	0.006*	0.23	

\*: statistically significant

Total scores reduced to 4.80 to 0.36, 5 to 0 and 5.13 to 0.77 from baseline to 3<sup>rd</sup> visit (9 week) in Griseofulvin, Itraconazole and Terbinafine drug respectively. Hence reduction was reported more in Itraconazole drug with statistically significant difference (table 3).

**Table 3: Total score comparison at different intervals according to drug**

Drug	Baseline		1st visit (3w)		2nd visit (6w)		3rd visit (9w)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Griseofulvin	4.80	1.19	3.33	1.63	1.47	1.38	0.36	0.20
Itraconazole	5.00	0.98	2.57	1.38	.47	0.97	0	0
Terbinafine	5.13	1.28	4.00	1.46	2.37	1.40	0.77	0.46
p value	0.53		0.002*		<0.01*		<0.01*	

\*: statistically significant

Complete clinical cure was reported in 3.33%, 70% and 26.67% of the subjects in Itraconazole drug at 1st visit (3w), 2nd visit (6w) and 3rd visit (9w) respectively. No cure was reported in Griseofulvin and Terbinafine drug at 1st visit (3w). 23.33%, 76.67% and 6.67%, 43.33% of the subjects in Griseofulvin and Terbinafine drug were completely cured at 2nd visit (6w) and 3rd visit (9w) respectively (table 4).

**Table 4: Complete clinical cure**

Drug	1st visit (3w)		2nd visit (6w)		3rd visit (9w)	
	N	%	N	%	N	%
Griseofulvin	0	0	7	23.33	23	76.67
Itraconazole	1	3.33	21	70	8	26.67
Terbinafine	0	0	2	6.67	13	43.33

## DISCUSSION

Dermatophyte infections are widespread and cause significant distress to the patients socially, emotionally and financially. Recurrent dermatophytosis is fast emerging as a challenge for dermatologists in India. Recurrent dermatophytosis constituted 9.3% of all patients presenting

with dermatophytosis in our study mostly afflicting young adult males<sup>3</sup>. Morbidities of tinea infection are not only because of its frequent relapses but also due to increasing resistance to antifungal drugs that has become a major concern of dermatologists and patients.

Maximum subjects were from the age group of 21-30 followed by 31-40 and 10-20 years. Only 12 subjects were having age >50 years. There was equal distribution of subjects w.r.t. age among the study groups. Similarly Mahajan S et al<sup>9</sup> in their study found that majority of patients were adults (20–40 years). Gopi A et al, Patel P et al and Sumana V et al in their study revealed similar finding.<sup>10-12</sup>

In our study there were more females (63.3%) as compared to males (36.7%). There was equal distribution of male and female among the study groups. Prabhu SR et al and Asadi MA et al in their study showed female predominance too. Females mainly having tinea pedis and manuum and onychomycosis due to kitchen and household work.<sup>13,14</sup>

34.44%, 15.56% and 50% of the subjects were suffering from this disease since 1-6 month, 6-12 month and >12 month respectively in this study. The reason behind such chronicity may be due to inadequate doses of anti-fungal medication, irregular treatment and application of topical steroids, which not only reduce inflammation and pruritus, but helps in proliferation of fungi by modifying their microenvironment. In an earlier study, Kumar et al<sup>15</sup> had found the duration of symptoms to be greater than 3 months in 53.3% of the patients, 1–3 months in 33.7% cases and less than 1 month in 13% of the cases. Mahajan S et al<sup>9</sup> in their study similarly found that a prolonged duration of illness of 6 months and above was found in 53.9% of the patients.

Tinea corporis was the principal dermatophytic lesion accounted for 93.33% of the study subjects followed by T.cruris and T.faciei in 35 and 22 subjects respectively. T.corporis+T.faciei, T.cruris+T.faciei and T.corporis+T.cruris+T.faciei was seen in 12.22%, 1.11% and 6.67% of the subjects respectively in our study. In concordance with the present study, Tinea corporis was also found to be the commonest presentation of Superficial mycosis by A Naglot et al.<sup>16</sup> Barnamoy Bhattacharjee et al<sup>2</sup> in their study similarly reported that Tinea corporis was found the most common form of both superficial mycosis & Dermatophytosis.

Most common organism was Trichophyton mentagrophytes (37.78%) followed by Trichophyton rubrum (20%). Least common organism was Epidermophyton Floccosum (1.11%) followed by T.verrucosum as well as T.violaceum in our study. Barnamoy Bhattacharjee et al<sup>2</sup> in their study similarly reported that Trichophyton mentagrophyte was the most isolated agent causing superficial mycosis. Similarly Sucheta Pathania et al<sup>3</sup> in their study revealed that T. mentagrophytes was the most common isolated organism.

This has been the most frequently isolated organism in other reports from India, although in some studies of tinea corporis and cruris, T. rubrum has been more frequently isolated. The taxonomy of dermatophytes is evolving with increased use of molecular techniques and T. mentagrophytes and T. rubrum are now considered as a species complex with many species defined within each species<sup>3</sup>.

Pruritus scores reduced significantly in all the drugs i.e. Griseofulvin, Itraconazole and Terbinafine. However reduction was reported more with Itraconazole drug in our study. Erythema scores reduced significantly with all the drugs i.e. Griseofulvin, Itraconazole and Terbinafine. However reduction was reported more with Itraconazole drug followed by Griseofulvin drug. Scaling scores reduced significantly with all the drugs i.e. Griseofulvin, Itraconazole and Terbinafine. However reduction was reported more with Itraconazole drug followed by Terbinafine drug. Total scores reduced to 4.80 to 0.36, 5 to 0 and 5.13 to 0.77 from baseline to 3<sup>rd</sup> visit (9 week) with Griseofulvin, Itraconazole and Terbinafine drug respectively. Hence reduction was reported more with Itraconazole drug with statistically significant difference in our study.

Itraconazole was the most effective antifungal agent against *T. mentagrophytes* (MIC- 90 of 0.5 µg/ml), *T. rubrum* (MIC- 90 of 0.03 µg/ml) and *T. interdigitale* (MIC- 90 of 0.125 µg/ml). High MIC for Terbinafine has been reported by Lakshmanan et al<sup>16</sup> from Iran and primary resistance to Terbinafine due to mutation in the squalene epoxidase gene has been reported in *T. rubrum*. Sucheta Pathania et al<sup>3</sup> in their study revealed similar results too. Mahajan S et al<sup>9</sup> in their study too find that Itraconazole was found to be the most sensitive drug among the tested antifungals. The second most sensitive drug was found to be ketoconazole, followed by Terbinafine and Fluconazole. Griseofulvin was the least effective drug among the tested antifungals. These findings are similar to our study. Scholz R et al<sup>17</sup> in their study revealed that resistance to Griseofulvin was found in 50% of strains, as they had a minimum inhibitory concentration >3 µg/ml which is considered as the limit of effectiveness. In a study conducted by Magagnin et al<sup>18</sup>, resistance to Itraconazole was observed in 42.3% of the strains.

Complete clinical cure was reported in 3.33%, 70% and 26.67% of the subjects in Itraconazole drug at 1st visit (3w), 2nd visit (6w) and 3rd visit (9w) respectively. No cure was reported in Griseofulvin and Terbinafine drug at 1st visit (3w). 23.33%, 76.67% and 6.67%, 43.33% of the subjects in Griseofulvin and Terbinafine drug were completely cured at 2nd visit (6w) and 3rd visit (9w) respectively.

## CONCLUSION

Dermatophytosis are commonly found fungal infections. They are predominantly found among females and more among 21-30 age groups. Skin infection types (tinea corporis and tinea cruris) are isolated more than other forms of Dermatophytoses. Itraconazole was found to be the best drug for the treatment of dermatophytes among the tested antifungals. The second most sensitive drug was found to be Terbinafine. Griseofulvin was the least effective drug among the tested antifungals.

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