ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 10 | October - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COMPARATIVE EFFICACY AND SAFETY OF SYSTEMIC TERBINAFINE AND ITRACONAZOLE IN RECALCITRANT TINEA CRURIS

Pharmacology

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ABSTRACT

Background: The prevalence of recalcitrant tinea is increasing despite available treatment options. Itraconazole and terbinafine are the most commonly prescribed agents for tinea. The relative efficacy of both the drugs is under focus and no standard guidelines exist for the recalcitrant tinea.

Objective: To compare their relative efficacy and safety of itraconazole and terbinafine in recalcitrant tinea cruris patients.

Methods: A prospective, randomized, open label study recruited 100 recalcitrant tinea cruris patients of 18-65 years age at dermatology OPD at GNDH hospital, Amritsar, India after obtaining Institutional Ethics Committee approval.

Patients who consented for study and follow up were included. Impaired hepatic/ renal function, secondary bacterial infections or deep mycoses patients were excluded. After randomization, group A comprised of 50 patients who were put on capsule itraconazole 100 mg BD and group B of 50 patients on tablet terbinafine 250 mg OD for eight weeks.

The treatment response was assessed as Complete cure, Treatment failure based on clinical (PGA Score) and mycological (KOH Smear) profile.

Results: Itraconazole resulted in complete cure in 28 patients whereas terbinafine cured 14 patients completely ($p < 0.05$). Treatment failure were observed as 1 and 8 (itraconazole and terbinafine respectively, $p < 0.05$). Both drugs had comparable safety profile with no serious adverse effects. Limitations of the study were short duration, small sample size and non-blinding.

Conclusion: Itraconazole seems relatively more efficacious than terbinafine in the treatment recalcitrant tinea cruris cases.

KEYWORDS

Tinea cruris, Dermatophytosis, Oral Antifungal Drugs, KOH smear

Background

Dermatophytosis is a disease of worldwide importance, especially concerning the developing countries. Its prevalence relates to geographical variations, being more in tropical and subtropical regions like India where the heat and humidity is high for almost the whole year.[1] It remains as one of the most common infections encountered by dermatologists in outpatient departments.[2]

Since last 5–7 years, India has seen an alarming rise in the number of chronic and recurrent dermatophytosis which are difficult to treat.[3] Prevalence of recalcitrant tinea is 3%–5% of outpatient clinic cases in India.[4]

Recalcitrant tinea includes relapse, recurrence, persistence of infection and chronic tinea cases.[5] Relapse can be defined as occurrence of dermatophytic lesions after an infection-free interval of usually 6–8 weeks, in a patient who has been cured clinically.[5] If lesions reoccur usually within < 6 weeks after completion of the treatment, they are said to be recurrent.[5] Chronic dermatophytosis is defined as " Persistence of disease for more than six months to one year, with or without recurrence, in spite of being treated."[6]

The most common causative agent is T. rubrum.[7] It begins with itching in upper medial thigh, involving the groins. The infection spreads centrifugally with partial central clearing. The infection may spread to perineum and perianal areas, gluteal cleft, and buttocks too.

Tinea can be predisposed by hot and humid climate, overcrowding, low socioeconomic status, poor hygiene and sanitary conditions, sharing of clothes/ footwear and certain host factors like physiological variation of skin barrier, age, obesity, immunosuppressive states.[3]

Diagnosis is mainly clinical and may be supplemented by 10% KOH smear, which is a quick, inexpensive and commonly used test for tinea.[8] Fungal culture can be performed as a confirmatory test if results from KOH smear are inconclusive.

Mild superficial infections can be treated by topical agents as these have better pharmacokinetics than their systemic counterparts. Some topical agents used for tinea cruris apart from terbinafine and naftifine are miconazole, clotrimazole, amolorfine, luliconazole. Usual duration of topical agents is once or twice daily for 2–4 weeks.[9]

Use of oral antifungals is advised where the tinea lesions are extensive or chronic, or where application of a topical agent is not feasible.[10] Commonly used systemic AFA include itraconazole, terbinafine, fluconazole and griseofulvin. Out of these Itraconazole, a fungistatic agent and terbinafine, fungicidal, are the most commonly prescribed antifungals because of their higher efficacy, good tolerability, shorter course of treatment and less rate of relapse. Griseofulvin and fluconazole are effective too but these require long-term treatment.[9]

Indian Expert Consensus on the management of dermatophytosis suggest that terbinafine (250 mg once daily) and itraconazole (100 mg – 200 mg/day) are equally effective in treating naive cases and itraconazole (200 mg – 400 mg/day, in divided dose) combined with appropriate topical therapy for recalcitrant cases.

The minimum duration of therapy in naive cases should be 2–4 weeks, while in recalcitrant cases, it should be 4 weeks.[5] It is recommended that antifungal drugs should be continued for 2 weeks post clinical cure in recalcitrant cases.[5] It is advisable to do liver function test (LFT) at baseline to rule out impaired liver function and in follow up too, if the treatment duration exceeds 4 weeks, as some systemic antifungal drugs can be hepatotoxic.

The prevalence of recalcitrant tinea is increasing despite effective treatment options available.[9] Resistance to these drugs is being seen increasingly. Also, due to lack of standard treatment guidelines for recalcitrant tinea cruris, relative efficacy of terbinafine and itraconazole are under focus. With the paucity of data for the same, this study is designed to compare the relative efficacy of itraconazole and terbinafine in the treatment of recalcitrant tinea cruris.

Objectives

The aim of this study was to compare the relative efficacy and safety of oral itraconazole and oral terbinafine in adult patients of recalcitrant tinea cruris.

METHODOLOGY

This was a prospective, randomized, open label study conducted in Department of Pharmacology, Government Medical College, Amritsar in collaboration with Department of Dermatology, Venereology and Leprosy, Guru Nanak Dev Hospital attached to the Government Medical College, Amritsar. Recruitment of the study subjects was started after obtaining the approval of the Institutional Ethics Committee, Government Medical College, Amritsar and the study is also registered with Clinical Trials Registry of India (CTRI/ 2019/ 07/019964).

A total of hundred patients suffering from recalcitrant tinea cruris visiting the Out Patient Department of Dermatology, Venereology and Leprosy and fulfilling the inclusion criteria were recruited in the study after taking an informed consent and after fully explaining the study procedure to their satisfaction in vernacular language.

INCLUSION CRITERIA

1. Male and female subjects between 18 to 65 years with recalcitrant tinea cruris.
2. Willingness to give written informed consent and comply with study procedure, and availability for regular follow up.

EXCLUSION CRITERIA

1. Patients aged less than 18 years and more than 65 years.
2. Patients with associated deep mycosis or mucosal involvement.
3. Patients with secondary bacterial infections.
4. Pregnant and lactating women.
5. Immunocompromised patients like severe uncontrolled diabetes, HIV or receiving chronic systemic glucocorticoid / immunosuppressant therapy.
6. Patients with pre-existing hepatic dysfunction or abnormal liver function test.
7. Patients with severe or advanced renal dysfunction.
8. Patients unwilling to participate or refused giving consent.

- Hundred patients who were clinically and mycologically diagnosed with tinea cruris were recruited in the study.
- These patients were randomized into two groups, A and B, of fifty each. Randomization was carried out with the help of computer software Random Number Generator.
- Patients in Group A were administered capsule itraconazole 100 mg orally twice a day and those in Group B were administered tablet terbinafine 250 mg orally once daily. Both the drugs were administered for a total period of 8 weeks. The patients were advised to take the medications regularly as prescribed at the same time of the day after food.
- Both groups received concomitant treatment with 0.25% amorolfine cream twice daily for local application.
- The severity and the extent of the lesions was assessed by quantification of the signs and symptoms of pruritis, erythema and scaling by:

4-point Physician Global Assessment (PGA) Score, 0 = absent; 1 = mild; 2 = moderate; 3 = severe.[11]

- Direct microscopy of the KOH wet mount of the skin scrapings was done at the baseline to confirm the diagnosis and repeated at 4th, 8th week to see the mycological cure.
- For clinical assessments patients were followed up every two weeks till 8th week. At each visit, clinical response of pruritus, erythema, and scaling was noted on PGA Scale.
- The scores and percentage change in scores of pruritus, erythema and scaling were evaluated at 4th and 8th week.
- The treatment response was assessed by the overall change in the baseline PGA score and the KOH smear test as follows:
- Complete cure - Non residual clinical signs and symptoms except post inflammatory hyperpigmentation (sum score 0) with negative KOH smear.
- Mycological cure - Minimal residual signs and symptoms (sum score<2) with negative KOH smear.
- Improvement – Significant clinical improvement (sum score < 2) with positive KOH or no clinical improvement (sum score ≥ 2) with negative KOH
- Treatment failure-No clinical (sum score >2) with positive KOH

Potassium hydroxide (KOH Smear)

Direct microscopy of Potassium Hydroxide (KOH) smear was done at baseline, 4th, 8th week.

Equipment required were microscope slide and cover glass, 10% KOH, microscope and a small scalpel blade for skin scraping. After placing the scraping of skin on a clean glass slide, 1-2 drops of 10% KOH were added to the collected specimen. Cover glass was placed on top of the glass slide and gently pressed to get rid of any air bubbles. This finished slide was placed on the microscope and examined after 15-20 minutes for fungal hyphae.

Data compilation and Statistical analysis

Data was compiled using Microsoft Office Excel. Data generated from study was tabulated with respect to all parameters at specific intervals. The results were expressed as mean ± SD for quantitative variables. Comparison between the two groups was done by Unpaired T-Test, Chi-Square Test and Mann-Whitney Test. Intragroup comparison was done by Wilcoxon Signed Rank Test. The level of significance was determined by p-value,p>0.05–Non-significant p<0.05–Significant p 0.001 – Highly significant

RESULTS

Mean age of the affected population was 36 years. The disease was more common in males with a male to female ratio of 1.5:1.

The baseline PGA score for itraconazole and terbinafine group were 8.3 ± 0.83 and 8.38 ± 0.87 respectively. There was an overall decrease in PGA score in both the groups at the end of 8 weeks which was 0.74 ± 1.10 and 1.28 ± 1.22 in itraconazole and terbinafine groups respectively (p 0.001, Wilcoxon Signed Rank Test) (Table 1).

Table 1 Intragroup comparison of Physician Global Assessment Score (PGA) from baseline to 8 weeks

	Baseline Mean ± SD	8 weeks Mean ± SD	p-value
Group A Total score	8.30 ± 0.83	0.74 ± 1.10	<0.001
Group B Total score	8.38 ± 0.87	1.28 ± 1.22	<0.001

p >0.05 – Non-significant, p <0.05 – Significant, p <0.001 - Highly significant (Wilcoxon Signed Rank Test)

The mean percent change from baseline to eight weeks for group A was 91.65 ± 12.29 and for group B was 85.34 ± 13.48 (p < 0.05, Unpaired T-Test) (Table 2).

Table 2 Comparison of mean % change in Physician Global Assessment Score from baseline to 8th week

	Group A	Group B	p-value
Mean % Change	91.65 ± 12.29	85.34 ± 13.48	<0.05

p >0.05 – Non-significant, p <0.05 – Significant, p <0.001 - Highly significant (Unpaired T-Test)

All the patients had positive KOH smear at baseline. At the end of 8 weeks, positive mycology was 2% (1/50) and 18 % (9/50) in group A and B respectively (p >0.05, Chi-Square Test) (Table 3).

Table 3- KOH smear for mycological cure (Positive KOH cases at 4th and 8th week)

	Itraconazole (n=50)	Terbinafine (n=50)	p-value
4th week	8	17	<0.05
8th week	1	9	<0.05

p >0.05 – Non-significant, p <0.05 – Significant, p <0.001 - Highly significant (Chi-Square Test)

At the end of eight weeks, itraconazole resulted in complete cure in twenty-eight patients whereas terbinafine cured fourteen patients completely (p <0.05). Mycological cure was attained in thirteen patients in itraconazole group and seventeen patients in terbinafine group (p >0.05).

Improvement was seen in two patients in itraconazole group and in one patient in terbinafine group (p >0.05). Failure of treatment resulted in one patient in itraconazole group compared to eight patients in terbinafine group (p < 0.05, Chi square test) (Table 4).

Table 4 Comparative results of Itraconazole & Terbinafine at the end of eight weeks

Results	Drug		p-value
	Itraconazole Group (n=50)	Terbinafine Group (n=50)	
Complete cure	28	14	< 0.05
Mycological cure	13	17	> 0.05
Improvement	8	11	> 0.05
Treatment failure	1	8	< 0.05

p >0.05 – Non-significant, p <0.05 – Significant, p <0.001 - Highly significant (Chi-Square Test)

DISCUSSION

Itraconazole and terbinafine, were considered for comparative evaluation of safety and efficacy in recalcitrant tinea cruris infection.

The results of the study were assessed on the basis of following four criteria:

Complete cure - Non residual clinical signs and symptoms except post inflammatory hyperpigmentation (sum of PGA score 0) with negative KOH smear.

Mycological cure - Minimal residual signs and symptoms (sum of PGA score <2) with negative KOH smear.

Improvement – Significant clinical improvement (sum of PGA <2) with positive KOH or No clinical improvement (sum of PGA ≥2) with negative KOH.

Treatment failure - No clinical (sum of PGA >2) with positive KOH

KOH smear was done to assess mycological cure. All the patients had positive KOH smear at baseline. At the end of the full course of treatment (eight weeks), positive mycology was 2% in group A and 18% in group B ($p < 0.05$) (Table 3). Shakya et al (2012) observed that at the end of 4 weeks of treatment, positive mycology had fallen from 100% to 8.6% and 17.1% in itraconazole and terbinafine groups respectively when given in similar doses as in our study.[12] These trends are in agreement and itraconazole shows greater mycological cure rates compared to terbinafine.

Physicians Global Assessment (PGA) score was used to assess the clinical improvement. At the end of eight weeks treatment, the PGA score for itraconazole group decreased to 0.74 ± 1.10 from 8.3 ± 0.83 at baseline and that of terbinafine group 1.28 ± 1.22 from 8.38 ± 0.87 at the baseline ($p < 0.001$), (Table 1). The mean percent change of PGA score from baseline to eighth week for group A was 92.49 ± 10.09 and for group B was 84.27 ± 14.83 ($p < 0.05$) (Table 2). Bhatia et al (2019) compared itraconazole (400 mg daily) and terbinafine (500 mg daily) treatment in tinea cruris and corporis patients. At the end of treatment (4 weeks), global clinical response was significantly better in the itraconazole group as compared to the terbinafine group ($p < 0.05$).[13] Singh et al (2020) conducted a randomized pragmatic trial with itraconazole (5 mg/kg/day) and terbinafine (7.5 mg/kg/day). At the end of eight weeks, authors concluded that the cure rates of itraconazole were significantly better ($p < 0.001$).[14]

Mycological cure was achieved in 13 and 17 patients. (Group A and B respectively, $p > 0.05$, Table 4). In total 41/50 (82%) patients attained negative KOH smear in itraconazole group compared to only 31/50 (62%) in terbinafine group. This gap was increased further when PGA scores were factored in, so that 56% (28/50) patients on itraconazole achieved complete cure compared to 28% (14/50) of terbinafine group ($p < 0.05$). However, Shakya et al (2012) in a similar study reported a negligible difference in the cure rates of itraconazole and terbinafine (complete cure 80% i.e. 28/35 : 71% i.e. 25/35, mycological cure 11% i.e. 4/35 : 11% i.e. 4/35).[12] They, however, did not include recalcitrant tinea cruris cases in their sample, which could be a factor contributing to difference in results. Sharma et al. (2019) studied the efficacy of oral terbinafine (250 mg daily) and itraconazole (200 mg daily) combination therapy in the management of recalcitrant dermatophytosis. After 3 weeks of treatment, 90% (18/20) of the patients achieved grade IV (76-100% improvement) in overall clinical symptoms with this combination therapy.[15]

Improvement was recorded in 8 and 11 patients (Group A and B respectively, $p > 0.05$, Table 4) and failure of treatment was observed as 1 and 8 patients (Group A and B respectively, $p < 0.05$, Table 4). Lower comparative failures are thus encountered with itraconazole compared to terbinafine in our study. The obstacles in complete cure of tinea are multiple. Resistance to antifungal drugs, inappropriate or incomplete treatment (non-compliance) and varying quality of drugs are some important factors. Yamada et al (2017) studied terbinafine resistance of dermatophytes due to specific point mutations in its target (squalene epoxidase gene). In 2,056 isolates, 17 were found to be resistant.[16] Similarly itraconazole resistance has also been reported.[17] Sultana et al (2018) studied the antifungal resistance of superficial dermatophyte infection with different antifungal drugs where 20.22% (18/89) patients were resistant to terbinafine 250 mg (once daily) and 76.47% (13/17) were resistant to itraconazole 100 mg (twice daily).[18] These results seem in contrast with our results, if treatment failure is attributed to resistance pattern only. However, design of Sultana et al involved inequal distribution of patients to terbinafine (89) and itraconazole (17) and their study population was also from a vastly different region. Also, some other studies have documented minimum inhibitory concentration (MIC) of itraconazole to be significantly lower than that of terbinafine for same isolates.[19,20] Along with that, there could be other reasons for the treatment failure as pointed out earlier. Although, patients in our sample were probed about the compliance during follow-up interviews and nobody reported missed doses, a lack of compliance could not be ruled out. Another issue is the reported significant Inter-brand variability of itraconazole formulations to the extent of compromising its quality.[21] This has not found with terbinafine.[22]

Due to the availability of numerous brands as well as generics of various antifungal drugs, the quality control becomes a serious concern.[4] Inter-brand variability should be eliminated to achieve similar efficacy of treatment in all the patients and accounted for to get valid results in clinical trials.[15] We took care of inter-brand variability by prescribing same brand of both drugs to all the patients.

Most common adverse effects observed with itraconazole were bloating sensation, nausea and fatigue. Terbinafine group experienced nausea, itching, headache and fatigue during the treatment. There were no serious side effects leading to drug withdrawal in any group implying the similar safety profile of both the drugs. Limitations of our study were non-blinding, small sample size and short duration.

CONCLUSION

Itraconazole 100 mg twice a day was relatively more efficacious than terbinafine 250 mg once daily in improvement of recalcitrant tinea cruris patients based on clinical and microbiological assessment when given for 8 weeks. Both the medicines were well tolerated showing comparative safety profile. Few treatment failures to both the medicines were observed, although the rates were relatively lower with itraconazole.

There is a need to develop strategies to prevent and control antifungal resistance. Over the counter antifungal-steroid combinations should be discouraged as this increases the prevalence of resistant strains. Development of standard guidelines would help in selection of appropriate antifungal agent and its right dose for improving quality of life of patients.

Conflict of Interests: Nil
Funding: Nil

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