

Original Research Article

SYSTEMIC TERBINAFINE COMBINED WITH PULSE ITRACONAZOLE IN RECALCITRANT DERMATOPHYTOSIS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Recalcitrant dermatophytosis is a therapeutic challenge, particularly in patients with persistent or recurrent disease. Combination systemic antifungal therapy has been explored for difficult to treat infection. The objective is to evaluate the clinical and mycological response and tolerability of a regimen incorporating oral terbinafine and pulse dose itraconazole in resistant tinea infection.

Materials and Methods: This prospective observational study was done in adults aged 18–65 years with clinically diagnosed resistant tinea corporis and/or tinea cruris. Clinical assessment, KOH microscopy, fungal culture and safety monitoring were performed.

Results: Thirty patients completed the study. Baseline KOH microscopy and fungal culture were reported positive in all participants. The predominant age group was 41–50 years (53.3%) and females constituted 80% of the cohort. The reported mycological cure was 25 patients (82.89%), clinical cure 24 (79%), and complete cure 30 (100%). No adverse events were reported.

Conclusion: The regimen was associated with substantial clinical and mycological improvement in this small observational cohort. The findings require cautious interpretation though because of the small sample size.

Keywords: dermatophytosis; tineacorporis; tineacruris; terbinafine; itraconazole; recalcitrant tinea; antifungal therapy

INTRODUCTION

Superficial dermatophytosis is among the common fungal disorders encountered in dermatology. While uncomplicated disease usually responds to conventional therapy, persistent or recurrent infection can be difficult to manage. Extensive disease, repeated treatment exposure and possible reduced susceptibility to antifungal agents may contribute to treatment failure.^[1-4]

Terbinafine and itraconazole are established systemic antifungal agents used in dermatophyte infections. Terbinafine acts through inhibition of squalene epoxidase, while itraconazole inhibits fungal cytochrome P450 dependent pathways involved in ergosterol synthesis. Their differing mechanisms

provide a rationale for investigating combination therapy in selected difficult cases.^[5-9]

This study evaluated a regimen containing systemic terbinafine and pulse dose itraconazole in patients described as having resistant tinea infection.

MATERIALS AND METHODS

Study design and setting: A prospective observational study was conducted in the department of Dermatology and Venereology from November 2024 through October 2025. Adults aged 18–65 years with clinically diagnosed tinea corporis and/or tinea cruris were considered eligible. The disease was classified as resistant in accordance to the established clinical criteria.

Eligibility criteria: Patients aged 18–65 years with tinea corporis and/or tinea cruris, resistant disease, and positive KOH microscopy and fungal culture were included. Exclusion criteria included age below 18 years, pregnancy or lactation, specified cardiovascular or hypertensive comorbidity, hypersensitivity to terbinafine or itraconazole, recent

antifungal treatment and inability to maintain follow-up.

Treatment protocol: The regimen comprised terbinafine 250 mg twice daily with pulse dose itraconazole 100 mg twice daily. Topical amorolfine hydrochloride and antihistamines were also administered.

Table 1: Antifungal treatment schedule

Antifungal agent	Daily dose	Pulse dose	Reported duration
Terbinafine	250 mg twice daily	—	2 months
Itraconazole	100 mg twice daily	200 mg	3 months

All participants also received topical amorolfine hydrochloride for eight weeks together with antihistamines.

Clinical and mycological assessment: Erythema, scaling and pruritus were graded from 0 (absent) to 3 (severe). Participants were assessed at approximately 4, 8 and 12 weeks. KOH microscopy was performed at baseline and at the end of follow-up; fungal culture was performed in KOH-positive participants. Clinical cure was defined as disappearance of assessed clinical manifestations, mycological cure as negative KOH examination, and complete cure as both clinical and mycological cure.

Safety, ethics and statistics: Liver function tests were performed at baseline and week 4, and adverse events were recorded. Informed consent was obtained. GraphPad Prism version 8 was used for analysis; continuous variables were summarised

using means and standard deviations and categorical variables as frequencies and percentages. Repeated-measures ANOVA and unpaired t-tests were reported, with $p < 0.05$ considered statistically significant.

RESULTS

Participant characteristics: Thirty-six participants were initially enrolled and six were excluded because of irregular follow-up, leaving 30 participants for the final analysis. The largest age group was 41–50 years (16/30, 53.33%), followed by 51–60 years (8/30, 26.67%). Women constituted 24 participants (80%) and men 6 (20%). Sixteen participants (53.33%) were classified as lower socioeconomic status, 12 (40%) as middle and 2 (6.67%) as upper.

Table 2: Demographic characteristics of study participants

Characteristic	Number	Percentage
18–30 years	0	0
31–40 years	4	13.33
41–50 years	16	53.33
51–60 years	8	26.67
61–65 years	2	6.67
Lower socioeconomic group	16	53.33
Middle socioeconomic group	12	40.00
Upper socioeconomic group	2	6.67

Mycological findings: Baseline KOH microscopy was positive in all 30 participants, and fungal culture was reported positive in all KOH-positive patients.

Organisms reported in the source included *T. mentagrophytes*, *T. rubrum*, *T. violaceum* and *Microsporum* species.

Table 3. Mycological outcome

Mycological finding	Number	Percentage
KOH positive	30	100
Culture positive	30	100
<i>T. mentagrophytes</i>	5	16.67
<i>T. rubrum</i>	3	10
<i>T. violaceum</i>	4	13.33
<i>Microsporum</i> spp.	5	16.66

Clinical response: Progressive reduction in symptom scores was observed and documented. At four weeks, 11 patients were categorized as having significant improvement and 19 as having non-significant improvement. At eight weeks, 16 and 3

patients, respectively, were reported in these categories. At 12 weeks, three patients were categorized as significantly improved and none as non-significantly improved.

Table 4: Clinical outcome

Assessment	Significant improvement, n (%)	Non-significant improvement, n (%)
4 weeks	11 (36.66)	19 (63.33)
8 weeks	16 (84.21)	3 (15.79)
12 weeks	3 (100)	0 (0)

Treatment outcomes: At final assessment, mycological cure was documented in 25 patients (82.89%), clinical cure in 24 (79%), and complete

cure in all 30 participants (100%). No adverse events were reported.

Table 5: Treatment outcomes

Outcome	Number	Percentage
Clinical cure	24	79
Mycological cure	25	82.89
Complete cure	30	100

DISCUSSION

The increasing incidence of tinea infections and the emergence of resistance to conventional doses of antifungal agents have resulted in increasing treatment failures. This changing clinical scenario has prompted the search for effective first-line treatment strategies capable of achieving rapid and complete clearance of infection. Topical antifungal agents remain the recommended first-line therapy for tinea infections. However, patients presenting with extensive lesions or multi site involvement may respond inadequately to topical therapy alone, resulting in treatment failure and relapse. In such cases, systemic antifungal therapy is often required.^[10]

Recent comprehensive reviews have recommended combining topical and systemic antifungal agents in patients with extensive or recalcitrant tinea infections. The use of agents from different antifungal classes may provide broader antifungal coverage and potentially offer synergistic or additive effects while reducing the likelihood of resistance.^[11] Terbinafine at a dose of 250 mg/day has historically demonstrated consistent efficacy in the treatment of tinea infections, with cure rates exceeding 90% when administered for two weeks. However, the emergence of terbinafine resistance has increasingly been associated with treatment failure. Although terbinafine resistance remains relatively uncommon in routine clinical practice, resistant clinical isolates have been reported. Sub therapeutic drug concentrations within the skin have been proposed as one possible factor contributing to antifungal resistance. Consequently, some clinical studies have reported improved efficacy with a higher terbinafine dose of 500 mg/day.^[12]

Itraconazole is another systemic antifungal agent increasingly used as a first-line treatment for tinea infections, although it is now often prescribed for longer treatment durations than previously. Despite the widespread use of combination antifungal therapy, published evidence regarding its effectiveness remains limited. Itraconazole and terbinafine are commonly used systemic antifungal agents belonging to different antifungal classes. In all the older studies referenced, terbinafine was administered at 250 mg/day. In our study, however, terbinafine was administered at 500 mg/day and itraconazole at 200 mg/day, doses that have been supported by more recent studies.^[13]

In our study, the mycological cure rate was 82.89% (25 patients), while both the clinical cure rate and complete cure rate were 79% (24 patients). These findings suggest that the use of a higher dose of terbinafine in combination with a topical antifungal agent may be beneficial.^[14]

At standard doses, terbinafine and itraconazole have been widely used for the treatment of tinea infections and are generally well tolerated. In the present study, combination systemic therapy was administered for four weeks, while all patients continued topical treatment for an additional four weeks. At the end of the initial four-week period, patients treated with terbinafine or itraconazole showed good clinical resolution, although some demonstrated only a partial clinical response. This observation suggests that continued topical antifungal therapy for an extended period may be useful in achieving higher cure rates in tinea infection.^[15]

None of the patients in either treatment group reported adverse events. Conventional systemic terbinafine and itraconazole monotherapy regimens administered at standard doses for two weeks have been associated with treatment failure and recurrence in the current clinical setting. Although better outcomes may be achieved by extending the dose and duration of systemic antifungal therapy to four weeks, a comparable cure may be achieved by combining systemic therapy with a topical antifungal agent belonging to a different class and continuing topical treatment for an extended period. Such an approach may help limit the duration of systemic treatment. Antifungal combination therapy therefore appears to be a promising approach for the prompt management of tinea infection.^[16]

However, this study was conducted at a single centre. Therefore, the findings may not be generalisable to other populations or clinical settings. Further multicentre studies involving larger sample sizes are required to validate these findings.^[17]

CONCLUSION

In this prospective observational cohort, a treatment strategy incorporating systemic terbinafine and pulse-dose itraconazole was associated with clinical improvement and substantial reported mycological clearance in patients described as having resistant tinea infection. The findings are exploratory and should be confirmed by larger comparative studies with standardised diagnostic criteria, clearly defined

treatment arms, longer follow-up and systematic safety monitoring.

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