

Original Research Article

Comparative study of terbinafine or itraconazole monotherapy versus combined therapy in dermatophytosis

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ABSTRACT

Background: Dermatophytosis, is a very frequent fungal infection of skin prevailing in underprivileged countries. As drug resistance of monotherapy is rising rapidly, combination therapy is blooming as the preferred choice. Itraconazole and terbinafine are widely used antifungal drugs in Bangladesh. Although many studies on monotherapy of these drugs have been done for the treatment of fungal infections, but study on their combined use showing difference with cure rates and recurrence rates in our country is still inadequate. Objectives were to determine and compare the clinical outcome of monotherapy with terbinafine or itraconazole comparing with combined therapy in various dermatophytosis (tinea infections).

Methods: Clinically diagnosed patients suffered from various tinea infections at multiple private clinics in Gazipur district of Bangladesh were treated from January to June 2024. Total 150 patients were divided into three groups (Itraconazole only, terbinafine only and combination of both). The therapeutic effects were evaluated by clinical cure rate by clinical symptoms, mycological cure rate by mycology examination, adverse effects, and recurrence rates of disease.

Results: The data of patients were evaluated biweekly period and at 4 and at end of 8 weeks of therapy. In the combined group, the symptoms were significantly cured, in comparison to the terbinafine or itraconazole group ($p1 < 0.05$ and $p2 < 0.05$). The clinical cure rate, mycological cure rate, recurrence rate showed 92%, 90% and 4% in combined group, 78%, 74% and 14% in terbinafine group, 74%, 70% and 18% in Itraconazole group respectively. The combination therapy achieved better results. Adverse effects were less in each group during follow-up. The 96% patients was satisfied with combined treatment.

Conclusions: Combination therapy is more efficacious than monotherapy for treatment of tinea infections and demonstrates more successful strategy for treating resistant dermatophytosis.

Keywords: Tinea infections, Terbinafine, Itraconazole, Combination therapy

INTRODUCTION

Over the past several decades, fungal infections have emerged as a substantial global health concern, with an estimated worldwide prevalence ranging between 20% and 25%. This rising burden contributes significantly to

morbidity and mortality and presents persistent therapeutic challenges for clinicians.¹ These infections are ubiquitous, adversely affecting life and frequently giving rise to social and psychological burden. Moreover, their chronicity and tendency for recurrence are key factors associated with superficial mycoses.^{2,3}

Dermatophytic infections involving the skin, hair, and nails—most commonly manifesting as tinea capitis, tinea pedis, and onychomycosis—constitute a major proportion of superficial fungal diseases. Such infections are generally amenable to treatment with either topical or systemic antifungal agents.⁴ Among the available therapeutic options, terbinafine and itraconazole have remained the most widely prescribed systemic antifungals owing to their favorable pharmacokinetic profiles and broad antifungal spectra.^{2,3}

Terbinafine, an allylamine antifungal agent, is widely regarded as the drug of choice for dermatophytosis caused by trichophyton species because of its potent fungicidal activity.⁵ Its primary mechanism of action involves inhibition of the enzyme squalene epoxidase, a critical component of the ergosterol biosynthetic pathway essential for maintaining fungal cell membrane integrity.⁶ This enzyme catalyzes the conversion of squalene to 2,3-oxidosqualene, a key intermediate in ergosterol synthesis.⁷ Inhibition of this step results in toxic intracellular accumulation of squalene, which underlies the fungicidal effect of terbinafine.⁸ Resistance to terbinafine among dermatophytes has been increasingly attributed to point mutations within the fungal squalene epoxidase (SQLE) gene.⁹

In contrast, Itraconazole, a triazole antifungal, exerts its effect by inhibiting the cytochrome P450-dependent enzyme lanosterol 14 α -demethylase, thereby blocking the conversion of lanosterol to ergosterol. This disruption compromises fungal cell membrane synthesis and confers broad-spectrum activity against both dermatophytes and yeasts.^{10,11} Due to its high protein-binding affinity and prolonged tissue persistence, itraconazole is particularly suited for pulse therapy, ensuring sustained drug concentrations at the site of infection that exceed corresponding plasma levels.¹²

Lately, the management of superficial mycoses has been increasingly complicated by rising antifungal resistance, with reports of chronic disease, frequent relapses, and therapeutic failure becoming more common.¹³⁻¹⁵ The global spread of antifungal-resistant dermatophytosis has been facilitated by increased international travel and population migration.¹⁶ Resistance is further promoted when conventional drug dosages and treatment durations are employed, partly due to reduced effective drug concentrations resulting from extensive sequestration of terbinafine and itraconazole within the skin and adipose tissue.^{12,17}

In spite of the fact that terbinafine and itraconazole demonstrate satisfactory efficacy as monotherapies, the growing prevalence of resistant infections and recalcitrant disease has necessitated exploration of combination regimens and alternative dosing strategies.¹⁸

Combination therapy represents a rational therapeutic approach aimed at achieving faster clinical and

mycological clearance by exploiting synergistic or additive pharmacodynamic effects while potentially mitigating resistance. *In vitro* studies have demonstrated synergistic activity between terbinafine and itraconazole against a broad spectrum of dermatophytes and non-dermatophyte fungi, suggesting enhanced efficacy and reduced treatment duration.^{19,20} Despite the relatively higher risk of adverse effects and drug–drug interactions associated with itraconazole, its combination with terbinafine may offer distinct advantages, particularly in infections caused by terbinafine-resistant strains. This synergy arises from their complementary inhibition of distinct steps within the same ergosterol biosynthetic pathway.^{7,21-23} Additionally, combination therapy may reduce drug-related toxicity by allowing lower individual dosages while optimizing pharmacokinetic performance.²⁴

The present randomized controlled trial aims to generate robust evidence regarding the safety and therapeutic efficacy of selected antifungal treatment regimens.²⁵ Specifically, this study evaluates the effectiveness of terbinafine and itraconazole administered as monotherapy and in various combination and dosing schedules for the treatment of tinea infections.²⁶ By integrating clinical evaluation with mycological assessment, this study seeks to provide comprehensive evidence supporting the clinical utility of terbinafine-itraconazole combination therapy compared with monotherapy in the management of dermatophytic infections.

METHODS

The study was designed as a randomized, controlled, parallel-group, single-blind trial to comparatively evaluate the efficacy and safety profiles of terbinafine and itraconazole when prescribed as monotherapy versus combined therapy. The study was carried out across multiple private clinics in Gazipur, Bangladesh, over a six-month period from January to June 2024.

Study population

A total of 150 patients with clinically and mycologically confirmed tinea infections—including tinea corporis, tinea cruris, tinea pedis, and tinea unguium—were taken, ranged in age from 18 to 55 years. Individuals were excluded if they had a known allergy to terbinafine or itraconazole, were pregnant or lactating, had underlying hepatic or renal dysfunction, or were receiving concurrent antifungal therapy. Ten participants were excluded due to poor treatment adherence.

Intervention and treatment allocation

Participants were randomly assigned in a one to one of three treatment groups: Oral terbinafine 250 mg once daily, oral itraconazole 200 mg daily in two divided doses and a combined regimen consisting of oral terbinafine

250 mg once daily plus itraconazole 200 mg daily in two divided doses.

Randomization and blinding

Randomization was performed using a computer-generated random number sequence. Given the single-blind design of the study, treatment strategy was concealed from participants but known to the investigators.

Follow-up and monitoring

Patients were evaluated at two-week intervals during the treatment phase and subsequently at four and eight weeks following completion of therapy. These follow-up visits were conducted to monitor treatment efficacy, detect adverse effects, and assess disease recurrence.

Outcome measures

The primary outcome measure was the clinical cure rate, defined as complete resolution of clinical signs and symptoms accompanied by a negative mycological culture. Secondary outcome measures included the frequency of adverse events, the rate of disease recurrence at eight weeks post-treatment, and the mycological cure rate.

Data collection and statistical analysis

Data regarding demographic characteristics, clinical presentation, infection type, treatment response, and adverse events were systematically recorded using standardized data collection forms. Statistical analyses were performed using SPSS software. Categorical variables were analyzed using the chi-square test, while continuous variables were assessed using analysis of variance (ANOVA). A p value of less than 0.05 was considered indicative of statistical significance.

Ethical considerations

Ethical approval for the study was obtained from the appropriate regulatory authority. Written informed consent was secured from all participants prior to study.

RESULTS

This clinical trial was carried out between January and June 2024 across several private clinics in Gazipur, Bangladesh, and enrolled 150 patients diagnosed with different forms of tinea infections. Participants were evenly allocated (50 in each group) into three treatment arms. The mean age of participants were 32 (\pm 11) years, 28 (\pm 13) years, 36 (\pm 9) years in terbinafine monotherapy, itraconazole monotherapy, and combined terbinafine-itraconazole therapy groups respectively. Number of male patients was higher than the females in all three treatment groups (Table 1).

With respect to the primary endpoint, clinical cure was observed in 78% of patients (39 individuals) treated with terbinafine alone and in 74% (37 individuals) receiving itraconazole alone. In contrast, a markedly higher clinical cure rate of 92% (46 patients) was achieved in the combination therapy group. Similarly, mycological cure was confirmed by negative fungal cultures documented in 74% (37 patients) of the terbinafine group and 70% (35 patients) of the itraconazole group, whereas 90% (45 patients) in the combination group attained mycological clearance (Figure 1).

Table 1: Demographic distribution of the participant of different treatment groups.

Treatment group	N	Age (in years)	Sex	
		Mean \pm SD	Male	Female
Terbinafine alone	50	32 \pm 11	31	19
Itraconazole alone	50	28 \pm 13	30	20
Combination therapy	50	36 \pm 9	27	23
Total	150	18 to 55	88	62

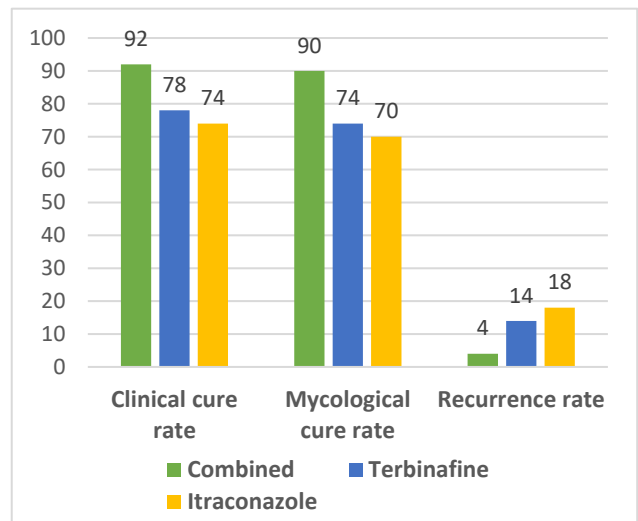


Figure 1: Comparison of clinical cure rate, mycological cure rate, recurrence rate among experimental groups in percentage.

Assessment of recurrence at eight weeks following treatment completion revealed that combined therapy was associated with the lowest relapse rate, occurring in only 4% of patients (2 individuals). Higher recurrence rates were recorded among those receiving monotherapy, with 14% (7 patients) in the terbinafine group and 18% (9 patients) in the itraconazole group experiencing disease recurrence (Figure 1).

Adverse events were generally mild to moderate in severity and occurred at comparable frequencies in the experimental groups, with gastrointestinal disturbances

being the most frequently reported complaints. Statistical evaluation demonstrated that combination therapy was significantly superior to either monotherapy in achieving both clinical and mycological cure outcomes, with the observed differences reaching statistical significance ($p < 0.05$).

DISCUSSION

This multicenter randomized controlled trial, conducted across several private clinics in Gazipur, Bangladesh between January and June 2024, evaluated the therapeutic performance of terbinafine, itraconazole, and their combined use in patients with tinea infections. The findings clearly indicate that patients receiving combination therapy achieved superior clinical and mycological cure rates, along with a lower frequency of disease recurrence, when compared with those treated with either agent alone. These observations reinforce the clinical value of combination antifungal therapy in improving treatment outcomes for dermatophyte infections.²⁷

Previous studies have consistently demonstrated the effectiveness of terbinafine and itraconazole as individual treatment options. Terbinafine, owing to its fungicidal activity and strong affinity for keratinized tissues such as skin, hair, and nails, has been reported to show high efficacy in tinea pedis, as highlighted by Gupta et al.¹⁰ Similarly, itraconazole has been widely used because of its broad antifungal spectrum. The present study extends existing evidence by demonstrating that the concurrent use of these agents results in enhanced therapeutic efficacy and a notable reduction in recurrence rates, which remain a major challenge in the management of tinea infections.

The improved outcomes observed with combination therapy may be attributed to the complementary mechanisms of action of terbinafine and itraconazole. By targeting different stages of fungal growth and affecting a broader range of fungal species, the combined regimen may exert a synergistic effect that enhances fungal eradication. This interpretation is supported by findings from Patel et al who reported that combination antifungal therapy can be an effective strategy for managing chronic and recurrent fungal infections, particularly in the context of antifungal resistance.^{11,28}

Supporting evidence from other clinical studies further strengthens these findings. A recent investigation involving 152 patients with superficial fungal infections, including cases of tinea and onychomycosis, demonstrated that the combination of terbinafine and itraconazole produced better outcomes than either drug administered alone.²⁹ Additional studies have reported higher cure rates, shorter time to resolution, and a greater proportion of cured patients in combination therapy groups compared with monotherapy arms.^{30,31}

With regard to safety, our study observed mild adverse effects among three experimental groups, which aligns with the long-term tolerability data reported by Seebacher et al for both terbinafine and itraconazole.²⁰ However, certain limitations should be acknowledged. The post-treatment follow-up period of eight weeks may be insufficient to fully assess delayed recurrence. Future studies employing double-blind designs and long term follow-up durations would provide more robust data on sustained treatment outcomes.

Despite these limitations, the results suggest that combination therapy may be particularly beneficial for patients with recurrent or extensive dermatophytosis. The combined regimen has the potential to reduce treatment duration, minimize relapse and improve patient adherence.^{32,33} The enhanced efficacy of terbinafine and itraconazole in combination is likely related to their successive interference of ergosterol synthesis in different enzymatic phases within the fungal cell membrane formation pathway.³⁴

The increasing prevalence of antifungal resistance and the variable bioavailability of these agents may limit the effectiveness of monotherapy.^{1,14,35} Nonetheless, treatment failure is multifactorial and may also involve host immune responses, fungal virulence, and host-pathogen interactions.³⁶⁻³⁹ The global rise in resistant superficial fungal infections, compounded by environmental changes that favor fungal proliferation, underscores the urgency of optimizing antifungal treatment strategies.^{35,40,41}

In light of these challenges, identifying a well-tolerated regimen that delivers maximal therapeutic benefit with minimal adverse effects is essential. The significant improvements observed with the terbinafine+itraconazole combination in this study support its role as a dependable treatment approaches for clinicians managing tinea infections.

This study demonstrates that terbinafine, itraconazole, and particularly their combined administration are effective treatment options for tinea infections, with combination therapy showing clear superiority over single use. The concurrent use of terbinafine and itraconazole yielded notably high clinical (92%) and mycological (90%) cure rates, along with a low recurrence rate of 4%, indicating a clear therapeutic advantage. These findings suggest that combination therapy can substantially enhance therapeutic response, even in relapse cases of dermatophytosis.

Limitations

The study was done across multiple private clinics in one geographical district and therefore the sample size was not representing mass population. As the dermatophytosis may vary with season or environmental factors like humidity, atmospheric temperature and personal hygiene;

the duration of study could be prospective and over the years to observe delayed recurrence and regional variations.

CONCLUSION

The observed benefits highlight the potential role of synergistic antifungal regimens in dermatological practice and support the clinical value of combining agents with complementary mechanisms of action. This study provides a foundation for future investigations aimed at refining dosing strategies, maximizing therapeutic efficacy, and improving overall patient management.

Recommendations

Further large-scale studies involving multicultural communities are warranted to comprehensively evaluate safety profiles, adverse effects, and long-term toxicity, thereby strengthening the evidence base and guiding broader clinical application.

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REFERENCES

- Gaurav V, Bhattacharya SN, Sharma N, Datt S, Kumar P, Rai G, et al. Terbinafine resistance in dermatophytes: time to revisit alternate antifungal therapy. *J Mycol Med.* 2021;31(1):101087.
- Gupta AK, Cooper EA. Update in antifungal therapy of dermatophytosis. *Mycopathologia.* 2008;166(5-6):353-67.
- Hay RJ. Therapy of skin, hair, and nail fungal infections. *J Am Acad Dermatol.* 1993;29(4):S55-9.
- Gupta AK, Ryder JE, Chow M, Cooper EA. Dermatophytosis: the management of fungal infections. *Skinmed.* 2005;4(5):305-10.
- Saunte DM, Hare RK, Jørgensen KM, Jørgensen R, Deleuran M, Zachariae CO, et al. Emerging terbinafine resistance in *Trichophyton*: clinical characteristics, squalene epoxidase gene mutations, and a reliable EUCAST method for detection. *Antimicrob Agents Chemother.* 2019;63(10):e01126-9.
- Jones TC. Itraconazole in the management of fungal infection. *J Am Acad Dermatol.* 1997;36(6):S7-11.
- Krishnan-Natesan S. Terbinafine: a pharmacological and clinical review. *Expert Opin Pharmacother.* 2009;10(16):2723-33.
- Ryder NS. Terbinafine: mode of action and properties of squalene epoxidase inhibition. *Br J Dermatol.* 1992;126(39):2-7.
- Bhattacharjee R, Dogra S. "End of the road for terbinafine" in dermatophytosis: is it a valid conclusion? *Indian J Dermatol Venereol Leprol.* 2018;84(6):706-7.
- Gupta KA, Chow M, Daniel CR, Aly R. Treatments of tinea pedis. *Dermatologic Clinics* 2003;21(3):431-62.
- Campitelli M, Zeineddine N, Samaha G, Maslak S. Combination Antifungal Therapy: A Review of Current Data. *J Clin Med Res.* 2017;9(6):451-6.
- De Doncker P, Pande S, Richarz U, Garodia N. Itraconazole: what clinicians should know. *Indian J Drugs Dermatol.* 2017;3(1):4-10.
- Ebert A, Monod M, Salamin K, Burmester A, Uhrlaß S, Wiegand C, et al. Alarming India-wide phenomenon of antifungal resistance in dermatophytes: a multicentre study. *Mycoses.* 2020;63(7):717-28.
- Singh A, Masih A, Khurana A, Singh PK, Gupta M, Hagen F, et al. High terbinafine resistance in *Trichophyton interdigitale* isolates in Delhi, India harbouring mutations in the squalene epoxidase gene. *Mycoses.* 2018;61:477-84.
- Panda S, Verma S. The menace of dermatophytosis in India: the evidence that we need. *Indian J Dermatol Venereol Leprol.* 2017;83(3):281-4.
- Saunte DML, Pereiro-Ferreirós M, Rodríguez-Cerdeira C, Sergeev AY, Arabatzis M, Prohić A, et al. Emerging antifungal treatment failure of dermatophytosis in Europe: take care or it may become endemic. *J Eur Acad Dermatol Venereol.* 2021;35(7):1582-6.
- Hutton B, Salanti G, Caldwell DM, Anna C, Christopher HS, Chris C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions. *Ann Intern Med.* 2015;162(11):777-84.
- Ryder NS, Favre B. Antifungal activity and mechanism of action of terbinafine. *J Antimicrob Chemother.* 1997;39(A):1-7.
- Leshner JL. Oral therapy of common superficial fungal infections of the skin. *J Am Acad Dermatol.* 1999;40:31-4.
- Seebacher C, Olafsson JH, Steinsson JB, Paul C, Billstein S, Evans EGV. Long-term effectiveness and safety of terbinafine and itraconazole in the treatment of fungal infections. *Mycoses.* 2007;50(2):112-8.
- Sardana K, Khurana A, Singh A. Scientific rationale of antifungal drug combination including oral itraconazole and terbinafine in recalcitrant dermatophytoses. *J Dermatolog Treat.* 2020;31:43-5.
- Ryder NS, Wagner S, Leitner I. *In vitro* activities of terbinafine against cutaneous isolates of *Candida albicans* and other pathogenic yeasts. *Antimicrob Agents Chemother.* 1998;42:1057-61.
- Sheehan DJ, Hitchcock CA, Sibley CM. Current and emerging azole antifungal agents. *Clin Microbiol Rev.* 1999;12(1):40-79.
- Vitale RG, Afeltra J, Dannaoui E. Antifungal combinations. *Methods Mol Med.* 2005;118:143-52.

25. Sigurgeirsson B. Prognostic factors for cure following treatment of onychomycosis. *J Am Acad Dermatol.* 2002;47(4):551-6.
26. Faergemann J, Baran R. Epidemiology, clinical presentation and diagnosis of onychomycosis. *Br J Dermatol.* 2003;149(65):1-4.
27. Baran R, Faergemann J, Hay RJ. Superficial white onychomycosis-a syndrome with different fungal causes and paths of infection. *J Am Acad Dermatol.* 2007;57(5):879-82.
28. Gupta AK, MacLeod MA, Foley KA, Gupta G, Friedlander SF. Fungal Skin Infections. *Pediatr Rev.* 2017;38(1):8-22.
29. Zhang D, Liao W, Chen C, Lai H, Liu S. Terbinafine hydrochloride combined with itraconazole for fungal skin diseases: a randomized controlled trial. *Am J Ther.* 2021;28:e179-86.
30. Sharma P, Bhalla M, Thami GP, Chander J. Evaluation of efficacy and safety of oral terbinafine and itraconazole combination therapy in dermatophytosis. *J Dermatolog Treat.* 2020;31:749-53.
31. Bidaud AL, Schwarz P, Chowdhary A, Dannaoui E. *In vitro* antifungal combination of terbinafine with itraconazole against isolates of Trichophyton species. *Antimicrob Agents Chemother.* 2022;66(1):e01449-21.
32. Choudhary S, Bisati S, Singh J, Koley D. Efficacy and safety of terbinafine hydrochloride 1% cream versus sertaconazole nitrate 2% cream in tinea corporis and tinea cruris. *Indian J Dermatol.* 2013;58(3):457.
33. Thomas J, Jacobson GA, Narkowicz CK, Peterson GM, Burnet H, Sharpe C. Toenail onychomycosis: an important global disease burden. *J Clin Pharm Ther.* 2010;35(5):497-519.
34. Dolton MJ, Perera V, Pont LG, McLachlan AJ. Terbinafine in combination with other antifungal agents for resistant or refractory mycoses: a physiologically based pharmacokinetic model. *Antimicrob Agents Chemother.* 2014;58(1):48-54.
35. Khurana A, Sardana K, Chowdhary A. Antifungal resistance in dermatophytes: recent trends and therapeutic implications. *Fungal Genet Biol.* 2019;132:103255.
36. Sardana K, Khurana A, Gupta A. Parameters that determine dissolution and efficacy of itraconazole and relevance to recalcitrant dermatophytoses. *Expert Rev Clin Pharmacol.* 2019;12(5):443-52.
37. Pasqualotto AC, Denning DW. Generic substitution of itraconazole resulting in sub-therapeutic levels and resistance. *Int J Antimicrob Agents.* 2007;30(1):93-4.
38. Sardana K, Kaur R, Arora P, Goyal R, Ghunawat S. Is antifungal resistance a cause for treatment failure in dermatophytosis? *Indian Dermatol Online J.* 2018;9(2):90-5.
39. Brunke S, Mogavero S, Kasper L, Hube B. Virulence factors in fungal pathogens of man. *Curr Opin Microbiol.* 2016;32:89-95.
40. Ameen M. Epidemiology of superficial fungal infections. *Clin Dermatol.* 2010;28(2):197-201.
41. Gnat S, Łagowski D, Nowakiewicz A, Dyląg M. A global view on fungal infections in humans and animals: opportunistic infections and microsporidiosis. *J Appl Microbiol.* 2021;131(5):2095-113.

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