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Original Article

Dermatology Section

Efficacy and Safety of Oral Terbinafine with Itraconazole or Griseofulvin Combination Therapy in the Management of Dermatophytosis- A Randomised Clinical Trial

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ABSTRACT

Introduction: Dermatophytosis is a common fungal infection caused by *Trichophyton*, *Epidermophyton*, *Microsporum* species. Combination of systemic and topical antifungal therapy is in vogue for all patients with dermatophytosis, except in cases of localised naïve Tinea. Recently, a rising prevalence of poor response to standard regimen of treatment has been noted. In this study, we tried to find out the benefits and adverse effects of systemic antifungal combination therapy in the treatment of tinea.

Aim: To compare the efficacy of oral terbinafine with itraconazole or griseofulvin combination therapy in the management of dermatophytosis and to assess the adverse effects associated with these combination therapies.

Materials and Methods: The present randomised clinical trial comprised of 60 patients with dermatophytosis who were divided into two groups. The study was conducted in the Department of Dermatology, Outpatient Department (OPD), Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India, from December 2020 to May 2021. Group I was treated with terbinafine 250 mg OD and itraconazole 200 mg OD and group II with terbinafine 250 mg OD with griseofulvin 250 mg BD for a period of four weeks and the patients were followed-up every two weeks with appropriate investigations. Outcome of the treatment was assessed at four weeks and eight weeks. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 16.0. Descriptive analyses were performed to compare the baseline characteristics of the participants between the two study groups. Student t-test was applied to compare the mean values of quantitative variables. Chi-square test was used for analysing the categorical variables. A p-value of <0.05 was considered as significant.

Results: Itraconazole containing group reported a better clinical cure rate than the griseofulvin containing group (p<0.05). Neither of the combination showed effectiveness against tinea infections pretreated with topical steroid containing formulations.

Conclusion: Combination of terbinafine with itraconazole produce higher clinical cure rate as compared to the combination of terbinafine with griseofulvin; but the percentage of clinical cure rate is less as compared to published studies in the past. Neither of the combination of systemic antifungals has shown efficacy against tinea infections pretreated with topical steroid containing formulations.

Keywords: Chronic dermatophytosis, Systemic antifungals, Tinea infections, Topical steroid formulations

INTRODUCTION

Fungal infections are a major concern for both patients and treating physician, especially those affecting skin. Dermatophytosis/tinea is one of the most common skin diseases affecting people across the world; caused by superficial fungus which invade and multiply within the keratinised tissue (skin, hair, nails). Approximately, 20-25% of the world population is affected by tinea [1]. Over the last 40 years, there have been significant advances in the management of this condition starting from simple antiseptics with non specific antifungal activity to the specific antifungal drugs available present day [2].

Major fungi causing dermatophytosis are *Trichophyton*, *Microsporum*, and *Epidermophyton* [3]. Recently, there is a change in the pattern of tinea seen as an increase in the occurrence of difficult to treat recalcitrant, recurrent, and chronic dermatophytosis [4]. Various factors such as global warming, hot and humid climate, migration of laborers, increased frequency of wearing tight and synthetic clothing, obesity, sedentary lifestyle, increasing prevalence of *Trichophyton mentagrophytes* and poor compliance of patients are reasons for the treatment resistant tinea [5,6]. Apart from this, another major factor contributing to this is the widespread abuse of topical steroid antifungal combination creams by the patients, mostly available as an Over The Counter (OTC) purchase or when prescribed by practitioners or quacks [7].

Terbinafine, the first line systemic drug for the treatment of dermatophytosis, acts by inhibiting the enzyme squalene epoxidase involved in the synthesis of ergosterol which is necessary for the formation of fungal cell membrane [8]. Itraconazole has fungistatic action through the inhibition of 14α-demethylase and griseofulvin causes disruption of microtubule spindle formation and thereby inhibits the fungal cell wall synthesis [9].

A combination therapy of systemic antifungal drugs with different mechanism of action enhances the cure rate and helps prevent drug resistance based on the concept of synergistic and additive effects of two or more drugs [10]. There is lacunae of studies in literature evaluating the efficacy and safety of systemic antifungal combination therapy with terbinafine, itraconazole and griseofulvin in the management of dermatophytosis. In this study we made an attemp to find out the benefits and adverse effects of various systemic combination therapy for the treatment of tinea. Therefore, this study aims to compare the efficacy of oral terbinafine in combination with either itraconazole or griseofulvin and to assess the adverse effects associated with this combination therapy. The null hypothesis of the present study was that, there was no significant difference in the therapeutic outcome of oral terbinafine in combination with either itraconazole or griseofulvin.

MATERIALS AND METHODS

A comparative non blinded randomised clinical trial was conducted among 60 patients with dermatophytosis who attended the OPD

of Department of Dermatology, Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, India, between December 2020 to May 2021. The trial was approved by the Institutional Ethical Committee- No:26122020.

Sample size calculation: The sample size was calculated to be 60 using OpenEpi software with 95% level of confidence, power of 80% and considering cure rate of 79%. The study population was randomly divided in two groups. Randomisation of the subjects was done using simple random sampling using lottery system. Due to the development of adverse effects, two patients were excluded from the study and one was lost to follow-up.

Inclusion criteria: Patients >18 years with Tinea corporis, Tinea cruris, Tinea faciei with total body surface area involved at least 50% were included in this study.

Exclusion criteria: Age <18 years, pregnant and lactating women, patient who were allergic to terbinafine/itraconazole/griseofulvin, h/o of intake of oral antifungals in last one month, patients with cardiac, renal, and hepatic disease, abnormal complete haemogram, renal function test and liver function test were excluded in this study.

Study Procedure

Patients satisfying the inclusion criteria were enrolled in the study after obtaining informed consent from the patient. Patients were randomly divided into two groups by random sampling using lottery system; each group consisting of 30 members; Group I was treated with oral terbinafine 250 mg OD (Terbest 250, manufactured by Systopic Laboratories Pvt., Ltd.,) with oral itraconazole 200 mg OD (Itrasys 200 mg, manufactured by Systopic Laboratories Pvt., Ltd.,) PO for four weeks and group II received oral terbinafine 250 mg OD with oral griseofulvin 250 mg BD (Grisovin FP 250 mg, manufactured by GSK pharmaceuticals) PO for four weeks. Patients were evaluated for the severity of clinical parameters namely erythema, and scaled using four-point scale as: 0=none, 1=mild, 2=moderate, and 3=severe [11].

At the time of initial visit and at the end of second and fourth weeks of treatment, Complete Blood Count (CBC), Liver Function Test (LFT), and Electrocardiography (ECG) were repeated in the terbinafine with itraconazole group and CBC and LFT in the terbinafine with griseofulvin group. Topical antifungals were not prescribed to both groups. Both groups received liquid paraffin and non sedative antihistamines as a part of supportive care. The patients were asked about any side effects experienced during the treatment course. Patients were followed-up at every two weeks interval up to a maximum of eight weeks (four weeks after therapy or cure, whichever occurred earlier). They were followed-up during the treatment period and also four weeks after the treatment completion Body Surface Area (BSA) was calculated using 'Rule of 9'.

Outcome measurements were as follows:

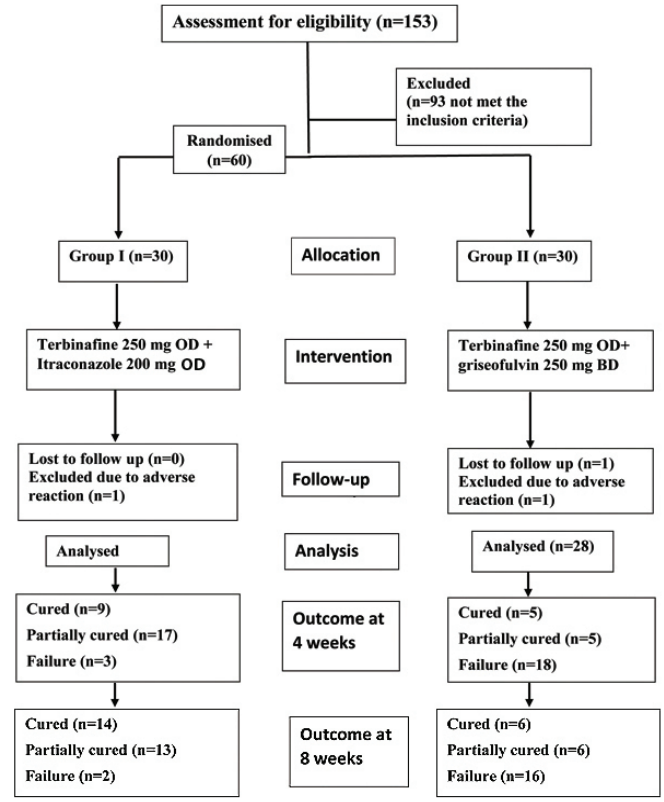
- Cured (complete clinical resolution of all lesions).
- Partially cured {more than 50% improvement in the involved total BSA} and
- Failure (increase in severity of the lesions or no improvement in the lesions after four weeks of starting antifungal agents or less than 50% involved total BSA improvement).

STATISTICAL ANALYSIS

Analysis of data was done using SPSS software version 16.0. Descriptive analyses were performed to compare the baseline characteristics of the participants between the two study groups. Student t-test was applied to compare the mean values of quantitative variables. Chi-square test was used for analysing the categorical variables. A p-value of <0.05 was considered as statistically significant. Patients who were excluded from study due to adverse reactions or lost to follow-up were not included in the data analysis (n=57).

RESULTS

A total of 60 participants were enrolled in the study with tinea infections which mainly affected the trunk, groin, and face. Two subjects were excluded due to adverse drug reactions and one lost to follow-up. The remaining 57 subjects were then segregated into two groups, that is group I and group II with n=29 and n=28, respectively (with n signifying the number of subjects) [Table/Fig-1].



[Table/Fig-1]: CONSORT flow chart.

The [Table/Fig-2] demonstrates that the age, sex, and disease duration were constant. The mean age of participants was calculated to be 36.47±11.03 years. Statistically, 64.9% of the overall participants were females and 66.7% of the entire study group belonged to the age group of 18-40 years. It was seen that 75.4% of the patients had the disease duration for less than or equal to six months. Majorly, 71.9% of the participants had a history of topical medicines application and 43.9% applied topical steroid combination cream prior to the first visit to OPD. Meanwhile, it was noted 21.1% have taken systemic drugs before the initial visit to our OPD. From the study, it was also noted that 54.4% of present

Characteristics	Group I (n=29)	Group II (n=28)	Total (n=57)	p-value
Age in years* (mean±SD)	35.62±11.45	37.36±10.71	36.47±11.03	0.74
Age group (18-40 years) n (%)	20 (69)	18 (64.3)	38 (66.7)	0.70
Male n (%)	9 (31)	11 (39.3)	20 (35.1)	0.53
Female n (%)	20 (69)	17 (60.7)	37 (64.9)	
Disease duration less than six months, n (%)	21 (72.4)	22 (78.6)	43 (75.4)	0.58
Topical application prior to the visit to OPD, n (%)	21 (72.4)	20 (71.4)	41 (71.9)	0.93
Topical steroid application prior to the visit to OPD, n (%)	12 (41.4)	13 (46.4)	25 (43.9)	0.35
Systemic therapy, n (%)	5 (17.2)	7 (25)	12 (21.1)	0.47
Co-morbities, n (%)	5 (17.2)	3 (10.7)	8 (14)	0.31
Family h/o of dermatophytosis n (%)	18 (62.1)	13 (46.4)	31 (54.4)	0.23

[Table/Fig-2]: Comparison between group I and group II in terms of baseline parameters of patients (n=57). Percentage mentioned inside the brackets.
Test used: *independent sample t-test others: chi-square test

patients had similar complaints in the family and seven out of the 57 patients were suffering from diabetes mellitus.

The [Table/Fig-3] shows, 71.9% of the patients included in this study were suffering from Tinea corporis et cruris and the baseline mean erythema and scaling score were found to be similar in both groups (p>0.05).

Characteristics	Group I (n=29)	Group II (n=28)	Total (n=57)	p-value
T. corporis et cruris, n (%)	19 (65.5)	22 (78.6)	41 (71.9)	0.001
T. corporis et cruris et faciei, n (%)	10 (34.5)	6 (21.4)	16 (28.1)	0.001
+Baseline erythema score (Mean±SD)	2.24±0.57	2.29±0.63	2.26±0.58	0.77
+Baseline scaling score (Mean±SD)	2.55±0.57	2.50±0.60	2.53±0.60	0.74

[Table/Fig-3]: Comparison of clinical characteristics of patients in group I and group II at the time of initial visit (n=57). Percentage mentioned inside the brackets.
Test used: *Pearson's chi-square test, +: Independent sample t-test

The [Table/Fig-4] shows that at four and eight weeks, erythema and scaling score were significantly improved as compared to the baseline values in both the groups (p<0.001), slightly higher improvement noted in the group I. This result indirectly implies that the clinical features of patients at the end of fourth and eight weeks improved in both groups due to the treatment given. There was no significant difference in the mean erythema score at eight weeks between both the groups (p=0.07); whereas mean scaling score at eight weeks significantly improved in the group I as compared to group II (p=0.02).

Groups	Erythema score (mean±SD)			Scaling score (mean±SD)		
	At 1st visit	4 weeks	8 weeks	At 1st visit	4 weeks	8 weeks
*Group I (n=29)	2.24±0.57	0.83±0.71 (p<0.001)	0.79±0.94 (p<0.001)	2.55±0.57	0.86±0.78 (p<0.001)	0.79±0.90 (p<0.001)
*Group II (n=28)	2.29±0.63	1.39±0.786 (p<0.001)	1.21±0.78 (p<0.001)	2.50±0.60	1.36±0.951 (p<0.001)	1.36±0.91 (p<0.001)
Total (n=57)	2.26±0.58	1.05±0.78 (p<0.001)	1.36±0.91 (p<0.001)	2.53±0.60	1.11±0.90 (p<0.001)	1.07±0.96 (p<0.001)
+Group I vs II (p-value)	0.77	0.006	0.073	0.74	0.03	0.02

[Table/Fig-4]: Comparison between the erythema score and scaling score of baseline at 4th and 8th weeks in each group
Test used: *paired sample t-test, +independent sample t-test

Statistical analysis of haematological investigations showed minimal decrease in the level of haemoglobin, White Blood Cells (WBC) and platelet count at the end of fourth week as compared to the baseline value in both group I and II (p<0.001); but the mean values were within the normal range at the end of four weeks. Mean values of total bilirubin, Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were raised at the end of four weeks treatment in both groups; but lied within the normal range. Baseline and ECG reports at the end of fourth week were within normal limits in all patients of group I.

The [Table/Fig-5] demonstrates that, at the end of four weeks, 9 (31%) people in group I and 5 (17.9%) people in the group II were completely cured. Meanwhile, at the end of eight weeks, 14 (48.3%) in group I and 6 (21.4%) patients in group II were completely cured. Clinical cure rates were high in itraconazole containing group at 4 and eight weeks than the group containing griseofulvin which was statistically significant.

The percentage of partially cured people at the end of four weeks in group I and group II were 58.6% and 17.9%, respectively. Whereas, at the end of eight weeks, 44.8% of people in group I and 21.4% in group II were partially cured of the infection. The failure rate of combination therapy seen in group I and II were 6.9% and 57.1%, respectively at the end of eight weeks.

Variables	Parameters	Group I (n=29) (n)	Group I (n=29) (%)	Group II (n=28) (n)	Group II (n=28) (%)	p-value
At the end of fourth weeks	Complete cure	9	31	5	17.9	<0.001
	Partial cure	17	58.6	5	17.9	
	Failure	3	10.3	18	64.3	
At the end of eight weeks	Complete cure	14	48.3	6	21.4	<0.001
	Partial cure	13	44.8	6	21.4	
	Failure	2	6.9	16	57.1	

[Table/Fig-5]: Comparison between group I and group II regarding therapeautic outcome (n=57).
p-value found using: Pearson's chi-square test

As [Table/Fig-6] depicts, there was no association between the duration of the infection and previous topical steroid application with treatment response in both groups (p-value was not statistically significant).

Parameters		Complete cure at eight weeks: Group I (n=29)	p-value	Group II (n=28)	p-value
Disease duration <6 months	Complete cure	9	0.12	4	0.72
	Partial cure	7		5	
	Failure	5		13	
Disease duration <6 months	Complete cure	1		2	
	Partial cure	6		1	
	Failure	1		3	
Previous topical steroid application	Complete cure	4	0.86	3	0.76
	Partial cure	6		2	
	Failure	2		8	

[Table/Fig-6]: Comparison of association between the disease duration and topical steroid application with the treatment outcome in group I and group II (n=57).
Test used: Pearson's chi-square test

Adverse drug reactions were reported in three patients. In group I, one patient experienced lichenoid drug eruption. One patient in group II developed severe burning and itching sensation over the body and another one had a headache.

DISCUSSION

In this study, combination of terbinafine with itraconazole produced higher clinical cure rate as compared to the combination of terbinafine with griseofulvin used; but the percentage of clinical cure rates in both groups were less when compared to similar studies published in the past. This indicates that susceptibility of fungal organism to the combination of systemic therapy has reduced recently. Itraconazole with terbinafine study group yielded a better cure rate when compared to terbinafine and griseofulvin group.

Indication for systemic therapy in dermatophytosis are extensive tinea corporis, involvement of multiple sites, recurrent or chronic dermatophytosis, immunocompromised patients, non responsive to topical antifungals, tinea involving scalp, palms and soles [12,13]. Patients with chronic or recalcitrant cases and tinea infections pretreated with topical steroid containing formulations need treatment for a longer duration than the naïve tinea [14,15]. Wide variety of systemic antifungals are available for the treatment of tinea which consists of terbinafine, griseofulvin, itraconazole and fluconazole. Out of these, the commonly prescribed drugs are itraconazole and terbinafine as the other two require a longer duration. Terbinafine is the only fungicidal drug among these.

In present study, majority of the patients were females (64.9%). In another study, by Singh SK et al., reported predominance of male patients [16]. This shows an increasing trend about the concern regarding cosmetological impact in dermatological diseases among women. It may also be due to the unbearable symptoms. Majority of the study population belonged to the age group of 18-40 years.

Most common variant seen in present study was tinea corporis et tinea cruris (71.9%), which is same as reported in the previous studies [11,16-18]. In present study, 43.9% patients had a previous history of topical steroid containing cream application and 54.4% had the history of similar complaints in the family. The main factors contributing to the resistance are easy availability of steroid containing topical antifungal creams OTC and persistence of infectious foci in the house, when the family members are simultaneously affected. It was seen that 75.4% of the patients had the disease duration of less than or equal to six months. Sharma P et al., also reported the same duration [11].

As previously mentioned, current study showed a comparatively better complete clinical cure rate with terbinafine and itraconazole (48.3%). This value was lesser as compared to the study conducted by Sharma P et al., and Singh SK et al. Sharma P et al., reported 90% complete clinical cure rate and Singh SK et al., reported 79.2% clinical and mycological cure rate after three weeks and four weeks of combination therapy respectively [11,16]. The clinical cure rate of terbinafine with griseofulvin group in our study was only 21.4%. Singh S et al., reported a clinical cure rate of 28.8% which is almost comparable to our study [19]. In this study, neither of the combinations showed effectiveness against tinea infections pre-treated with topical steroid containing formulations.

Adverse drug reaction was reported in three patients. One had burning and itching sensation and another one experienced headache in griseofulvin containing group. In itraconazole containing group one had lichenoid drug eruption. No one developed significant derangement of liver function. Sharma P et al., reported diffuse hair fall, gastritis, constipation, unpleasant taste in the combination group [11]. Teraki Y and Shiohara T and Zheng Y et al., have reported lichenoid drug eruption following terbinafine therapy [20,21]. Bailey EM et al., and Tucker RM et al., have reported erectile dysfunction as a rare side effect following itraconazole therapy [22,23]. Singh S et al., found no adverse effects in terbinafine with griseofulvin group [19].

Limitation(s)

This study was limited by it's small sample size and short follow-up duration. Mycological investigations (culture with antifungal susceptibility and Potassium hydroxide examination) and pharmacokinetic studies were not done. Effectiveness of continuation of same treatment regimen for an extended duration in the partially cured group was not assessed. Further studies with a large sample size with mycological investigations and pharmacokinetic studies will throw more light on this topic.

CONCLUSION(S)

Combination of terbinafine with itraconazole produces higher clinical cure rate as compared to the combination of terbinafine with griseofulvin; but the percentage of clinical cure rate was less when compared to published studies in the past. Neither of the combination showed effectiveness against tinea infections pretreated with topical steroid containing formulations. Strict legislation against irrational use of topical corticosteroid antifungal combination cream is the need of the hour. Awareness has to be made among the general practitioners regarding incorrect use of topical steroid-antifungal preparations. Sensitisation among the public regarding the general measures in prevention of tinea and proper treatment of their family members will also help to reduce the burden of infection.

REFERENCES

[1] Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. Mycose. 2008;51:02-15.
[2] Hay R. Therapy of skin, hair and nail fungal infections. J. Fungi (Basel). 2018;4(3):99.
[3] Rajabian A, Hosseinzadeh H. Dermatological effects of nigella sativa and its constituent, thymoquinone. In: Preedy VR, Watson RR, editors. Nuts and Seeds in Health and Disease Prevention. San Diego, CA: Elsevier; 2020. Pp. 329–55.
[4] Dogra S, Uprety S. The menace of chronic and recurrent dermatophytosis in India: Is the problem deeper than we perceive? Indian Dermatol Online J. 2016;7(2):73-76.
[5] Rengasamy M, Chellam J, Ganapati S. Systemic therapy of dermatophytosis: Practical and systematic approach. Clin Derm Rev. 2017;1(3):19.
[6] Babu PR, Pravin A, Deshmukh G, Dhoot D, Samant A, Kotak B. Efficacy and safety of terbinafine 500 mg once daily in patients with dermatophytosis. Indian J Dermatol. 2017;62:395-99.
[7] Dutta B, Rasul E, Boro B. Clinico-epidemiological study of tinea incognito with microbiological correlation. Indian J Dermatol Venereol Leprol. 2017;83(3):326.
[8] Lipner SR, Scher RK. Onychomycosis: Treatment and prevention of recurrence. J Am Acad Dermatol. 2019;80(4):853-67
[9] Gupta AK, Mays RR, Versteeg SG, Piraccini BM, Shear NH, Piguet V, et al. Tinea capitis in children: A systematic review of management. J Eur Acad Dermatol Venereol. 2018;32(12):2264-74.
[10] Johnson MD, MacDougall C, Ostrosky-Zeichner L, Perfect JR, Rex JH. Combination antifungal therapy. Antimicrob Agents Chemother. 2004;48:693-715.
[11] 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(7):749-53.
[12] Gupta AK, Chaudhry M, Elewski B. Tinea corporis, tinea cruris, tinea nigra, and piedra. Dermatol Clin. 2003;21:395 400.
[13] Ellis D, Watson A. Systemic antifungal agents for cutaneous fungal infections. Aust Prescr. 1996;19:72-75.
[14] Janaki VR. Therapeutic options in mycoses. In: Sentamilselvi G, Janaki VR, Janaki C, editors. The Hand book of Dermatomycology & Colour Atlas. 1st ed.. India: Sentamilselvi; 2006. Pp. 61-82
[15] Thursky KA, Playford EG, Seymour JF, Sorrel TC, Ellis DH, Guy SD, et al. Recommendations for the treatment of established fungal infections. Intern Med J. 2008;38:496-520.
[16] 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;65:284-89.
[17] Mahajan S, Tilak R, Kaushal SK, Mishra RN, Pandey SS. Clinico-mycological study of dermatophytic infections and their sensitivity to antifungal drugs in a tertiary care center. Indian J Dermatol Venereol Leprol. 2017;83:436-40.
[18] Singh BS, Tripathy T, Kar BR, Ray A. clinicomycological study of dermatophytosis in a tertiary care hospital in eastern India: A cross- sectional study. Indian Dermatol Online J. 2020;11:46-50.
[19] Singh S, Anchan VN, Raheja R. Futility of combining griseofulvin and terbinafine in current epidemic of altered dermatophytosis in India: Results of a randomized pragmatic trial [Internet]. medRxiv. 2019 [cited 2021 Oct 28]. Pp. 19007617. Available from: https://www.medrxiv.org/content/10.1101/19007617v1.
[20] Teraki Y, Shiohara T. Spontaneous tolerance to terbinafine-induced lichenoid drug eruption. Dermatology. 2004;208:81-82.
[21] Zheng Y, Zhang J, Chen H, Lai W, Maibach HI. Terbinafine-induced lichenoid drug eruption. Cutan Ocul Toxicol. 2017;36:101-03.
[22] Bailey EM, Krakovsky DJ, Rybak MJ. The triazole antifungal agents: A review of itraconazole and fluconazole. Pharmacotherapy. 1990;10:146-53.
[23] Tucker RM, Haq Y, Denning DW, Stevens DA. Adverse events associated with itraconazole in 189 patients on chronic therapy. J Antimicrob Chemother. 1990;26:561-66.

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