Original Article

Efficacy and Safety of Oral Itraconazole and Griseofulvin versus Itraconazole Alone in Patients with Tinea Corporis and Cruris Infection: A Comparative Clinical Study

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Abstract

Background: Dermatophytosis (tinea) is a worldwide prevalent superficial fungal infection limited to the epidermis, mucosa, hair, and nails. Iraq, like many other countries around the world, is facing the emergence of chronic, resistant, and relapsing tinea infections. **Aims:** The aim of this study is to evaluate the efficacy, safety, and relapse rate of a combination of itraconazole and griseofulvin versus itraconazole alone in the treatment of chronic tinea infections. **Patients and Methods:** The research was conducted over 14 months. Patients were divided equally into two groups, each with 55 patients. Group I received a combination of itraconazole and griseofulvin, whereas Group II was on itraconazole alone for 8 weeks. For the assessment of the relapse rate, follow-up was for another 2 months. **Results:** The mean age (±standard deviation) of the total was 31.27 ± 12.08 years. Males were 71 (64.5%) and females were 39 (35.5%). There was no significant difference in their residency. Family history was positive in the majority of patients, 90 (81.8%). After 2 weeks of treatment, a marked cure was achieved by 34 (61.8%) patients in Group I and 21 (38.2%) in Group II. After 8 weeks, the complete cure was 51 (92.8%) in Group I and 38 (69%) in Group II ($P < 0.00$). The marked cure was 4 (7.2%) in Group I, whereas 17 (31%) in Group II. The relapse rate after 16 weeks was 7 (12.7%) in Group I and 34 (61.8%) in Group II ($P < 0.00$). **Conclusions:** We concluded that therapeutic regimens of itraconazole and griseofulvin were effective, safe, and well tolerated, with a low relapse rate.

Keywords: Antifungal, chronic dermatophytosis, griseofulvin, itraconazole

Introduction

Dermatophytosis (tinea) is a worldwide prevalent superficial fungal infection limited to the epidermis, mucosa, hair, and nail, affecting about 20%–25% of the population.[1,2] It is caused by keratinophilic dermatophytes, which are the leading cause of the most common fungal infection in humans.[3] Dermatophytes are classified according to the mode of transmission: geophilic from soil, zoophilic from animals, and anthropophilic from humans.[4]

There are about 40 species of dermatophytes belonging to the genera *Trichophyton*, *Epidermophyton*, or *Microsporum*.[5] All ages, races, and both sexes may be infected by dermatophytes.[6,7] There are high rates of chronicity and recurrence of dermatophytosis, and it is difficult to control their spreading; however, they are rarely cause serious or invasive disease.[8,9] The most common isolate in humans is *Trichophyton rubrum*, which causes a high incidence in Europe, whereas *Trichophyton mentagrophytes* is the second-most common isolate, causing a high incidence of tinea infections in Asia.[10,11]

Delay in the diagnosis and treatment of dermatophytosis is due to its clinical similarity to dermatitis and other related

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inflammatory superficial skin diseases, leading to the misuse and overuse of different antifungal agents.[9]

A combination of two antifungal drugs having different mechanisms of action, such as a drug that inhibits the synthesis of the cell membrane (DNA/or protein) with a drug that inhibits cell wall synthesis is promising to minimize adverse drug reactions, increase the spectrum of antifungal activity, reduce the dosage of combined drugs, and decrease the possibility of drug resistance.[12]

Itraconazole is a selective inhibitor of fungal cytochrome P450-dependent sterol 14-α-demethylase, leading to inhibition of ergosterol biosynthesis, fungal growth arrest, and ultimately cell death. Itraconazole binds more weakly to mammalian cytochrome P450 enzymes.[13] Griseofulvin disrupts the mitotic spindle by inhibiting the formation of intracellular microtubules by inducing conformational changes of both the alpha and beta subunits.[14] Destruction of microtubules may lead to inhibition of the synthesis of new cell wall constituents at the growing hyphal tips.[15]

Differences in etiological agents, clinical presentation, and antifungal susceptibility among different countries of the world as well as a lack of documented or published data for specific regions, like Iraq. This adds challenges to the diagnosis and treatment of tinea infection. This study tried to evaluate the efficacy and safety of a novel combination of itraconazole and griseofulvin and compare their action with that of itraconazole alone in the treatment of chronictinea corporis and/or tinea cruris (TCC).

Patients and Methods

Informed written consent was obtained from the participant patients after understanding the clinical study information and describing in detail the risks and benefits of this study.

The inclusion criteria were males and females older than 18 years with chronic tinea corporis, tinea cruris, or both (TCC). Patients with single or multiple lesions are included in the study. Chronic cases are those who have had the illness for longer than 3 months, with or without a history of therapy.[16]

The exclusion criteria were hypersensitivity to itraconazole or griseofulvin, immunocompromised status, pregnancy or lactation, presence of cardiac disease, diabetes, Cushing's syndrome, porphyria, and systemic lupus erythematosus, and patients with abnormal results in complete blood counts, liver function tests (LFT), renal function tests, and those with extensive, widespread lesions.

The diagnosis of tinea infections was made clinically by the dermatologist and supported by a potassium hydroxide examination. Patients with positive chronic tinea infections were divided equally into Groups I and II. Patients in Group I were treated by itraconazole 100 mg twice daily and griseofulvin 500 mg once daily, whereas patients in Group II were treated by itraconazole 100 mg twice daily. All patients in both groups were treated for 2 months.

The follow-up period was biweekly for 8 weeks. At the baseline visit, information such as age, sex, residence, and family history was provided by all patients. The clinical type and morphology of lesions were provided by the dermatologist. LFTs were assessed before the start of the study for inclusion of the patients and at the end of the treatment course for evaluating the side effects.

After 2, 4, 6, and 8 weeks were the second, third, fourth, and fifth visits, respectively, for assessments of the efficacy and safety of the used drugs.

At the end of the treatment course, mycological cure and clinical cure were considered for the assessment of the treatment efficacy. The mycological cure is a negative microscopic examination. The clinical cure is the cure of all the clinical symptoms of tinea, such as pruritus, erythema, desquamation, and hyperpigmentation.

Mycological and clinical cures in response to treatment were graded as follows:[17,18]

- Complete cure: negative microscopic examination and cure of all the clinical symptoms
- Marked cure: negative microscopic examination, no pruritus, no erythema, no desquamation, and just hyperpigmentation
- Incomplete cure: positive microscopic examination, hyperpigmentation, no pruritus, no erythema, no desquamation
- Not changed: positive microscopic examination, presence of all the clinical symptoms
- Worsen.

After cessation of the treatment period (8 weeks), patients returned monthly for 2 months to evaluate the presence or absence of relapse. Relapse is the appearance of new or even the previous lesions during the follow-up period.[16] For the assessment of safety, attention was paid to the serious or severe adverse effects. To test the hypothesis, all collected data were entered in IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. A *t*-test and a Chi-square test were applied, and the *P* value was considered significant if it was ≤0.05.

Results

There were 110 participants, grouped equally into two groups, each with 55 patients. They completed the duration of treatment (2 months). The demographic characteristics of the enrolled patients were reported [Table 1]. The mean age (±standard deviation) of all patients was 31.27 ± 12.08 years, and it was 30.71 ± 12.22 years, and 31.84 ± 12.04 years in Groups I and II, respectively. There was no significant difference between the two groups ($P = 0.45$). Males were 71 (64.5%) and females were

Table 1: Demographic characteristics of enrolled patients

Characteristic	Total	Group I - itraconazole and griseofulvin, *n* (%)	Group II - itraconazole, *n* (%)	*P* (between two groups)
Number of patients	110	55 (50)	55 (50)	
Age (years), mean±SD	31.27±12.08	30.71±12.22	31.84±12.04	0.45
Sex				
Male	71 (64.5)	37 (67.3)	34 (61.8)	0.55
Female	39 (35.5)	18 (32.7)	21 (38.2)	
Residence				
Urban	53 (48.2)	26 (47.3)	27 (49.1)	0.84
Rural	57 (51.8)	29 (52.7)	28 (50.9)	
Family history				
Positive	90 (81.8)	49 (89.1)	41 (74.5)	0.04
Negative	20 (18.2)	6 (10.9)	9 (25.5)	
Type of infection				
Tinea corporis	46 (41.8)	23 (41.8)	23 (41.8)	0.02
Tinea cruris	29 (26.4)	20 (36.4)	9 (16.4)	
Both (TCC)	35 (31.8)	12 (21.8)	23 (41.8)	

SD: Standard deviation, TCC: Tinea corporis and cruris

39 (35.5%). In their residency, 53 (48.2%) patients lived in urban areas and 57 (51.8%) lived in rural areas. Family history was positive in the majority of patients, 90 (81.8%), whereas only 20 (18.2%) have a negative family history. About 46 (41.8%) of cases presented with tinea corporis, and 29 (26.4%) had tinea cruris, whereas both types (TCC) were in 35 (31.8%). There was no significant difference ($P = 0.76$) between males and females in the frequency of these types of tinea infections [Table 2].

For the assessment of response to the treatment, patients were followed up every 2 weeks for 2 months. After cessation of treatment, patients were followed up for another 2 months for the assessment of the relapse rate of the disease [Table 3].

After 2 weeks of treatment (second visit), there was a significant difference in response to treatment between Groups I and II ($P = 0.00$), where a marked cure was achieved by 34 (61.8%) patients in Group I and 21 (38.2%) patients in Group II. The incomplete cure was achieved by 18 (32.7%) patients in Group I and 21 (38.2%) in Group II. Only 3 (5.5%) patients in Group I showed no change to treatment, whereas 13 (23.6%) in Group II [Figure 1].

After 1 month (third visit), there was a significant difference between the two groups ($P = 0.00$). Patients who achieved complete cure of lesions: 14 (25.4%) patients in Group I and 8 (14.5%) in Group II. Marked cure was reported in 34 (61.9%) of patients in Group I and 25 (45.5%) of patients in Group II. An incomplete cure had been shown by 7 (12.7%) patients in Group I and by 22 (40%) in Group II. At this visit, all patients in both groups showed a response to the treatment modalities [Figure 2].

After 6 weeks (fourth visit), there was a significant difference between Groups I and II ($P = 0.00$). Patients who achieved complete cure: 39 (71%) in Group I, whereas only 19 (34.5%) in Group II. The marked cure was achieved by 15 (27.2%) in Group I and 26 (47.3%) in Group II. One patient in Group I still showed incomplete cure versus 10 (18.2%) in Group II [Figure 3].

Table 2: Frequency of types of tinea for sex

Sex	Tinea corporis	Tinea cruris	Both (TCC)	*P*
Male	28	20	23	0.76
Female	18	9	12	

TCC: Tinea corporis and cruris

After 8 weeks (fifth visit), there was a significant difference in patients who achieved complete cure: 51 (92.8%) in Group I and 38 (69%) in Group II ($P = 0.00$). Marked cure in Group I was 4 (7.2%) in Group I, whereas 17 (31%) in Group II [Figure 4]. None of the patients, at this last visit, still showed an incomplete cure.

At the sixth visit, for the assessment of relapse, after 1 month of completion of treatment, only 5 (9%) patients relapsed in Group I, whereas 26 (47.2%) patients relapsed in Group II, and the difference was highly significant ($P = 0.00$) [Figure 5].

At the seventh visit, after 2 months, 7 (12.7%) relapses were in Group I, whereas 34 (61.8%) relapses were in Group II, and there was a significant statistical difference between the two groups ($P = 0.00$) [Figure 6]. All reported side effects were mild and transient and did not warrant withdrawing from the study.

Discussion

The chronic morbidity of dermatophytosis is increasing, and it is more common in developing countries. The exact mechanisms behind the emergence of chronic dermatophytosis are still unknown, but the standard antifungal agent resistance, poor treatment adherence, and the fact that patients did not complete the well-organized course can provide strong possible explanations for the epidemic of resistant skin fungal infection in Iraq.[19]

Table 3: Response of both groups

Assessment	Visits (weeks)	Grades of response	Groups		*P* (between two groups)
			Group I - itraconazole and griseofulvin, *n* (%)	Group II - itraconazole, *n* (%)	
Response to treatment	Second visit (2)	Marked cure	34 (61.8)	21 (38.2)	0.00
		Incomplete cure	18 (32.7)	21 (38.2)	
		Not changed	3 (5.5)	13 (23.6)	
	Third visit (4)	Complete cure	14 (25.4)	8 (14.5)	0.00
		Marked cure	34 (61.9)	25 (45.5)	
		Incomplete cure	7 (12.7)	22 (40)	
	Fourth visit (6)	Complete cure	39 (71)	19 (34.5)	0.00
		Marked cure	15 (27.2)	26 (47.3)	
		Incomplete cure	1 (1.8)	10 (18.2)	
	Fifth visit (8)	Complete cure	51 (92.8)	38 (69)	0.00
	End of treatment	Marked cure	4 (7.2)	17 (31)	
Relapse of disease	Sixth visit (12)	Present	5 (9)	26 (47.2)	0.00
		Absent	50 (91)	29 (52.8)	
	Seventh visit (16)	Present	7 (12.7)	34 (61.8)	0.00
		Absent	48 (87.3)	21 (38.2)	

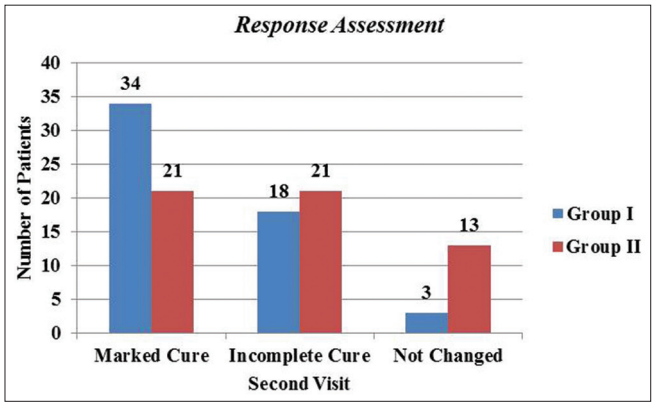

Figure 1: Response of both groups after 2 weeks

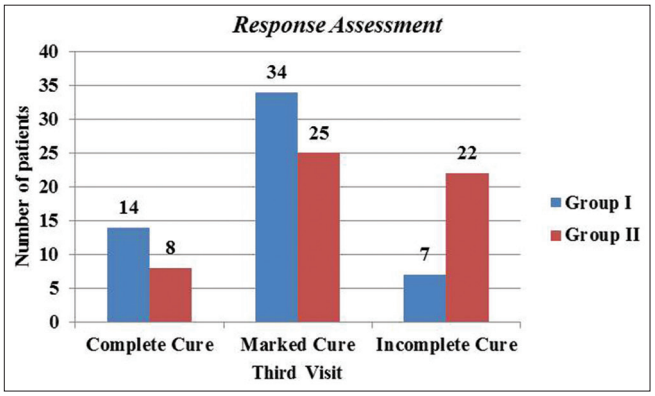

Figure 2: Response of both groups after 4 weeks

Dermatophytosis is a worldwide prevalent disease and is common and challenging in Iraq and other neighboring countries such as Iran and Syria.[19-22] The distribution of tinea infection in relation to sex has been reported in previous studies, some of them found sex differences and a higher incidence of infection in males than females,[17,23-25] and this was in agreement with our results, where males were 71 (64.5%) and females were 39 (35.5%). This difference in incidence may be related to male outdoor activities. Others found incidence was higher in females than males,[26,27] whereas Alshehri *et al*.[28] reported no significant differences.

In the majority of patients in this study, family history was positive in 90 (81.8%), whereas it was negative in 20 (18.2%), and this finding was consistent with previous studies.[29,30] This may be explained by the easy transfer of spores among different family members,[31] but not all of them are equally susceptible to tinea infection.[4]

Sterol 14-α-demethylase is inhibited by itraconazole, and this step leads to the inhibition of ergosterol biosynthesis and, ultimately, fungal growth arrest and cell death.[13] Griseofulvin inhibits the formation of intracellular microtubules and disrupts the mitotic spindle, leading to the inhibition of the synthesis of new cell wall constituents at the growing hyphal tips.[14,15] Itraconazole was superior to fluconazole, griseofulvin, and terbinafine in the treatment of cutaneous mycosis, with a high cure rate,[32,33] especially against *Trichophyton* and *Microsporum nanum*.[34] Griseofulvin showed similar efficacy to terbinafine and to itraconazole in different studies for obtaining a complete cure in the treatment of *Trichophyton* fungal infections, and it was superior to ketoconazole in another study.[35,36] Some studies appear to have found terbinafine to be less effective than griseofulvin against *Microsporum* spp.[37,38]

Literature-standard recommendations for the treatment of dermatophytosis are no longer valid or even realistic.[31] The majority of dermatologists tried to use other strategies (experience-based treatment) such as a combination of drugs, higher doses of antifungals, or prolonged treatment duration, or even drug use, which are not approved in the treatment of tinea infections.[17,20,31,39] Therefore, in this study, we tried to assess

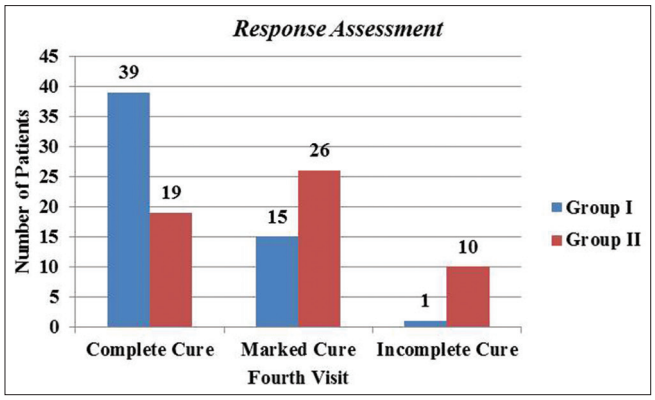

Figure 3: Response of both groups after 6 weeks

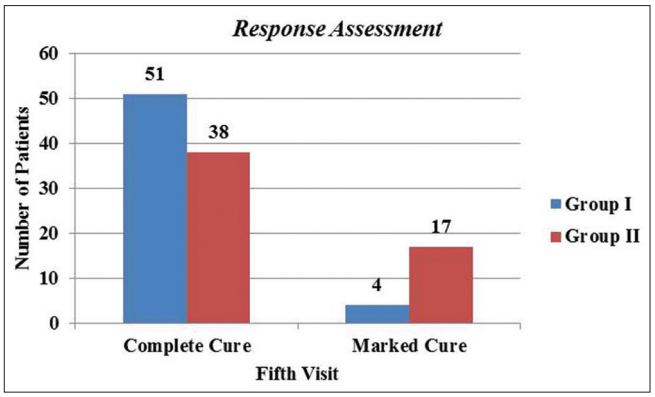

Figure 4: Response of both groups after 8 weeks

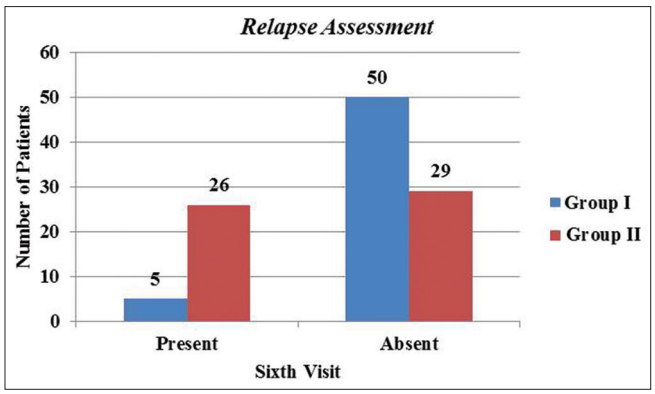

Figure 5: Relapse of both groups after 12 weeks

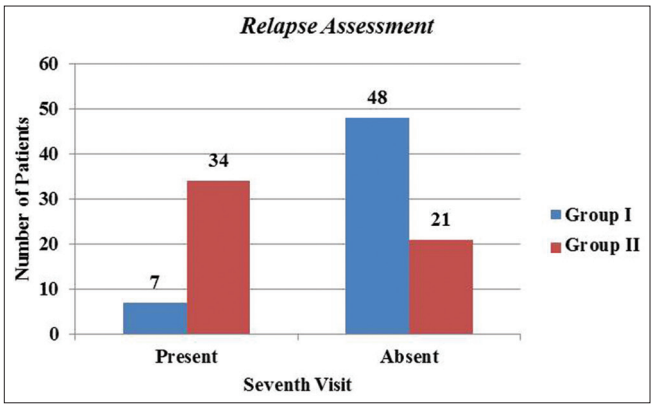

Figure 6: Relapse of both groups after 16 weeks

the response of chronic tinea infection to a novel combination therapy by itraconazole and griseofulvin, as they may provide synergistic effects by their different mechanisms of action.

During the follow-up period, there was an increasing response to treatment. After 2 weeks of treatment, a marked cure was achieved by 34 (61.8%) patients in Group I and 21 (38.2%) in Group II. After 1 month, a complete cure of lesions was reported by 14 (25.4%) patients in Group I and 8 (14.5%) in Group II. A marked cure was reported in 34 (61.9%) of patients in Group I and 25 (45.5%) in Group II. Incomplete cure had been shown by 7 (12.7%) patients in Group I and by 22 (40%) in Group II, ($P < 0.00$). At the end of the treatment duration (2 months), the complete cure in Group I was 51 (92.8%) and 38 (69%) in Group II. A significant difference was in patients who achieved a marked cure in Groups I and II, with 4 (7.2%) in Group I, whereas 17 (31%) in Group II ($P < 0.00$). None of the patients still showed an incomplete cure.

After 2 months of completion of the treatment, the observed relapse rate was 7 (12.7%) in Group I, whereas it was 34 (61.8%) in Group II, and there was a significant statistical difference between the two groups ($P < 0.00$). The relapse rate with monotherapy was higher than the dual therapy. The reported relapse rate for itraconazole 200 mg/day was 41.5%.[40] Relapse rates after 4 and 8 weeks of cure in the fluconazole, griseofulvin, itraconazole, and terbinafine groups were similar.[41] Itraconazole and griseofulvin were relatively safe drugs and did not cause serious adverse effects.[17,42-44] None of the patients showed a serious or toxic rise in liver enzymes.

Conclusions

Itraconazole plus griseofulvin was superior to itraconazole alone in inducing an early and persistent complete and marked cure with a decreased relapse rate.

They were safe and well tolerated, and they were approved as a better alternative choice for the treatment of patients with chronic tinea corporis and/or tinea cruris.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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