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Original Article

Efficacy and Safety of Oral Itraconazole vs Oral Itraconazole Plus Oral Isotretinoin in Treatment of Chronic Recurrent Dermatophytosis

Alina Abbass, Hira Tariq, Saelah Batool, Uzma Amin, Faria Altaf, Javeria Bushra Touqir

ABSTRACT

Objective: To compare the efficacy and safety of oral itraconazole alone versus oral itraconazole in combination with oral isotretinoin in the treatment of chronic recurrent dermatophytosis.

Methodology: This quasi-experimental study was conducted in the Department of Dermatology, Services Hospital, Lahore, over a duration of one year from January to December, 2025, after institutional ethical approval. Written informed consent was obtained, and a total of 125 patients with recurrent tinea cruris and/or tinea corporis were enrolled using a non-probability consecutive sampling technique. Patients were allocated into two groups: group A (n=61) received oral itraconazole alone, while group B (n=64) received oral itraconazole in combination with oral isotretinoin for one month. Patients were followed weekly during the treatment period to assess clinical cure and adverse effects. Mycological cure was assessed at the end of one month of treatment, and patients were then followed monthly for three months posttreatment to evaluate relapse. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26.

Results: The mean age of our study participants was 33.95±7.59 years. This study found no statistically significant difference in clinical and mycological cure at treatment completion between the groups (p=0.06). However, relapse was significantly more frequent in group A (55.7%) compared to the group B (34.4%) (p=0.013). Group B experienced a significantly higher frequency of adverse effects, particularly cheilitis and lip dryness (p <0.001).

Conclusion: There was no significant difference in initial clinical or mycological cure rates between the groups. However, group B receiving combination therapy significantly reduced relapse rates but was associated with a higher frequency of adverse effects in the treatment of chronic recurrent dermatophytosis.

Keywords: *Dermatophytes. Itraconazole. Drug Resistance. Isotretinoin. Antifungal agents.*

INTRODUCTION

Superficial fungal infections affect approximately 20-25% of the global population.[1] Dermatophytosis accounts for 31.29% of all superficial skin infections in Pakistan.[2] Commonly used antifungal treatments are terbinafine and itraconazole. But literature has shown that the cure rates of these treatments are declining, and there is an increasing incidence of terbinafine and itraconazole resistance. A multicenter study in France observed terbinafine resistance in their patients.[3] The molecular basis for this terbinafine resistance is a mutation of the squalene epoxidase enzyme gene, which is involved in the biosynthesis of ergosterol in the fungal cell membrane. [3] Similarly, a study in India also recorded an increased incidence of tinea corporis & tinea cruris, which are resistant to terbinafine and itraconazole, because of irrational use of over-the-counter corticosteroid and antifungal combinations.[4] Dermatophyte infection rates are increasing worldwide due to a complex interaction of host factors, environmental conditions, fungal characteristics, and antifungal drug use.[5] Contributing factors include hot and humid climates, unsupervised use of corticosteroid containing antifungal creams, self-medication with antibiotics, widespread use of oral antifungal agents, extensive agricultural use of antifungals, and the rising incidence of antifungal resistance.[6] To overcome treatment resistance, dermatologists have increasingly prescribed oral antifungal agents at higher doses or for prolonged durations in an attempt to improve cure rates. Previous studies have reported comparatively better treatment outcomes in recurrent dermatophytosis with the combination of oral antifungal therapy and oral isotretinoin. Retinoids are believed to enhance epidermal desquamation, thereby accelerating the shedding of keratinocytes and removal of fungal spores, which may help reduce the fungal burden.[7]

A study conducted in Pakistan in 2021 concluded that combination therapy with oral itraconazole and isotretinoin is efficient and safe for the treatment of chronic tinea.[8] However, clinical evidence regarding the efficacy and safety of combining itraconazole with isotretinoin remains limited in our local population. This study was designed to evaluate

Sharif Medical & Dental College, Sharif Medical City.
Sharif Medical City Road, Off Raiwind Road, Jati Umra,
Lahore 54000, Pakistan.

Correspondence: Dr. Alina Abbas
Senior Registrar, Department of Dermatology
Services Hospital, Lahore
E-mail: alina07aimc@gmail.com

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whether the addition of oral isotretinoin to itraconazole provides superior clinical outcomes and reduces relapse and adverse effect rates compared with itraconazole alone in patients with chronic recurrent dermatophytosis. The findings are intended to address an existing evidence gap and to contribute to the development or modification of evidence-based local clinical guidelines.

METHODOLOGY

This quasi-experimental study was conducted in the Department of Dermatology, Services Hospital, Lahore, over a period of one year from January to December 2025, after obtaining ethical approval from the Institutional Review Board (Letter No. IRB/2025/1511/SIMS, 15-01-2025). Prior studies have reported cure rates of approximately 50-60% with itraconazole monotherapy and 70-90% with combination or higher dose regimens.[9,10] Assuming a cure rate of 55% in the itraconazole group and 80% in the combination group, with a confidence level of 95% and 80% power, the minimum required sample size was 56 patients per group, which was increased to account for potential dropouts and non-compliance. Therefore, a total of 125 patients were enrolled using non-probability consecutive sampling and allocated into two groups: group A (n=61) receiving oral itraconazole alone and group B (n=64) receiving a combination of oral itraconazole and oral isotretinoin. The allocation to one of the two groups was based on clinical decision and eligibility, which resulted in a minor variation in group sizes. This difference in group size was minimal (<5%) and unlikely to introduce significant bias.

Patients aged 18 to 60 years, of either gender, and having chronic recurrent infection with a history of two or more episodes having more than 5 lesions, in the last 6 months, that clear up with treatment but return shortly within 4 weeks were included. Exclusion criteria encompassed the patients who were pregnant, lactating, immunocompromised, with comorbidities such as diabetes mellitus, depression, dyslipidemia, hepatic, renal, cardiac, or neurological disorders, as well as those hypersensitive to itraconazole or isotretinoin, and patients with a history of photosensitive disorders or drug-induced photosensitivity reactions (e.g., exaggerated sunburn, photodermatitis).

A detailed, informed written consent was obtained from all the patients before enrollment, and clear instructions were provided regarding the use of contraception for married females during the study period, as isotretinoin is a potentially teratogenic drug. Additionally, all females of childbearing age underwent monthly pregnancy testing. Patients fulfilling inclusion criteria underwent baseline investigations, including complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), fasting blood sugar, lipid profile, and urine pregnancy test (for women of reproductive age).

Group A received oral itraconazole monotherapy (ICON, Ferozesons Laboratories) at a dose of 100 mg twice daily. Group B received combination therapy consisting of oral itraconazole (ICON, Ferozesons Laboratories) 100 mg twice daily, and oral isotretinoin (Arynoin-Pharma health) 10 mg once daily. Both groups received treatment for a duration of four weeks. Patients were followed weekly during the treatment period to assess clinical cure and adverse effects. Mycological cure was assessed at the end of one month of treatment, and patients were then followed monthly for three months posttreatment to evaluate relapse.

Efficacy was measured by clinical cure, mycological cure, and relapse rate. The safety profile was assessed based on adverse effects. Potassium hydroxide (KOH) examination was performed at baseline to confirm the diagnosis of dermatophytosis and repeated after one month of treatment to assess mycological cure, defined as the absence of fungal elements on KOH microscopy. Clinical cure was considered as >80% resolution of erythematous plaques, while incomplete clinical cure was <80% lesion improvement. Any treatment related side effects like dryness of the eyes and mouth, skin irritation, and redness, reported by the patient or observed during follow-up, were also recorded. Relapse was defined as recurrence of clinical lesions with positive KOH within 12 weeks after completion of therapy.[11]

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables were expressed as mean±standard deviation, while categorical variables were reported as frequencies & percentages. Categorical variables were compared using the Chi-square and Fisher's exact tests, and a p-value <0.05 was considered statistically significant.

RESULTS

The mean age of the 125 patients was 33.95±7.59 years. The majority (57.5%) were females, and nearly half (51%) had <5% body surface area involvement. The disease duration in 44.8% of patients was between six months and one year.

Tinea cruris was the most common presentation (36.8%), followed by tinea corporis with cruris (32.8%) and tinea corporis (30.4%). Family history of dermatophytosis was positive in 84.8% of patients. Both groups had comparable baseline clinical and mycological characteristics, and all patients showed positive KOH findings at baseline. (Table 1). No statistically significant difference was observed between the two groups regarding baseline demographic and clinical characteristics ($p > 0.05$).

By the end of treatment, KOH negativity and clinical cure were achieved in 55.7% of patients in group A and 71.9% in group B. Although a higher proportion of patients in the group B achieved KOH negativity and clinical cure, the difference was not statistically significant (p=0.06). However, a significant difference was observed in relapse rate, with 55.7% in group A compared to 34.4% in group B (p=0.016), suggesting a lower relapse rate with the addition of isotretinoin. Adverse effects such as dryness of eyes and mouth, skin irritation, and erythema were significantly more common in group B (42.2%) than in the itraconazole only group (6.6%) ($p < 0.001$) (Table 2). However, these effects were mild to moderate in severity, managed symptomatically with supportive care (e.g., emollients and lubricating eye drops), and did not require treatment discontinuation.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variables		Group A Itraconazole Only (n=61)	Group B Itraconazole & Isotretinoin (n=64)	Total (n=125)	p-value
Age (Years)	**Mean±SD**	34.12 ± 7.44	33.79 ± 7.76	---	0.81
Gender	**Male**	25(41.0%)	28(43.8%)	53(42.4%)	0.74
	Female	36(59.0%)	36(56.2%)	72(57.6%)	
Body Surface Area Involvement	**<5%**	30(49.2%)	34(53.1%)	64(51.2%)	0.69
	5–10%	22(36.1%)	21(32.8%)	43(34.4%)	
	>10%	9(14.7%)	9(14.1%)	18(14.4%)	
Duration of Disease	**6 Months - 1 Year**	27(44.3%)	29(45.3%)	56(44.8%)	0.77
	>1 Year	34(55.7%)	35(54.7%)	69(55.2%)	
Clinical Type	**Tinea Cruris**	22(36.1%)	24(37.5%)	46(36.8%)	0.83
	Tinea Corporis with Cruris	21(34.4%)	20(31.3%)	41(32.8%)	
	Tinea Corporis	18(29.5%)	20(31.3%)	38(30.4%)	
Positive Family History of Dermatophytosis		51 (83.6%)	55(85.9%)	106(84.8%)	0.72
KOH Positivity at Baseline		61 (100%)	64(100%)	125(100%)	—

Table 2: Comparison of Mycological Cure, Clinical Cure, Relapse Rate, and Adverse Effects between Treatment Groups

Outcome Variables		Group A (Itraconazole) (n=61)	Group B (Itraconazole & Isotretinoin) (n=64)	p-value
Mycological Cure (KOH at the end of Treatment)	**Positive**	27(44.3%)	18(28.1%)	0.06
	Negative	34(55.7%)	46(71.9%)	
Clinical Cure at the end of Treatment	**Complete**	34(55.7%)	46(71.9%)	0.06
	Incomplete	27(44.3%)	18(28.1%)	
Relapse	**Yes**	34(55.7%)	22(34.4%)	0.016*
	No	27(44.3%)	42(65.6%)	
Adverse Effects	**Observed**	4(6.6%)	27(42.2%)	<0.001*
	Not Observed	57(93.4%)	37(57.8%)	

**Significant p-value*

DISCUSSION

A study from India showed that the cure rates of commonly used antifungal treatments, such as terbinafine and itraconazole are declining due to increased virulence of dermatophytes and development of antifungal resistance in patients. For the same reasons, 17% dermatologists reported adding isotretinoin to their routine antifungal regimen.[12] The mean age of the 125 patients in our study was 33.95±7.59 years, and the disease duration in 44.8% of patients ranged between six months and one year. A study from Pakistan reported a mean age of 36.03±6.11 years and a mean disease duration of 6.83±1.86 months. However, unlike our findings, which demonstrated a female predominance, their study reported a male predominance. Furthermore, only 15% of patients in their study had a family history of dermatophytosis compared to 84.8% in the present study.[13]

Our study evaluated the effect of combining isotretinoin with itraconazole and found no statistically significant difference in clinical and mycological cure rates at the end of treatment between both groups (p=0.06). However, relapse was significantly more frequent in group A (55.7%) compared with group B (34.4%) (p=0.016). In contrast, a study reported that 88.3% of 60 patients treated with a combination of itraconazole and isotretinoin achieved significant clinical improvement, while only 5% experienced relapse. The authors concluded that pulse therapy with itraconazole combined with daily adjunctive isotretinoin is an effective treatment regimen for recurrent and recalcitrant superficial dermatophytosis.[13] Alhamdi et al. evaluated low dose isotretinoin combined with itraconazole and reported significantly higher cure rates (97.5%) and lower relapse rates (12.8%) compared with itraconazole monotherapy (53.7% cure and 68.1% relapse). In contrast to their findings of no significant adverse effects, the present study observed significantly more adverse effects, particularly cheilitis and lip dryness, in the group B receiving combination therapy (p <0.001).[11] The evidence indicates variable effects of isotretinoin-itraconazole combination therapy on efficacy and safety outcomes across different studies. Khattab et al. also reported significantly higher clinical (70%) and mycological (83.3%) cure rates in the isotretinoin/itraconazole combination group compared to the itraconazole monotherapy group. Contrary to our findings, they observed no significant adverse effects in the isotretinoin group. They also reported higher cure rates in the voriconazole group, which were comparable to those achieved with combination therapy, highlighting its potential as an effective antifungal agent with relatively low resistance.[14]

A study from India concluded that oral isotretinoin may serve as an effective adjunct in the management of superficial dermatophytosis by promoting earlier remission and reducing recurrence rates. In that study, an earlier mycological cure was achieved with combination therapy. However, no statistically significant difference was observed in mycological cure rates between the combination therapy group (97.5%) and the itraconazole monotherapy group (89.2%) (p=0.06). A significantly lower recurrence rate was observed in the combination therapy group (p=0.01), consistent with our findings.[15] Verma et al. conducted an open label trial comparing isotretinoin plus terbinafine with terbinafine alone in recurrent dermatophytosis and found no significant difference in cure or relapse rates between the groups. Both groups achieved cure rates of approximately 43% with comparable relapse rates (63-65%), suggesting limited additional benefit of isotretinoin with terbinafine therapy. Consistent with the present study, the isotretinoin group experienced more adverse effects, particularly cheilitis and lip dryness.[16]

Difficult to treat dermatophytosis leaves clinicians with the options of increasing the dose, prolonging the duration of therapy, or using combination treatment. The regimens other than retinoids combined with itraconazole are also being explored. Hassaan et al. evaluated the combination of terbinafine with itraconazole and reported no statistically significant difference in clinical and mycological cure rates compared with monotherapy (p=0.207). Notably, the cure rate in the itraconazole monotherapy group (86.7%) was higher than that observed in the present study (55.7%).[17] Another study reported a lower cure rate in the itraconazole group for recurrent chronic dermatophytosis compared to groups receiving higher (supra-pharmacological) doses of itraconazole or combination therapy.[9]

Khurana et al. conducted a broader narrative review of therapeutic strategies in dermatophytosis and highlighted both the potential benefits and safety concerns of combining isotretinoin with antifungals. The keratolytic and epidermal turnover–promoting effects of isotretinoin may enhance fungal clearance. However, the authors concluded that the available evidence remains insufficient to recommend isotretinoin routinely as an adjuvant therapy because

of unresolved safety concerns.[18] To minimize these concerns, Alhamdi et al. used a shorter (2 month) duration combination regimen with low dose isotretinoin (10 mg on alternate days) and reported no significant adverse effects.[11] In contrast, the present study observed a significantly higher frequency of adverse effects in group B receiving combination therapy at the end of the one month treatment period. These findings suggest that the safety profile of isotretinoin remains a key limiting factor, particularly with shorter yet relatively intensive regimens.

CONCLUSION

The addition of isotretinoin to itraconazole did not result in a significant difference in initial clinical or mycological cure rates between the treatment groups. A significantly higher frequency of adverse events was observed in patients receiving itraconazole & isotretinoin combination therapy. However, the combination of isotretinoin significantly reduced relapse rates in patients with chronic recurrent dermatophytosis.

LIMITATIONS & RECOMMENDATIONS

The non-randomized design may introduce selection bias and limit comparability between groups. The single-centered setting restricts the applicability of the findings. The short follow-up period may not adequately capture long term recurrence and delayed adverse effects. In addition, potential confounders such as treatment adherence and environmental factors were not fully controlled, which may have influenced the outcomes.

Adding retinoids to itraconazole is recommended to prevent relapse in patients with chronic recurrent dermatophytosis not responding to itraconazole or terbinafine monotherapy, but the safety concerns should be carefully considered before recommending routine use. Future studies with longer follow-up periods are recommended to assess the durability of response, recurrence patterns, and late onset adverse effects, thereby providing more robust evidence to guide clinical decision-making.

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Authors' Contributions:
Authors approved the draft and are accountable in ensuring that questions related to accuracy or integrity of the work are duly investigated and resolved.
A.A: Conceptualization, study design, data collection, manuscript drafting.
H.T: Data collection, patient follow-up, data analysis.
S.B: Literature review, data interpretation, manuscript writing.
U.A: Methodology, supervision, critical revision of manuscript.
F.A: Statistical analysis, results interpretation, manuscript editing.
J.B.T: Study supervision, final review and approval of manuscript.

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