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Original Research Article

Combination of systemic terbinafine (250 mg) twice daily and itraconazole (100 mg) twice in a pulse dose in resistant tinea infection

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ABSTRACT

Background: The management of tinea is challenging in Bangladesh and there are reports of using systemic antifungals at higher doses. The aim of the study was to find out the effectiveness of systemic terbinafine (250 mg) twice daily and itraconazole (100 mg) twice in a pulse dose in resistant tinea infection.
Methods: It was a prospective, observational study conducted in the department of dermatology and venereology, Dhaka Dermatology Institute, Dhaka, Bangladesh from November 2020 to October 2021. Clinically confirmed cases of tinea corporis et cruris were recruited by random sampling techniques for the study and followed up for 12 weeks, till the completion of their treatment. Patients who were pregnant, lactating, non-consensual, as well as those who had a history of anti-mycotic treatment within 2 weeks prior to baseline visit were excluded from the study.
Results: A total of 30 patients were randomly assigned treatment and included in the study. According to within 4 weeks 11 (36.33%) patients were significantly improved and 19 (63.33%) patients were non-significantly improved, >4 week to till 8 weeks 16 (84.21%) patients were improved significantly and 3 (15.79%) patients were improved non-significantly and >8 week to till 12 weeks 3 (100%) patients were improved properly. Mycological cure was achieved in 25 (82.89%) patients, clinical cure rate was achieved same in 24 (79%) patients and complete cure rate was achieved 30 (100%) patients.
Conclusions: The combination of systemic terbinafine (250 mg) twice daily and itraconazole (100 mg) twice in a pulse dose therapy may be aneffective and safe therapeutic strategy in the management of registrant tinea infection.

Keywords: Terbinafine, Itraconazole, Antifungal, Resistant, Tinea

INTRODUCTION

Tinea caused by trichophyton, microsporum, and epidermophyton is the most common fungal infection affecting 20–25% population globally, with varying geographic distribution.[1,2] Due to Bangladesh's hot and humid climate, there has been a rampant increase in the cases of tinea infection and a typical presentation in recent years.[3,4] In addition, the recommended treatment of commonly prescribed antifungal agents no longer seems to be valid in the current scenario, resulting in treatment failures and relapses when given in conventional doses and for standard duration.[5] Hence, the management of tinea infection is becoming more subjective in order to overcome these challenges.[6,7] Moreover, the choice of therapy is further influenced by multiple factors like simultaneous involvement of extensive body area, hair follicles and a previous history of treatment failures, recurrences and relapses. The combination therapy is a well- established concept of using synergistic and additive

effects of two or more drugs to improve therapeutic efficacy and overcome drug resistance Sahoo et al and Murlidhar et al in their comprehensive reviews recommended the use of a combination of topical and systemic antifungals in the management of patients with large lesions or recalcitrant tinea infections.[8-10] Authors also commented that while using combination therapy, drugs from two different classes should be used for wider coverage, synergistic or additive action and to reduce the chance of resistance. For the management of tinea infection, terbinafine is considered to be a first-line drug due to its favorable mycological and pharmacokinetic profile.[11] It acts by inhibiting the enzyme squalene epoxidase, thereby inhibiting ergosterol synthesis.[12] Till recent years, the drug was consistently effective with cure rates of >90% achieved at doses of 250 mg once a day for two weeks.[11, 12] But recently, due to the overuse of the drug, there has been an increase in the incidence of terbinafine resistance resulting in increasing numbers of clinical failures and relapses.[13,14] Hence it is advisable to use higher dose of terbinafine as seen in an article by Murlidhar et al.[10] In a recent study, terbinafine was reported to be efficacious and safe in the management of tinea infection at higher doses of 500 mg/day.[15] Itraconazole is another antifungal drug which acts by inhabition of cytochrome P450 thus inhibiting ergosterol synthesis. It has shown good results in the treatment of tinea infection at doses of 100 mg once a day for two weeks and with 200 mg once a day for seven days.[16,17] But due to frequent relapses at short intervals, some physicians in Bangladesh have used it in doses of 200 mg once a day for prolonged periods.[17,18]

High dose of itraconazole may not be beneficial due to non-linear pharmacokinetic property.[10] Ciclopirox olamine (CPO), a hydroxypyridone derivative has been recently approved in Bangladesh. It differs in structure and mechanism of action from the other known antifungal agents.[19] It acts through the chelation of polyvalent metal cations, such as ferric (Fe^{3+}) and aluminium (Al^{3+}), thereby causing inhibition of metal-dependent enzymes (cytochromes, catalase, and peroxidase) leading to the disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across cell membrane.[20] It also alters membrane permeability causing blockage of intracellular transport of precursors. Due to widespread resistance to various antifungal agents and a high relapse rate when used in conventional doses, there is a need to find an effective first-line therapy for the management of tinea infection to achieve the maximum results with fewer relapses. Some recent trials compared the efficacy of terbinafine and itraconazole but in standard doses and duration.[16,21] Recently, a combination of itraconazole and terbinafine has also been studied suggesting need of either high dose or combined dose of different systemic antifungals in current settings in Bangladesh.[22] But there is no any study comparing high dose of terbinafine against standard dose of itraconazole. Hence, the present study was conducted to find out the effectiveness of systemic terbinafine (250 mg) twice daily and itraconazole (100 mg) twice in a pulse dose in resistant tinea infection.

METHODS

It was a prospective, observational study conducted in the department of dermatology and venereology, Dhaka Dermatology Institute, Dhaka, Bangladesh from November 2020 to October 2021. Clinically confirmed cases of tinea corporis et cruris were recruited by using random sampling techniques for the study and followed up for 12 weeks, till the completion of their treatment. All consenting patients, in the age group of 18-65 years, who were diagnosed by the dermatologist as suffering from tinea corporis et cruris were included in the study, irrespective of the presence and extent of tinea infection in other regions of the body. Patients who were pregnant, lactating, non-consensual, as well as those who had a history of anti-mycotic treatment within 2 weeks prior to baseline visit were excluded from the study. The patients were randomly allocated to combination of itraconazole 100 mg twice in a pulse dose and terbinafine 250 mg twice a day for 8 weeks and 4 weeks only itraconazole pulse dose monotherapy for prevention of tinea infection for long time. Both the groups received additional topical amorolfine hydrochloride cream for eight weeks along with anti-histamines.

Table 1: Antifungal agent.

Antifungal agent	Daily doses (mg)	Pulse dose (mg)	Duration of treatment (months)	
Terbinafine	250×2		2	-
Itraconazole		100×2	2	3

Mycological and clinical assessments

During the screening visit, a detailed medical history was obtained, and a thorough examination was performed. Various clinical signs and symptoms were rated according to a four-point scale from 0-3 (0=absent, 1=mild, 2=moderate and 3=severe). After commencement of the therapy, patients were followed up at a 4 weeks' interval, at an 8 weeks' interval and up to 12 weeks (end of treatment). Potassium hydroxide (KOH) examination was done at the time of enrolling the patient and at the end of the 12 weeks. Fungal culture was done in all KOH positive patients only at the beginning of the therapy. Liver function tests were done at the start of the therapy and at the end of the fourth week. At each visit, a clinical assessment was made. The therapeutic efficacy was evaluated at 12 weeks. Patients were considered cured when there was an absence of any signs and symptoms (scaling, erythema, and pruritus), and negative KOH.

The study was approved by the institutional ethics committee, and informed consent was taken from all patients before recruiting.

Inclusion criteria

Patients who were KOH positive and culture positive; age limit 18-65 years; resistant tinea infection; and both sex were included.

Exclusion criteria

Age below 18 years; patients having hypertension and heart diseases; hypersensitivity to the drags (terbinafine and itraconazole); and patients irregular in follow-up were excluded.

Statistical analysis

Descriptive statistics were used to summaries the effectiveness and safety endpoints using Graph Pad Prism version 8 (San Diego, California: Graph Pad Software Inc., 20057). Quantitative variables were analyzed using means and standard deviations, while categorical variables were analyzed using frequencies and percentages. For follow-up measurable data, repeated measure analysis of variance (ANOVA) was applied to see the trend of mean values over the period. At those endpoints, unpaired t test was applied and p values 0.05 were considered as statistically significant.

Primary effectiveness endpoint

The primary effectiveness endpoint was the percentage of patients achieving complete cure at the end of the treatment period from the baseline. Complete cure was defined as the patients achieving both clinical cure and mycological cure at the end of the treatment.

Secondary effectiveness end point

Secondary effectiveness endpoints were: the percentage of patients achieving clinical cure at the end of the treatment period, clinical cure was defined as absence of all symptoms [scaling, erythema and pruritus] at the end of the treatment; the percentage of patients achieving mycological cure at the end of the treatment period, mycological cure was defined as negative microscopy under KOH examination at the end of the therapy; and improvement in total symptom score from the baseline in each visit.

Safety assessment

Safety assessment was done by analyzing all the AEs reported by the patients during the treatment and by monitoring the liver function tests.

RESULTS

A total of 36 patients were randomly assigned treatment and included in the study. Six patients were excluded from the study because of irregular follow-up. Hence, a total of 30 patients were enrolled in the final study. Thirty patients were treated with to combination of itraconazole 100 mg twice in a pulse dose and terbinafine 250 mg twice a day for 8 weeks and 4 weeks only itraconazole pulse dose monotherapy for prevention of tinea infection for long time, how's the demographic profile of patients, the diagnosis and the culture reports of study patients. The age range stared from 18-30 years to 61-65 years, respectively, in Table 2. It also carried the socioeconomically status where 16 (53.33%) patients were from lower, 12 (40.00%) patients were from middle and 2 (6.67%) patients were from upper level (Table 2). There were 6 males (20%) and 26 females (80%) in Figure 1. All the patients were co-prescribed CPO and anti-histamines. The baseline KOH examination was positive in 30 (100%) patients, whereas the same was positive in 30 (100%) patients in Table 3. Fungal culture was positive in all KOH positive patients. At the end of eight weeks, there was a statistically significant improvement (p value <0.05) in the total symptom score (erythema, scaling, and pruritus) compared to baseline (Figure 2). The significant improvement started from 0-2 weeks (terbinadine and itraconazole) after 4 weeks (only itraconazole) and then persisted till the end of the treatment. On comparing the groups, there was a significant improvement in the total symptom score at the end of 4 weeks (p value <0.05) but no statistically significant change was observed at the end of 8 weeks (p value >0.05). According to Table 4 within 4 weeks 11 (36.33%) patients were significantly improved and 19 (63.33%) patients were non-significantly improved, >4 week to till 8 weeks 16 (84.21%) patients were improved significantly and 3 (15.79%) patients were improved non-significantly and >8 week to till 12 weeks 3 (100%) patients were improved properly (Table 4). Mycological cure was achieved in 25 (82.89%) patients, clinical cure rate was achieved same in 24 (79%) patients and complete cure rate was achieved 30 (100%) patients (Figure 3). Treatment wise improvement was showed by digital photography comparing baseline (left) with 4 weeks of treatment (Figure 4), digital photography comparing bassline (left) with 8 weeks of combine treatment (right) (Figure 5) and digital photography comparing bassline (left) with 8 weeks of combine treatment with use of itraconazole monotherapy only up to 12 weeks (right) of treatment (Figure 6).

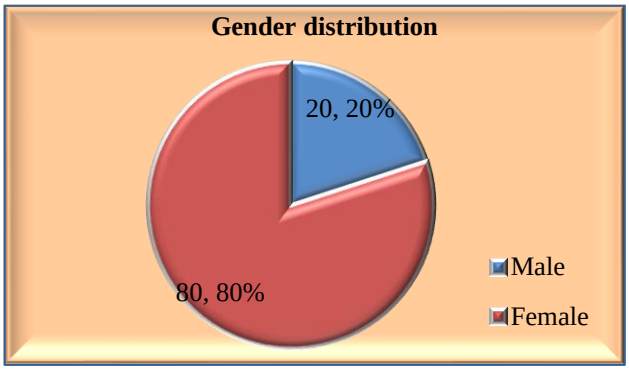

Figure 1: Gender distribution of study patients (N=30).

Table 2: Demographical characteristics of study patients (N=30).

Demographical characteristics	Frequency	Percentage
Age		
18-30	0	0.00
31-40	4	13.33
41-50	16	53.33
51-60	8	26.67
61-65	2	6.67
Socioeconomically status		
Lower	16	53.33
Middle	12	40.00
Upper	2	6.67

Table 3: Mycological examination of study patients (N=30).

Mycological examination n (%)	Frequency	Percentage
KOH positivity	30	100.00
Culture positivity	30	100.00
T. Mentagrophytes	5	16.67
T. Rubrum	1	3.33
T. Violaceum	3	10.00
T. Gypseum	2	6.67
T. Verrucosum	1	3.33
Microsporum	4	13.33
Syncephalastrum	1	3.33

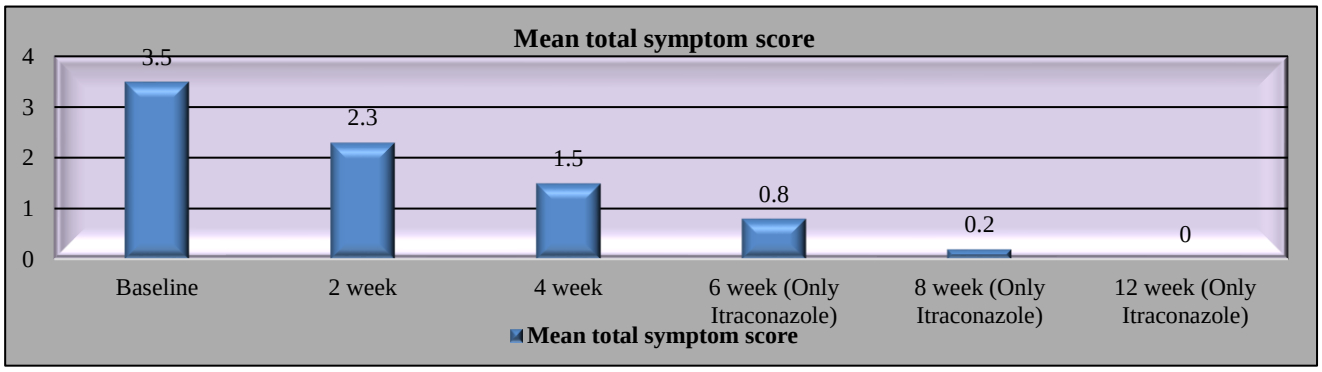

Figure 2: Mean total symptoms score (N=30).

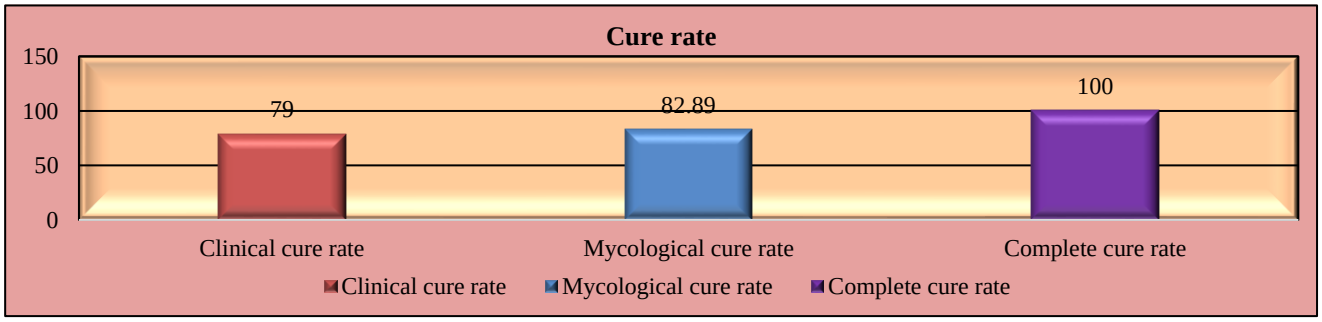

Figure 3: Cure rate of study patients (N=30).

Table 4: Clinical outcome of study patients (N=30).

Week wise improvement				
4 week	Significant improvement			Non-significant improvement
	n	%	n	%
	11	36.66	19	63.33
8 week	Significant improvement			Non-significant improvement
	n	%	n	%
	16	84.21	3	15.79
12 week	Significant improvement			Non-significant improvement
	n	%	n	%
	3	100	0	0

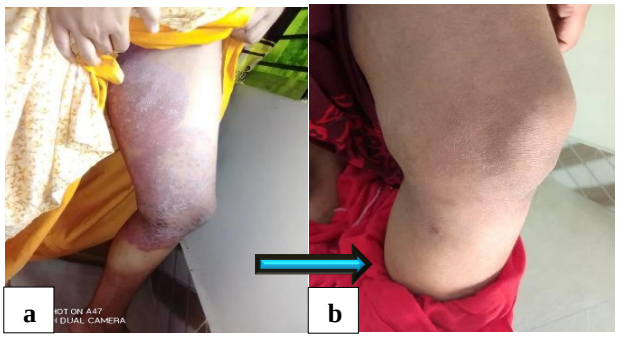

Figure 4: First example - digital photography (a) comparing baseline with (b) 4 weeks of treatment.

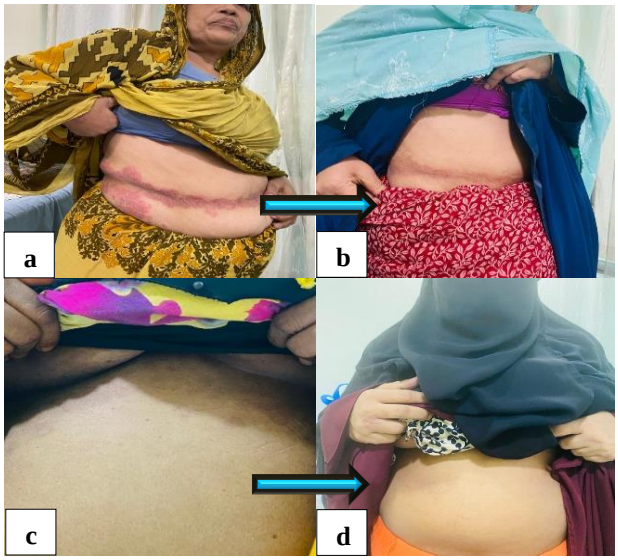

Figure 5: Digital photography comparing baseline (left) with 8 weeks of treatment (right) (a) and (b) second example and (c) and (d) third example.

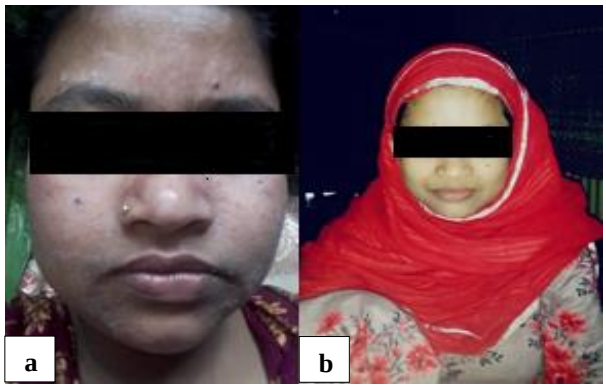

Figure 6: Digital photography comparing baseline (a) with 8 weeks of combine treatment and (b) use of itraconazole monotherapy only up to 12 weeks of treatment.

DISCUSSION

In recent years, the medical fraternity in Bangladesh has been observing an increase in the prevalence of tinea infection and resistance to conventional dosage of anti-fungal drugs. This change in the clinical scenario with increasing frequency of treatment failures has given rise to the search for an effective first-line treatment strategy that brings about rapid and complete clearance of tinea infection. Based on initial studies and recommendations, topical antifungals are the first line drugs in the management of tinea infection. However, in the current clinical scenario in Bangladesh, patients with large lesions or multisite tinea infection, only topical therapy fails to clear the lesions, leading to treatment failures and relapses. In such patients, systemic therapy is often recommended. Recently, Sahoo et al and Murlidhar et al in their comprehensive reviews recommended the use of a combination of topical and systemic antifungals in the management of patients with large lesions or recalcitrant tinea infections.[9,10] Authors commented that while using combination therapy, drugs from two different classes should be used for wider coverage, synergistic or additive action and to reduce the chance of resistance. CPO is a hydroxypyridone derivative that differs in structure and mechanism of action from the other known antifungal agents.[19] It acts through the chelation of polyvalent metal cations, such as Fe^{3+} and Al^{3+}, thereby causing inhibition of metal-dependent enzymes (cytochromes, catalase, and peroxidase) leading to a disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across cell membranes.[20] It also alters membrane permeability causing a blockage of the intracellular transport of precursors. CPO is widely available in nail lacquer formulation but has been recently approved in Bangladesh in cream formulation. Systemic antifungal agents such as griseofulvin, terbinafine, fluconazole, and itraconazole have been known to be active against dermatophytes, terbinafine being the only fungicidal drug.[23,24] Among these, itraconazole and terbinafine are more often prescribed compared to griseofulvin and fluconazole, probably because the latter require a longer duration of treatment.[25] In the past, terbinafine, in the dosage of 250 mg/day, has shown consistent efficacy against tinea infection, achieving more than 90% cure rates at a dose of 250 mg/day when administered for two weeks.[11,12] However, recently, an increase in the incidence of terbinafine resistance has resulted in treatment failure.[14] Although resistance to terbinafine in tinea infection is not common in clinical practice, it has been reported in clinical isolates by a few authors.[26,27] It has been seen that ineffective drug concentration in skin tissues may lead to anti-fungal resistance.[28] Hence, a higher concentration of terbinafine 500 mg/day has seen found to be more effective in some clinical studies.[15,29,30] Itraconazole is a itraconzole antifungal drug which is also increasingly being used as a first-line drug for tinea infection, but it is being given for longer periods as compared to before.[6,18] Though combination therapy is widely practiced in Bangladesh, no much of the literature is available regarding the effectiveness of the combination therapy. Only one study is available indicating efficacy of combination therapy.[31] As per that study, terbinafine with itrtaconazole achieved

better efficacy than terbinafine and itraconazole combination though results are not statistically significant. Secondly, there is still the question on the right combination of systemic and topical antifungal agents. Hence we conducted this study to compare the effectiveness and safety of itraconazole plus CPO versus terbinafine plus CPO combination to better understand the outcome of the result. As mentioned earlier, itraconazole and terbinafine are commonly used systemic anti-fungal agents. CPO was selected in view of different classes of mechanism of action and its recent introduction in Bangladesh. In our study, both the combination therapy options were efficacious in the management of tinea infection. Although the patients achieved clinical cure (Figure 3), there is no statistical difference in the complete cure at the end of eight weeks. A recent study by Majid et al could achieve only 43% cure rate after two weeks of daily 250 mg terbinafine oral treatment in tinea infection.[14] This recent decrease in the clinical efficacy is well corroborated by an upsurge in the cases encountered by dermatologists in daily clinical practice along with a failure to respond to the standard oral terbinafine therapy. Another study showed the mycological cure rate of terbinafine as 74% 21 and 71%.[16] In another study, three-week therapy of terbinafine 250 mg/day showed a 35% cure rate, which was even lower as compared to other studies.[22] In all these studies, terbinafine 250 mg/day was used. But in our study, we have used terbinafine in the dose of 500 mg/day and itraconazole in dose of 200 mg/day, which was well supported by some recent studies. In a recent study, three-week treatment with itraconazole 200 mg/day showed a cure rate of 50% which was lower as compared to previous studies showing variable cure rates of 80-92%.[16,21,22] These variable results of clinical efficacy of itraconazole are well evidenced in some of the literature. In our study, the mycological cure rates were 25 (82.89%) and clinical cure rate and complete cure rate both were same 24 (79%) respectively. This clearly indicates the need of using a higher dose of terbinafine along with a topical antifungal agent. Though many studies showed resistance or no clinical response to terbinafine, our study showed reverse results. This could be due to the fungicidal property of terbinafine and its ability to persist in stratum corneum for several months after stopping the treatment.[32] In the standard dosage, terbinafine and itraconazole have been used extensively for the treatment of tinea infection and have been found to be safe and well tolerated.[6,33] In the present study, the duration of the combination therapy was only four weeks but all the patients continued with topical for another four weeks. At the end of four weeks, patients who was treated with terbinafine and itraconazole showed good clinical resolution, there was partial clinical response. This indicates the need of monotherapy with topical for an extended duration in order to achieve higher cure rates in the treatment of tinea infection as suggested by Verma et al.[33] In the present study, none of the patients in either group reported any adverse events. The conventional systemic terbinafine and itraconazole monotherapy regimens at standard doses for two weeks' duration have shown high treatment failure and recurrence rate in the present scenario. Though better results can be achieved by extending the dose and duration of systemic anti-fungal agents up to four weeks, a comparable cure can be achieved by combining with topical of different classes of anti-fungal agents with extended use. This combination can thus limit the duration of the treatment. In the present scenario, antifungal combination therapy appears to have a promising future in the prompt management of tinea infection.

Limitations

This study was conducted at a single center and hence these findings cannot be generalized. For this purpose, further multicenter studies with larger sample size are required.

CONCLUSION

The systemic terbinafine (250 mg) twice daily and itraconazole (100 mg) twice in a pulse dose regimens of 4 weeks duration has shown high treatment failure and recurrence rate in the present scenario. Though better results can be achieved by extending the duration of treatment up to 8 weeks and use of itraconazole monotherapy only up to 12 weeks a comparable cure can be achieved by combining terbinafine and itraconazole for 4 weeks. This combination can thus limit the duration of treatment, is well tolerated and does not appear to have significant adverse effects. New vistas of antifungal combination therapy appear to have promising future in the prompt management of treatment failures in resistant tinea infection. After completing full dose, the patients become save long term.

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Ethical approval: The study was approved by the institutional ethics committee

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