SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 8.
Issue: 8
Page N. 72-76
Year: 2024

Original Article www.wjahr.com

TREATMENT OF CHRONIC AND RECURRENT TINEA CORPORIS ET CRURIS: A COMBINATION OF ITRACONAZOLE & TERBENAFINE VERSUS TERBENAFINE

Shamil Al-Jebori[1]* and Haitham B. Fathi[2]

[1]Dermatology Unit, Mosul General Hospital, Mosul-Iraq.
[2]Dept. of medicine, College of Medicine, University of Ninevah, Mosul-Iraq.

Article Received date: 04 June 2024 **Article Revised date:** 24 June 2024 **Article Accepted date:** 14 July 2024

***Corresponding Author: Shamil Al-Jebori**
Dermatology Unit, Mosul General Hospital, Mosul-Iraq.

ABSTRACT

Background: In the era of exponential increase in recalcitrant dermatophytoses, short course monotherapy is no more sufficient to eradicate the fungus and prevent its relapse. **The aim of the study:** To evaluate the effectiveness of long-term use of combined oral itraconazole and terbinafine in the treatment of chronic and recurrent tinea corporis et cruris. **Patients and methods**: From January to June, 2023, 50 patients with chronic or recurrent tinea corporis et cruris participate in this open-labeled randomized trial. Patients assigned to either monotherapy terbinafine group or combined therapy group (Itraconazole and terbinafine) administered daily for 8 weeks. The patient with partial cure was provided by another eight weeks therapy. The patients were assessed using clinic symptom & clinical outcome scores. **Results:** 84 patients with chronic tinea corporis et cruris participate in the current open trial. 45 patients used combined therapy of itraconazole and terbenafine while 39 patients treated by terbenafine alone for 16 weeks. The duration of dermatophytosis in the studied sample was 10.15 ± 2.85 months and the extent of BSA involved was 6.12 ± 2.19 %. At the end of 16 weeks, persistence of pruritus was significantly higher in monotherapy group (17.9% Vs. 2.2%). The erythema vanish almost completely in combination therapy group (95.6%) compared to 74.4% in monotherapy group (p=0.02). Active border persist only in monotherapy group in 10.3% of patients. All patients treated by combined therapy were cured, while 31 (79.5%) of monotherapy were cured, 6 (15.4%) classified as partially cured and 2 (5.1%) failed to response. **Conclusion:** A long-term of Combination therapy of itraconazole and terbinafine is superior to monotherapy of tebenafine alone. It is strongly advised to reevaluate the appropriate antifungal dosage for combination therapy in the future.

KEYWORD: Tinea corporis et cruris, Chronic, Recurrent, terbinafine, itraconazole, Monotherapy, Combined therapy.

INTRODUCTION

Dermatophytes are widespread pathogens that can be encountered in a various ecosystems.[1] The current dermatophytosis epidemic may be attributed to a number of factors, including: global warming; increased emigration and travel; socioeconomic challenges; changes in contemporary fashion trends; and pet contact.[2] Furthermore, dermatologists face a major challenge when a mild, easily treatable superficial infection unexpectedly develops into extensive, persistent, and recalcitrant atypical mycoses. The disease spread exponentially, affecting around a quarter of the world's population, causing significant public health problems.[3]

A short course of topical or systemic antifungals was the standard treatment of superficial mycoses. But difficult-to-treat mycoses first appeared in South Asian countries and quickly spread to other countries, including Iraq. Majid et al. found that at least 35% of patients with superficial dermatophytoses had a persistently positive fungal culture (persisters) after taking a conventional dose of oral terbenafine for a short period of two weeks.[4] Accordingly, these results suggest that the recommended duration and dose may not be enough to eradicate fungus in the current clinical setting, and the new guideline needs to be updated. Unfortunately, there is still disagreement over the ideal length of antifungal treatment.[5] Further, the decision to continue with monotherapy or to adopt a new combination therapy is controversial.

Due to the distinct mechanisms of action of several antifungals and their tolerable side effects, combining treatment regimens is now becoming increasingly popular. This is particularly relevant for mycoses that are difficult to cure. The combination of antimycotics is intended to enhance the killing effect via synergy, reduce toxicity, minimize the development of resistance, and expand the spectrum of action.[6] In addition, the patient initially benefits from the fungicidal effect of the drug; altimetry requires long-term suppression by a fungistatic agent.[7]

Itraconazole and terbinafine are the most commonly prescribed systemic antifungals in clinical settings for the treatment of extensive and rapidly relapsing dermatophytosis.[8] Both medications inhibit the activity of enzymes essential for the synthesis of ergysterol in the cell wall in a distinct way.[9] Consequently, their combination results in a synergistic inhibitory effect rather than an additive effect.[10] Their combination is superior to monotherapy (using each medication alone), especially in treating chronic, difficult-to-treat fungi. Unfortunately, the majority of combination studies are still conducted in vitro or in animal models.

The aim of the current investigation is to evaluate the effectiveness of oral itraconazole and terbinafine combination therapy administered daily for 16 weeks for the treatment of chronic or recurrent tinea corporis et cruris.

PATIENTS AND METHODS

Hundred patients with chronic or recurrent tinea corporis et cruris who attended the dermatology outpatient clinic of Mosul General Hospital in Mosul, Iraq, between January 2023 and June 2023 participated in the current comparative, non-blinded, randomized study. The Research Ethics Committee of Ninevah Health Directorate granted approval for the trial.

Patients were identified based on physical symptoms and signs of tinea coropis et cruris. The chronic patient (dermatophytosis for ≥ 6 months) and the recurrent patient (recurrence of lesions within 6 weeks after completion of treatment) were asked to participate in the study after signing informed consent.

Patients were randomly assigned to either a monotherapy group (half of the group used oral terbinafine 250 daily) or a combined therapy group (used oral itraconazole 200 mg daily with oral terbinafine 250 mg daily). The treatment was administered for 8 weeks. An additional eight weeks of therapy were provided for patients with partial cures.

Patients were examined at the beginning and at the end of the study. The assessment includes clinical symptoms and outcome scores. Clinic symptom scores were used to determine the severity of mycoses. The scores include the extent of dermatophytosis, pruritus, erythema, and active border. Each clinic's symptom is assigned a 4 point scale as follows: "0" for none, "1" for mild, "2" for moderate, and "3" for severe. The hand units (one hand unit corresponding to 1% BSA) were applied to determine the extent of the lesion. The final clinical symptom score is equal to the sum of the total (BSA) multiplied by the sum of the scores for pruritus, erythema, and actively raised borders. The clinical outcome was categorized as "failure" if there was no response or even an increase after starting antifungal drugs, "partial cured" if <50% of the initial score was improved, and "cured" if all lesions cleared entirely.

Statistical analysis

Percentages, means, and standard deviations (SD) were used to summarize the demographic and clinical symptom scores at baseline and at the end of the trial. A percent alteration in the clinical symptom score was used to measure the effectiveness of treatment responses in both groups of the study. A c2 test was used to compare the significance of differences in proportion of clinical symptoms and clinical outcome score between monotherapy and combination therapy. An independent two-sample t-test was used to assess the significance of the difference in continuous variables (age, duration, and total clinical symptom score) between monotherapy and combination therapy. A paired t-test was used to assess the changes in clinical symptom scores at the end of the trial. A significance criterion of less than 0.05 was applied.

RESULTS

45 out of 50 patients in the combination group and 39 out of 50 patients in the monotherapy group finished the trial at the end of the study. The patient's age ranges from 15 to 47 years, with a mean age of 29.30±6.64.84 years. The studied sample male-to-female ratio of 1.21:1, with 45 (54.76%) males and 38 (45.23%) females. The mean duration of dematophytosis ± standard deviation was 10.15 ± 2.85 months, with a range of 6 to 18 months. Dermatophytosis affects between 4–13% of the body's surface area, with a mean and standard deviation of 6.12 ± 2.19 percent. The extends of lesion range from 2 to 11% of BSA, with an average and standard deviation of 8.21 ± 2.23%. The clinical symptom score has a mean of 51.82±22.49 and a range of 10 to 88. Table 1 compares the differences in demographics and clinical symptom scores between terbenafine monotherapy and itaconazole and terbenafine combined therapy.

Table 1: Comparison of demographic and clinical characteristics between monotherapy (terbenafine) and combined therapy (itaconazole and terbenafine) at the initial assessment.

Characteristics	Monotherapy N= 39	Combined therapy N= 45	Total N= 84	P-value
Age in year, mean±SD	30.26±7.01	28.66±6.15	29.30±6.84	0.2
Male, No. (%)	19 (48.71%)	27 (60.0%)	46 (54.76%)	0.6
Female, No. (%)	20 (51.28%)	18 (40.0%)	38 (45.23%)	
Duration in month, mean±SD	10.75±2.10	11.50±3.10	10.15±2.85	0.1
Extent of lesion (BSA)	5.50±2.23	6.75±2.02	6.12±2.19	0.07
Itching, No. (%)				0.3
None	-	-	-	
Mild	14 (35.9%)	10 (22.2%)	24 (28.6%)	
Moderate	19 (48.7%)	27 (60.0%)	46 (54.8%)	
Severe	6 (15.4%)	8 (17.8%)	14 (16.7%)	
Erythema, No. (%)				
None	-	-	-	0.009
Mild	14 (35.9%)	4 (8.9%)	18 (21.4%)	
Moderate	17 (43.6%)	25 (55.6%)	42 (50.0%)	
Severe	8 (20.5%)	16 (35.6%)	24 (28.6%)	
Active border, No. (%)				
None	-	-	-	0.02
Mild	6 (15.4%)	-	6 (7.1%)	
Moderate	21 (53.8%)	29 (64.4%)	50 (59.5%)	
Severe	12 (30.8%)	16 (35.6%)	28 (33.3%)	
Clinic symptom scores	31.84±17.76	45.93±19.75	39.39±20.03	0.01

The changes in the clinical symptom scores in between the monotherapy and combination therapy at the end of trial are demonstrated in table 2. The persistence of pruritus was significantly higher (p = 0.01) in monotherapy group (17.9% Vs. 2.2%). The erythema was vanish completely in almost all of the patient used combination therapy group (95.6%) compared to 74.4% of the patients used monotherapy group (p=0.02). Active border persist only in monotherapy group in 10.3% of patients (p = 0.04). The extent of lesions dropped significantly (p <0.0001) from 7.50±2.23 to 0.43±0.82 in monotherapy group while the extend in combination group dropped significantly (p <0.0001) from 8.75±2.02 to 0.01±0.02. All patients treated by combined therapy were cured, while 31 (79.5%) of monotherapy were cured, 6 (15.4%) classified as partially cured and 2 (5.1%) failed to response (fig 1, 2a & b). The differences in cure rate between both groups of the study was statistically significant (0.001).

Table 2: Comparison of clinical symptom score and clinical cure characteristics between monotherapy and combined therapy groups at the end of sixteen weeks.

Characteristics		Monotherapy N=39	Combined therapy N=45	P-value
Clinic symptom scores		0.741±0.37	0.04±0.20	0.001
Itching				0.01
	0	32 (82.1%)	44 (97.8%)	
	1	7 (17.9%)	1 (2.2%)	
	2	-	-	
	3	-	-	
Erythema				0.02
	0	29 (74.4%)	43 (95.6%)	
	1	9 (23.1%)	2 (4.4%)	
	2	1 (2.6%)	-	
	3	-	-	
Active border				0.04
	0	35 (89.7%)	45 (100.0%)	
	1	4 (10.3%)	-	
	2	-	-	
	3	-	-	
Extent of lesion		0.43±0.82	0.01±0.02	0.003

Clinical outcome score				
	Cured	31 (79.5%)	45 (100.0%)	
	Partial	6 (15.4%)	-	
	Failure	2 (5.1%)	-	

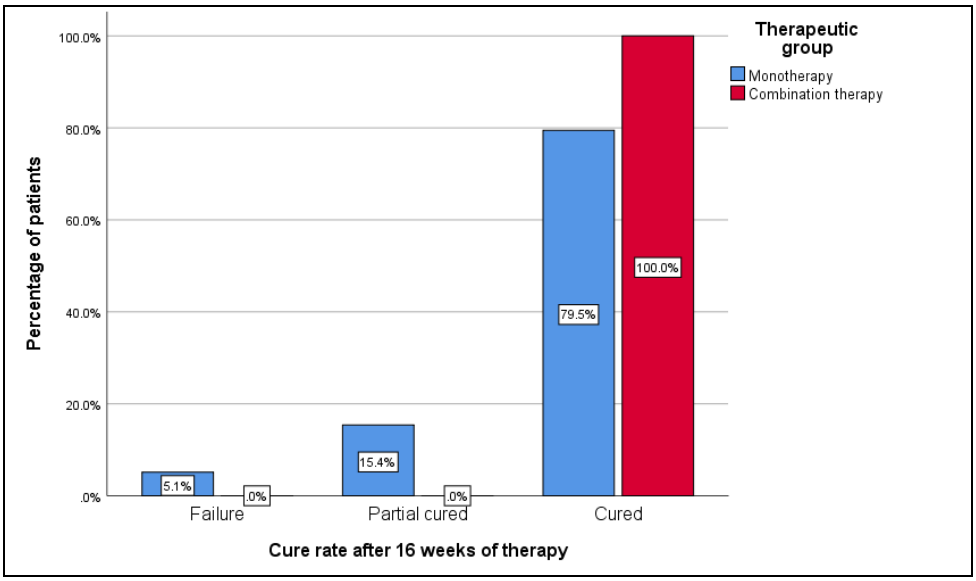

Fig. 1: Comparison of cure rate between monotherapy (terbenafine) and combined therapy (itraconazole and terbenafine) groups at the end of sixteen weeks.

DISCUSSION

In their recent publication, Gupta et al. raise awareness of the issue of fungal resistance to currently available medications and alert us to the need for an antifungal stewardship program.[11] As a result, numerous fungi have developed drug resistance due to inappropriate use of antifungals (insufficient dose/or duration).[12] However, a too-long treatment period can increase the risk of toxicity and cause fungi to adapt to stress.[13] The results of the current study indicate that using antifungals for sixteen weeks is a balanced way to combat the fungi's innate ability to trigger chronic infections or early relapses.

Clinicians cannot always assume that using two effective active ingridents with different modes of action will produce a better result (synergistic effect) than using each alone. Drug interaction may minimize effectiveness (antagonism), increase toxicity, or simply add extra costs without demonstrable therapeutic benefit (Inertism).[14] Theoretically, terbinafine and azoles have a synergistic effect, as both drugs sequentially target and inhibit the biosynthesis of ergosterol.[15] The potentiation of these agents upon combination makes these approaches particularly appealing and is used by physicians without adequate studied evidence. The literature retrieved comparing combination therapy versus terbinafine and itraconazole monotherapy shows inconsistent results ranging from significantly superior, not-significantly superior, to insignificant differences.

Zang et al., treat 152 with terbinafine, itraconazole monotherapy, or combination therapy. After 28 days of combined therapy, fungal eradication occurred in 37 patients, compared to 26 patients in the terbinafine group and 19 patients in the itraconazole group (P1 < 0.05, P2 < 0.05).[16] Sharma found that the combination resulted in maximum clinical and mycological cure after 6 weeks of treatment (90%), followed by itraconazole (50%), and least in those receiving terbinafine (35%).[17] Shumi et al., used a modified combination therapy (terbinafine twice daily and itraconazole pulse dose) for resistant ringworm infection.[18] They found that the improvement within 4 weeks was 36.33%, between 4 and 8 weeks, 84.21%, and between 8 and 12 weeks, it was 100%.

While Hassan et al. reported a better, but not significant, difference in the cure rate of recalcitrant dermatophytosis after the use itraconazole and terbinafene compared to monotherapy with either drug alone (p= 0.2).[19] Singh et al. conclude that the combination is not superior to Itraconazole alone in the epidemic of modified dermatophytosis facing India.[20] A similar conclusion was made by Shah et al.; however the tinea corporis et cruris treated with combined therapy achieved a much faster clinical cure much.[21]

In a recent meta-analysis published in November 2023, Ramzi et al. evaluated the pooled effectiveness of treating superficial mycoses with a combination of terbinafine and itraconazole, comparing the outcome to either monotherapy.[22] While studies compared combined therapy to terbinafine monotherapy demonstrate a higher significant cure rate (RR=2.01 [1.37, 2.94]; p=0.0003), studies compared it to

traconazole monotherapy revealed a non-significant difference (RR (0.91, 2.49); p=0.11).[16,11,17,20]

CONCLUSION

A Combination of Itraconazole plus Terbinafine in prolonged course is an effective therapeutic strategy. The clinical cure rate is superior to both short-term combination therapy and monotherapy with terbenafine. It is strongly recommended re-evaluate proper antifungal dose for combined therapy.

REFERENCES

1. Segal MF. Dermatophyte infections in environmental contexts. Research in Microbiology, 2015; 166(7): 564-569.
2. Verma, S.B.; Panda, S.; Nenoff, P.; Singal, A.; Rudramuruthy, S.M.; Uhrlass, S.; Das, S.; Bisherwal, K.; Shaw, D.; Vasani, R. The unprecedented epidemic-like scenario of dermatophytosis in India: I. Epidemiology, risk factors and clinical features. Indian J. Dermatol. Venereol. Leprol, 2021; 87: 154–175.
3. Havlickova, B.; Czaika, V.A.; Friedrich, M. Epidemiological trends in skin mycoses worldwide. Mycoses, 2008; 51(Suppl. 4): 2–15.
4. Majid I, Sheikh G, Kanth F, Hakak R. Relapse after Oral Terbinafine Therapy in Dermatophytosis: A Clinical and Mycological Study. Indian J Dermatol., 2016; 61(5): 529–533. doi: 10.4103/0019-5154.190120
5. Bassetti M, Giacobbe DR, Berruti M, Del Puente F, Vena A. Adequate duration of therapy in severe fungal infections. Curr Opin Crit Care, 2020; 6(5): 466-472. doi: 10.1097/MCC.0000000000000758.
6. Lewis RE. Decision making in antifungal monotherapy versus combination therapy. Pharmacotherapy, 2006; 26(6 Pt 2): 61S-67S. doi: 10.1592/phco.26.6part2.61S
7. Lewis JS, Graybill JR. Fungicidal versus Fungistatic: what's in a word? Expert Opin Pharmacother, 2008; 9(6): 927-35. doi: 10.1517/14656566.9.6.927.
8. Singh SK, Subba N, Tilak R. Efficacy of terbinafine and itraconazole in different doses and in combination in the treatment of tinea infection: a randomized controlled parallel group open labeled trial with clinico-mycological correlation. Indian J Dermatol., 2020; 65: 284–289.
9. Ramesh, A., Devasena, S. & Mathew, D. Efcacy and safety of oral terbinafne with itraconazole or griseofulvin combination therapy in the management of dermatophytosis: A randomised clinical trial. J. Clin. Diagn. Res., 2022; 16(1): 5–8.
10. Ryder NS, Leitner I. Synergistic interaction of terbinafine with triazoles or amphotericin B against Aspergillus species. *Med Mycol.,* 2001; 39: 91–95.
11. Gupta AK, Venkataraman M, Renaud HJ, Summerbell R, Shear NH, Piguet V. The increasing problem of treatment-resistant fungal infections: a call for antifungal stewardship programs. Int J dermatol., 2023; 37(9): 1706-1717.
12. Lange T, Kasper L, Gresnigt M, Brunke S, Hube B. "Under Pressure" – How fungi evade, exploit, and modulate cells of the innate immune system. Seminars in Immunology, 2023; 66: 101738.
13. Benitez L, Carver PL. Adverse Effects Associated with Long-Term Administration of Azole Antifungal Agents. Drugs, 2019 Jun; 79(8): 833-853. doi: 10.1007/s40265-019-01127-8.
14. Odds FC. Synergy, antagonism, and what the chequerboard puts between them. *J Antimicrob Chemother,* 2003; 52: 1.
15. 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: 43–45.
16. 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. 10.1097/MJT.0000000000001075
17. Sharma P, Bhalla M, Thami GP, Chander J: Evaluation of efficacy and safety of oral terbinafine and itraconazole combination therapy in the management of dermatophytosis. J Dermatolog Treat., 2020; 31: 749-53. 10.1080/09546634.2019.1612835
18. Shumi FR, Shamim SMA, Afroz R, SharminS. Combination of systemic terbinafine (250 mg) twice daily and itraconazole (100 mg) twice in a pulse dose in resistant tinea infection. Int J Res Dermatol 2022; 8(2): 199-205.
19. Hassaan ZRA, Mohamed HA, Eldahshan RM, Elsaie ML. Comparison between the efcacy of terbinafne and itraconazole orally vs. the combination of the two drugs in treating recalcitrant dermatophytosis. Scientifc Reports., 2023; 13: 19037. | https://doi.org/10.1038/s41598-023-46361-z
20. Singh SK, Subba N, Tilak R: Efficacy of terbinafine and itraconazole in different doses and in combination in the treatment of tinea infection: a randomized controlled parallel group open labeled trial with clinico-mycological correlation. Indian J Dermatol., 2020; 65: 284-9. 10.4103/ijd.IJD_548_19
21. Shah B , Shah S, Jangid N, Dhoot D, Deshmukh G, Barkate H.Comparative evaluation of efficacy and safety of terbinafine and itraconazole in the management of. IP Indian J Clin Exp Dermatol, 2020; 6(3): 231–236.
22. Ramzi SHT, Arif SA, Abdul Majid , Kumar S, Shumail H, Qudsia F, Zainab Y , Varrassi G, Khatri M. Efficacy of Terbinafine and Itraconazole Combination Therapy Versus Terbinafine or Itraconazole Monotherapy in the Management of Fungal Diseases: A Systematic Review and Meta-Analysis. Cureus, 15(11): e48819. doi:10.7759/cureus.48819