

## Original Research Article

# Comparative safety and efficacy evaluation of terbinafine and itraconazole: dose-based monotherapy versus combination therapy in the management of dermatophytosis: a pilot study in Bangladesh

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### ABSTRACT

**Background:** Dermatophytosis is highly prevalent in South Asia and increasingly chronic and treatment-resistant, with poor responses to standard systemic regimens in Bangladesh. This study compared dose-based terbinafine and itraconazole monotherapies and their combination to identify an optimal regimen.

**Methods:** In a randomized, open-label, parallel-group trial at a tertiary hospital, adults (18-60 years) with KOH-confirmed tinea corporis/cruris/faciei were assigned to: T1 (terbinafine 250 mg/day), I1 (itraconazole 200 mg/day), T+I (terbinafine 250 mg+itraconazole 200 mg/day), T2 (terbinafine 500 mg/day), or I2 (itraconazole 400 mg/day). Follow-up at weeks 2, 4, 6 and 8 assessed total symptom score (itching, erythema, scaling; 0-9), Physician global assessment, composite cure (clinical plus negative KOH) and safety.

**Results:** One hundred fifty patients (30/group) were randomized with comparable baselines. Symptom scores declined significantly in all arms ( $p < 0.001$  within-group). Week-8 composite cure was highest with I2 (96.3%), followed by T+I (89.7%) and I1 (83.3%); T1 and T2 had higher failure (both 51.9%). Adverse events were mild and infrequent.

**Conclusions:** Itraconazole, particularly 400 mg/day, achieved the best efficacy with good tolerability, whereas escalating terbinafine to 500 mg/day conferred no benefit. Treatment of contemporary dermatophytosis in Bangladesh should prioritise itraconazole-based regimens.

**Keywords:** Dermatophytosis, Itraconazole, Terbinafine, Anti-fungal resistance

## INTRODUCTION

Superficial dermatophyte infections of skin tinea corporis, tinea cruris and tinea faciei-represent a substantial share of dermatologic morbidity worldwide, with point prevalence estimates of 20-25%.<sup>1</sup> The hot and humid climate in tropical and subtropical regions of the subcontinent, especially in India and Bangladesh, makes dermatophytes the most prevalent superficial fungal infection.<sup>2</sup> Over the last decade, clinicians across South

Asia have reported dramatic epidemiologic and clinical shifts, including expansion of body surface involvement, family clustering, frequent recurrences and attenuated response to prior first-line regimens.<sup>3</sup> Multiple hypotheses ranging from species shifts and higher inoculum to host and environmental factors, sub-optimal drug exposure and antifungal resistance have been proposed.<sup>4</sup> In Bangladesh, year-round heat and humidity, dense living conditions, and over-the-counter access to topical steroid-antifungal combinations likely amplify

both transmission and treatment failure.<sup>5,6</sup> During the last decade, there has been an uncontrolled rise in atypical and treatment-resistant dermatophytosis has been reported in India and Bangladesh, with trichophyton mentagrophytes/interdigitale emerging as a dominant resistant species complex.<sup>7</sup> Oral terbinafine and itraconazole have long been mainstays for treating tinea corporis, tinea cruris and tinea faciei.<sup>8</sup> However, recent pragmatic cohort studies and clinical experience indicate that clinical cure rates with standard-dose terbinafine have sharply declined, while itraconazole retains better but variable efficacy.<sup>9,10</sup>

In vitro studies suggest that allylamines (e.g., terbinafine), which inhibit squalene epoxidase, and azoles (e.g., itraconazole), which inhibit 14- $\alpha$ -demethylase, may demonstrate additive or synergistic activity when combined, raising interest in dual therapy for difficult-to-treat cases.<sup>11</sup> Clinicians have also experimented with higher systemic doses and prolonged regimens; however, rigorous, locally generated evidence remains scarce.<sup>12</sup> Given the growing specter of antifungal resistance and shifting epidemiology in the subcontinent, individualized dosing and regimen modification have become a clinical necessity rather than an exception.<sup>13</sup>

In recent years, a terbinafine-resistant clonal dermatophyte, trichophyton indotineae (formerly classified within the T. mentagrophytes/interdigitale complex), has emerged as an important cause of extensive, recalcitrant tinea corporis and cruris in South Asia and other regions.<sup>5,12-16,17</sup> T. indotineae has now been reported from multiple continents and is frequently associated with high terbinafine minimum inhibitory concentrations and variable susceptibility to triazoles, underscoring the need for species-level diagnosis and antifungal stewardship.<sup>8-12,15,16,17</sup>

Accordingly, we conducted a randomized, parallel-group pilot trial at a tertiary care hospital in Bangladesh to evaluate the efficacy and safety of five treatment strategies conventional and escalated doses of terbinafine and itraconazole, and their combination at conventional doses with standardized follow-up over 8 weeks. We hypothesized that higher-dose itraconazole and combination therapy would outperform standard monotherapies, while terbinafine dose escalation would not yield additional benefit. This pilot study aims to contribute evidence for guiding future therapeutic strategies for difficult-to-treat dermatophyte infections in high-burden tropical settings.

## METHODS

### Study design

This randomized, open-label, parallel-group pilot clinical trial was conducted at the Department of Dermatology and Venereology, Dhaka Medical College Hospital, from January 2023 to June 2023. The protocol was approved

by the Ethical Review Committee and adhered to the Declaration of Helsinki. The study was registered on ClinicalTrials.gov (Registration Number: NCT05881980). All adult patients participated voluntarily and provided written informed consent.

### Inclusion and exclusion criteria

Inclusion criteria were age 18-60 years, clinical suspicion of tinea corporis, cruris, or faciei and KOH microscopic confirmation of dermatophytosis. Exclusion criteria included pregnancy or lactation, concomitant tinea unguium, pedis, or manuum, use of systemic antifungals or steroids within 4 weeks, comorbid hepatic, renal, or cardiac disease, drug allergies and abnormal baseline laboratory tests.

### Randomisation and interventions

Block randomization allocated 150 participants equally into five groups, each containing 30 patients. All patients were interviewed face-to-face by the researcher. The five treatment groups were: T1 (terbinafine 250 mg once daily), I1 (itraconazole 200 mg once daily), T+I (terbinafine 250 mg once daily plus itraconazole 200 mg once daily), T2 (terbinafine 500 mg/day, administered as 250 mg twice daily) and I2 (itraconazole 400 mg/day, administered as 200 mg twice daily).

All regimens were prescribed for a fixed continuous course of 8 weeks; treatment was not stopped earlier even if apparent clinical improvement occurred. The same brand and batch of medications were used across all patients. Topical antifungals were withheld during the study. All patients received fexofenadine 180 mg at night and an emollient (liquid Paraffin).

### Assessments and outcomes

Follow-ups were conducted at weeks 2,4,6 and 8. The intensity of itching, erythema and scaling was carefully rated at each visit with each of the symptoms rated on a scale ranging between 0 that was absent and 3 (severe). The three individual components scores summed to give the Total symptom score (TSS) which ranged from 0 to 9 indicating the general burden of disease of each patient.

Physician global assessment categorized overall improvement as: I (1-25%), II (26-50%), III (51-75%), and IV (76-100%). Composite cure was defined as clinical cure (erythema and scaling scores of 0; itching score of 0-1) combined with negative KOH microscopic confirmation. Failure was defined as no improvement or worsening by week 4, persistent erythema or scaling at week 8 or positive KOH at week 8.

Safety assessments included adverse events and laboratory tests -Complete blood count (CBC), Liver function test (LFT), Renal function test (RFT) and ECG monitoring was performed routinely because both

itraconazole and terbinafine have rare but recognized associations with QT prolongation and other cardiac effects, and institutional practice is to screen all trial participants receiving prolonged systemic antifungals, regardless of age or baseline cardiovascular risk. Patients who missed two consecutive follow-up visits were considered dropouts.

**Statistical analysis**

Continuous variables were summarized as mean±standard deviation and compared using one-way ANOVA. Categorical variables were presented as numbers (percentages) and compared using Chi-square tests. Within-group changes were assessed with paired tests. Two-sided p values less than 0.05 were considered statistically significant. Analyses were performed using SPSS version 26.

**RESULTS**

A total of 194 patients were screened for eligibility (Figure 1). "Forty-four were excluded for failure to meet inclusion criteria, fulfillment of exclusion criteria, or declining consent. The remaining 150 patients were enrolled after providing written informed consent and were randomized equally into five treatment groups: T1 (terbinafine 250 mg/day), T2 (terbinafine 500 mg/day), I1 (itraconazole 200 mg/day), I2 (itraconazole 400 mg/day), and T+I (terbinafine 250 mg+itraconazole 200 mg/day).

**Patient flow**

All enrolled participants commenced the assigned therapy and also completed their follow-up schedule through the weeks 2, 4, 6 and 8. Seven patients discontinued early (T1: 2; T2: 1; T+I: 1; I1: 1; I2: 2), primarily due to personal reasons or loss to follow-up rather than adverse events. Data from 143 patients were included in the per-protocol efficacy analysis (Figure 1).

**Baseline characteristics**

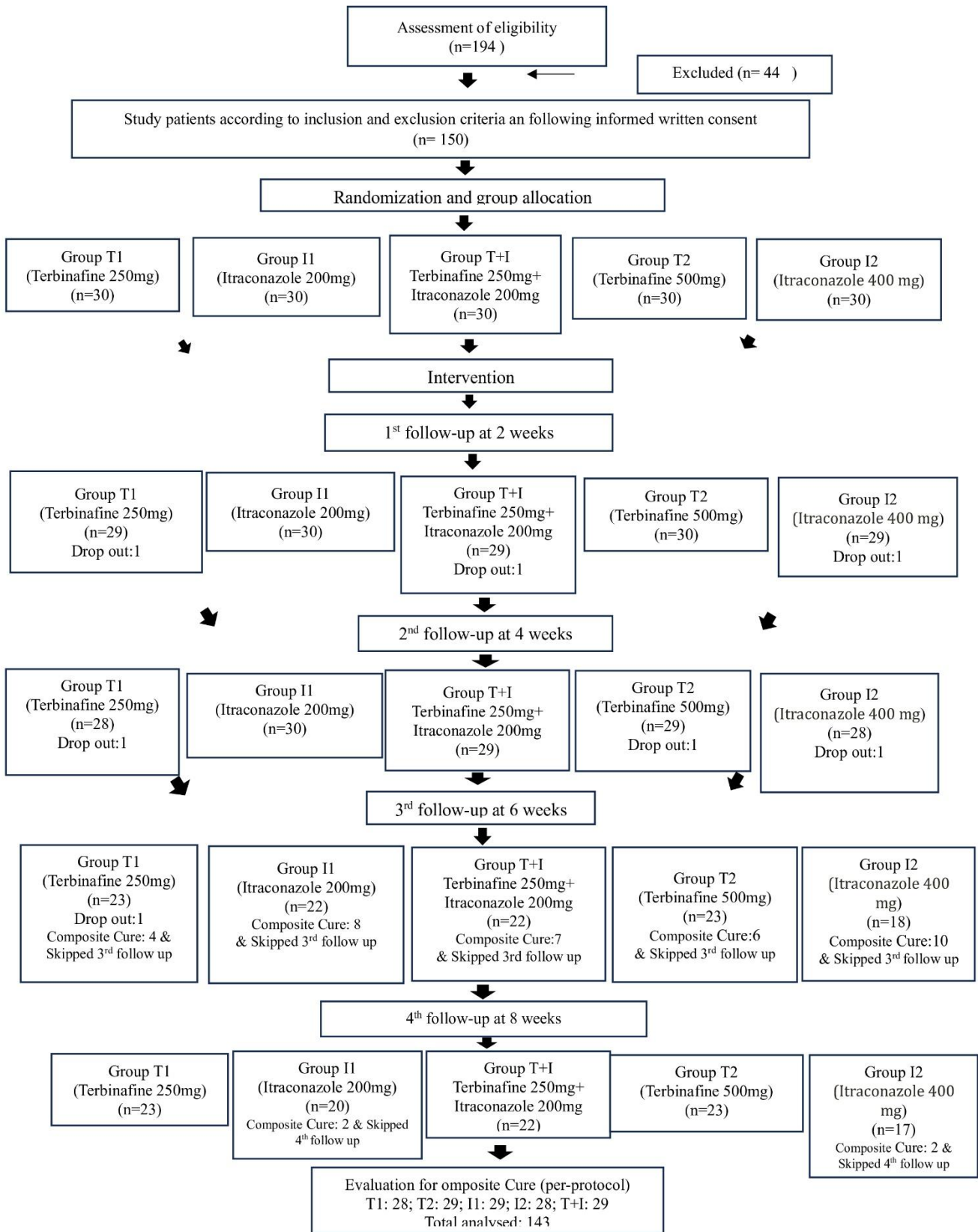
The five groups were comparable with respect to age, sex, education, occupation, disease duration, body surface area and family history of dermatophytosis (Table 1).

The majority (61%) were aged 18-30 years. Combined tinea corporis and tinea cruris was the predominant clinical presentation, with the mean duration of dermatophytosis at enrollment, averaged across groups, was 9.6±2.9 months.

Mean baseline Total symptom scores (TSS) comprising erythema, scaling and pruritus severity (range 0-9) were similar across all arms (T1:8.3±1.26;T2:7.8±1.62; I1:7.63 ±1.67; I2:7.8±1.51;T+I:7.93±1.57; p=0.527). Baseline liver and renal parameters were within normal limits for all participants. Percentages in parentheses are derived from the total of each column (or group). Missing data were excluded. P value was determined by one way ANOVA.

**Table 1: Baseline socio-demographic and clinical characteristics of the study groups.**

Characteristics	T1 (n=30) N (%)	I1 (n=30) N (%)	T+I (n=30) N (%)	T2 (n=30) N (%)	I2 (n=30) N (%)	P value
<b>Age (mean±SD, years)</b>	30.66±10.86	37.06±12.33	32.56±11.66	35.06±10.11	30.16±9.44	0.077
<b>Age 18-30 (%)</b>	21 (70.0)	11 (36.7)	16 (53.3)	10 (33.3)	17 (56.7)	0.067
<b>Sex</b>						
Male (%)	17 (56.7)	12 (40.0)	10 (33.3)	16 (53.3)	16 (53.3)	0.398
Female (%)	13 (43.3)	18 (60.0)	20 (66.7)	14 (46.7)	14 (46.7)	
<b>Clinical variables, types of dermatophytosis</b>						
T. corporis	7 (23.3)	0 (0)	2 (6.9)	4 (13.8)	4 (13.3)	0.119
T. cruris	6 (20)	2 (6.9)	7 (24.1)	7 (24.1)	4 (13.3)	
T. faciei	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.3)	
T. corporis and T. cruris	17 (56.7)	27 (93.1)	19 (65.5)	18 (62.1)	17 (56.7)	
<b>Clinical variables, duration of dermatophytosis</b>						
Baseline disease duration (months) mean±SD	6.9±6	12.03±13.74	7.1±4.76	8.73±9.2	13.18±14.91	0.068
<b>Clinical variables, family history</b>						
Positive family history of dermatophytosis	14 (46.7)	14 (48.3)	12 (40)	14 (46.7)	12 (40)	0.942
<b>Clinical variables, affected body surface area</b>						
Body surface area (%) mean±SD	7.05±7.20	6.71±5.03	5.55±4.03	6.28±4.22	5.51±5.36	0.733
<b>Clinical variables, total symptom score (severity of erythema, scaling, pruritus)</b>						
Total symptom score (mean±SD)	8.3±1.26	7.63±1.67	7.93±1.57	7.8±1.62	7.8±1.51	0.527



**Figure 1: Consort flow diagram of participant progress through the trial.**

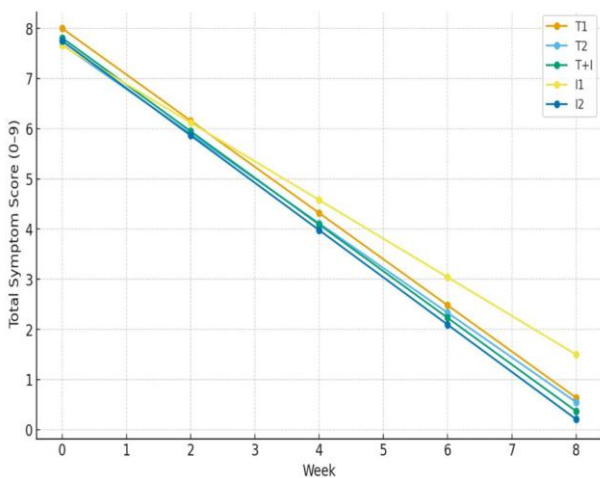
**Table 2: Changes in serum creatinine and SGPT levels during 8 weeks of therapy in the study groups.**

	Group	Baseline mean±SD	4th week mean±SD	8th week mean±SD	P value
<b>Serum creatinine (mg/dl)</b>	T1	0.88±0.25	0.88±0.18	0.94±0.29	0.427
	I1	0.82±0.23	0.82±0.18	0.87±0.14	0.404
	T+I	0.84±0.21	0.83±0.16	0.86±0.31	0.411
	T2	0.86±0.24	0.92±0.23	0.88±0.19	0.261
	I2	0.84±0.20	0.79±0.14	0.82±0.18	0.472
<b>SGPT (u/ml)</b>	T1	30.43±14.14	31.32±16.95	36.78±21.04	0.072
	I1	30.03±14.73	28.06±16.71	31.25±13.16	0.326
	T+I	25.13±12.70	25.89±11.09	28.63±13.71	0.068
	T2	25.65±9.77	29.81±14.08	31.42±20.63	0.163
	I2	25.46±10.89	28.01±14.97	25.47±13	0.887

**Symptom trajectory**

A progressive, statistically significant decline in mean TSS was observed in all groups over 8 weeks ( $p < 0.001$  within-group; Figure 2). At week 8, TSS values were: T1:  $1.65 \pm 1.87$ ; T2:  $2.19 \pm 2.24$ ; I1:  $1.10 \pm 1.68$ ; I2:  $0.42 \pm 1$  and T+I:  $0.45 \pm 0.73$ .

The Itraconazole 400 mg group (I2) exhibited the greatest symptom reduction, followed by T+I and I1. Between-group analysis confirmed a significant difference favoring itraconazole-based regimens.



**Figure 2: Total symptom score trajectories by treatment group over 8 weeks.**

Figure 2 shows Mean total symptom score (TSS; sum of itching, erythema and scaling, range 0-9) at baseline and weeks 2, 4, 6 and 8 for each treatment group (T1, T2, I1, I2, T+I). All groups showed a progressive decline in TSS over 8 weeks. The itraconazole 400 mg/day group (I2) exhibited the greatest and most sustained symptom reduction, followed by combination therapy (T+I) and itraconazole 200 mg/day (I1), whereas terbinafine monotherapy groups (T1 and T2) showed higher residual symptom scores at week 8.

The proportion of participants in both monotherapy groups receiving terbinafine (T1 or T2) achieving this clinical and mycologic end point was 48.1% in each group (Figure 3). Bar chart showing the proportion of participants in each treatment group achieving composite cure at week 8, defined as clinical cure (erythema and scaling scores of 0; itching score 0-1) plus negative KOH microscopy. Cure rates were highest with itraconazole 400 mg/day (I2), followed by combination therapy (T+I) and itraconazole 200 mg/day (I1), while both terbinafine monotherapy groups (T1 and T2) demonstrated lower composite cure rates and higher treatment failure.

Moreover, as shown in Physician global assessment, a significant clinical improvement (reduction of symptoms over 75% or grade III-IV) was experienced in over 80% of study participants with itraconazole-based groups and in less than half of study participants in terbinafine-monotherapy groups. The treatment with an augmented amount of terbinafine did not produce any significant amount of advantage in comparison with normal dose (250 mg) Figure 3.

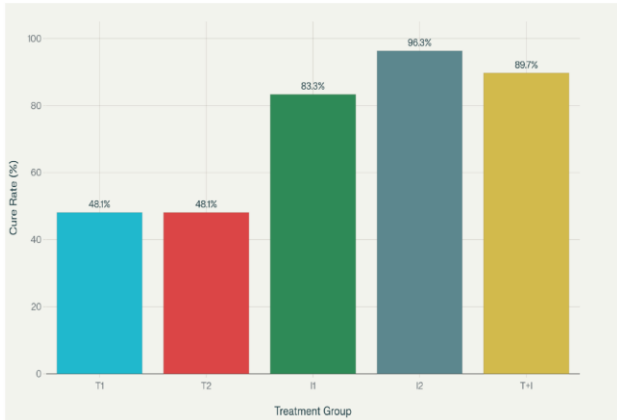
Each bar depicts the percentage of participants in that arm who achieved composite cure, defined as simultaneous resolution of clinical signs and a negative KOH microscopic finding. This visual summary facilitates direct comparison of the efficacy profiles for each therapeutic strategy evaluated in the study.

**Safety**

Each groups had no serious adverse reactions and none was discontinued of therapy due to safety concerns as noted in Table 2. Reported minor adverse events included dizziness (1 case), gastric irritation (1) and vertigo (4), distributed sporadically across groups without dose association.

Mean serum creatinine and SGPT levels remained within normal limits at baseline, week 4, and 8. Transient fluctuations were observed but were clinically insignificant: creatinine ( $p = 0.26-0.47$ ) and SGPT ( $p = 0.07-0.89$ ) showed no meaningful variation between-

groups. No participant developed hepatotoxicity or elevated creatinine. No cardiac-related complaints were noted during itraconazole therapy; ECG monitoring was performed as per protocol, with no abnormal findings reported.



**Figure 3: Week 8 composite cure rates by treatment group.**

## DISCUSSION

This was a randomized pilot trial conducted in Bangladesh to compare the efficacy and safety of dose-based monotherapy of terbinafine, itraconazole, itraconazole and terbinafine combination therapy for the treatment of dermatophytosis. Composite cure rate of 96.3% was achieved with itraconazole 400 mg/day at 8 weeks and this result was very similar to the study by Singh et al, itraconazole 200 mg/day and itraconazole 200 mg/day with terbinafine 250 mg/day combination therapy also performed well with composite cure rate 83.3% and 89.7% respectively.<sup>16</sup> These results align with regional observational study that clinical effectiveness of terbinafine has declined, whereas itraconazole retains activity against contemporary dermatophytes strains.<sup>2,9,12,13</sup>

The itraconazole 400 mg/day regimen used in this trial exceeds the standard labeled doses for tinea corporis and tinea cruris, where product characteristics typically recommend 100-200 mg/day for 1-2 weeks in immunocompetent adults.<sup>18-23</sup> By contrast, higher daily doses of 400 mg given in short pulses are widely used and well tolerated for onychomycosis, reflecting the need to achieve adequate drug levels in keratinized tissues.<sup>18,21</sup> Pulse regimens (e.g., itraconazole 200 mg twice daily for 1 week per month) are attractive from a convenience and safety perspective and are endorsed for nail disease; however, their role in extensive chronic tinea corporis/cruris in high-burden settings remains uncertain, and several South Asian series have instead favored continuous therapy for 4-8 weeks to address high fungal load and frequent recurrences.<sup>19-23</sup> Our findings suggest that, in this context, a higher continuous dose of itraconazole can be effective and generally well tolerated,

but future studies should directly compare continuous and pulse regimens across different disease severities and body weights.

Our data, consistent with previous reports, indicate that doubling the dose of terbinafine provides minimal additional clinical benefit, because of growing antifungal resistance in South Asia, which further substantiates the role of insufficient treatment duration over any attempt to treat infection efficiently.<sup>16</sup> It has been proved that in this region, doubling the dose of terbinafine in specific treatment arms, does not show the linear benefits due to increasing resistance. Studies from different geo-regions show that this happens mainly because trichophyton species develop resistance through mutations in the squalene epoxidase gene.<sup>5</sup>

Itraconazole, which acts by attacking a different fungal enzyme (14- $\alpha$ -demethylase), has always shown good cure rates, and this finding is in accordance with the proposed mechanisms that treatments of various steps in ergosterol biosynthesis will have additive therapeutic effect.<sup>24</sup> The combination regimen has had an equivalent efficacy as demonstrated by high-dose itraconazole, indicating the proposed mechanisms in this instance.<sup>16</sup> However, since combination therapy was not found to be better than high-dose itraconazole, using it routinely may not be necessary either clinically or financially especially for patients with stubborn, severe, or recurrent infections.

Most treatment groups showed that the medications were well tolerated, with no serious drug-related problems. Some patients had mild side effects like dizziness, stomach upset or brief vertigo, but these were short-lived and did not require stopping treatment. Blood tests for liver (SGPT) and kidney (S. creatinine) function stayed within normal limits during follow-up, showing that short-term itraconazole is generally safe for the liver.<sup>19</sup>

Also, no patients developed heart rhythm problems or QT prolongation on ECG while taking itraconazole and has a very low risk of causing heart issues when used at the recommended dose for short period of time.<sup>27-30</sup> A further practical limitation of high-dose itraconazole is its potential for clinically relevant drug-drug interactions, mediated by potent inhibition of cytochrome P450 3A4. Although our trial population was relatively young and major comorbidities requiring interacting medications were exclusion criteria, careful review of concomitant drugs and monitoring for interactions remain essential in routine practice, especially in older patients or those receiving cardioactive agents, anticoagulants, or other narrow-therapeutic-index drugs.<sup>31,32</sup> High humidity, easy access to steroid-antifungal creams, and ongoing household spread are likely causes of antifungal resistance in Bangladesh, similar to neighboring countries.<sup>6</sup>

This trial has important limitations. Diagnosis and follow-up were based on clinical assessment and direct

KOH microscopy, without fungal culture, species identification or antifungal susceptibility testing, so the causative dermatophyte species and underlying resistance mechanisms could not be confirmed.<sup>5,12,14,16,32</sup> In particular, we were unable to determine whether *T. indotineae* or other terbinafine-resistant genotypes contributed to the high failure rates observed in the terbinafine monotherapy arms, despite regional and global reports of *T. indotineae*-associated recalcitrant dermatophytosis and escalating terbinafine resistance.<sup>8,12,14,16,32</sup> These microbiological constraints reflect limited access to routine dermatophyte culture, sequencing, and susceptibility testing in many resource-constrained settings and should be considered when extrapolating our findings.<sup>3,4,6,9,12</sup> In addition, the trial was single-center, open-label, and limited to 8 weeks of follow-up, without post-treatment relapse assessment; larger multicenter studies with extended follow-up and comprehensive mycological work-up are needed to validate and refine these observations. Nevertheless, strengths include randomized allocation, standardized assessments, uniform drug sourcing and prespecified outcomes relevant to routine practice. The consistency between symptom trajectories and cure rates strengthens internal validity. Considering the overall situation, itraconazole appears to be the systemic agent of choice for managing dermatophytosis.

## CONCLUSION

Itraconazole particularly 400 mg/day doses achieved superior week-8 composite cure and symptom resolution compared with terbinafine, while terbinafine dose escalation conferred no benefit. Combination therapy performed well. In contemporary dermatophytosis in Bangladesh, clinical practice should shift toward itraconazole-based regimens with appropriate safety monitoring.

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*Conflict of interest:* None declared

*Ethical approval:* The study was approved by the Institutional Ethics Committee (NCT05881980)

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