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COMBINATION DRUG TREATMENT IN *Tinea* INFECTIONS OF CUTANEOUS SOFT TISSUES

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between all authors. Author AG performed the clinical examinations and prescribed the medicine to patients. Author SK managed the literature searches and analyses of the study. Author PKG designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Systemic antifungals are the most effective treatment and three major groups of antifungal agents in clinical use are azoles, polyenes and allylamine/thiocarbamates. Unlike the azoles, which are primarily fungistatic, terbinafine has a fungicidal mode of action through its ability to inhibit the enzyme squalene epoxidase, leading to a fungicidal accumulation of squalene within the fungal cell. The oral therapy is usually reserved for more severe infections and will lead to better mycological clearance. Therefore, the present study included the topical (1% terbinafine cream) and oral terbinafine drug (250 mg for 4-6 weeks) treatment with combination of itraconazole (100 mg/day for 4-6 weeks) was advised in *Tinea* infections. Of these, 40% (n=84) were male, while 60% (n=126) were female with mean age group was 35 years. The erythema (28.57%) and pruritis (21.42%) were the most common diagnosed symptoms. The 57.14% patients investigated with the moderate severity of *Tinea* infection, whereas 15.71% patients showed severe infections, in which older aged female patients reported more severe infections. In the present study about 70% patients reported 100% cure only with terbinafine, whereas 30% patients had slight improvements and further combination with itraconazole resulted in 100% cure rate. Henceforth further study is underway for molecular identification of different dermatophytes along with antimicrobial susceptibility testing so that better treatment with short interval of time should be recommended to the patients.

Keywords: Dermatophytes; terbinafine; *Tinea* infection; antifungal drugs; oral therapy.

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1. INTRODUCTION

During the last 100 years, the dermatophytes spectrum has markedly changed over the world with differences depending on the geographic area, socioeconomic factors, modern life, intensification of travel, and migration of population [1]. The mycosis is caused by dermatophytes which developed in the dead part of keratinized tissue of the *stratum corneum*, within and around skin, hair and in the nails [2]. The growth of dermatophytes is associated with the production of hyphae and arthroconidia, this characteristic being used as a diagnostic feature. The pathogenicity of dermatophytes is associated with different factors including the production of keratinolytic enzymes [3], a genetic predisposition and the presence of host factors [4]. The possible route of entry for the dermatophytes into the host body is through the injured skin, scars, burns and the arthrospores which caused the infection [5]. The pathogen invade the uppermost, non-living, keratinized layer of the skin namely the *stratum corneum*, produces exo-enzyme keratins and induces inflammatory reaction at the site of infection [6]. However, the dermatophytes in general lack the ability to invade deeper tissues or organs of the host, but in chronic conditions the fungi invade deeper tissues particularly in simultaneous infection with other organisms.

The typical infections of dermatophytes are generally referred to as ringworm infections due to their ring like appearance [7]. The customary signs of inflammatory reaction such as redness and swelling are seen at the site of infection. Inflammation causes the pathogen to move away from the site of infection and take a residence at a new site. This movement of the organism away from the infection site produces the classical ringed lesions [8]. Dermatophytes spread indirectly from fomites (hair brushes, towel and hat) and by direct contact from other people, animals and soil [9]. The World Health Organization estimates universal occurrence of dermatomycosis to be related to 20%. The dermatophytes are significantly varying in diverse level of the world. They increased at exterior temperature of 25-28°C and membrane mycosis is continued by warm and humid conditions [10].

In Asia the predominant clinical pattern are varied with geographical regions. *Tinea corporis* is the commonest clinical pattern reported in India, followed by *Tinea cruris*, *Tinea unguium* and *Tinea capitis*. *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the major dermatophytes species frequently isolated in India [11]. The most effective treatment for dermatophytosis is systemic antifungals drugs, which included three major groups of antifungal agents: azoles, polyenes and allylamine/thiocarbamates. All owe their antifungal activities by inhibiting the synthesis or direct interaction with ergosterol, which is the predominant component of the fungal cell membrane. The most commonly used antifungal agents are azoles, which contain either two or three nitrogens in the azole ring and are classified as imidazoles (ketoconazole, miconazole, clotrimazole) or triazoles (itraconazole, fluconazole), respectively. The use of the imidazoles is limited to the treatment of superficial mycoses with the exception of ketoconazole, whereas the triazoles have a broad range of applications in the treatment of both superficial and systemic fungal infections. Terbinafine is a synthetic antifungal agent of the allylamine class with a potent *in vitro* activity that embraces all dermatophytes of the genera *Trichophyton*, *Epidermophyton* and *Microsporum* [12,13]. Unlike the azoles, which are primarily fungistatic, terbinafine has a fungicidal mode of action through its ability to inhibit the enzyme squalene epoxidase, leading to a fungicidal accumulation of squalene within the fungal cell [14]. These properties have allowed reduction of treatment duration in dermatomycosis and onychomycosis without affecting the cure rate [15].

The antifungal activity of the allylamine derivative terbinafine [SF 86-327; (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-l-naphthalenemethanamine hydrochloride] against a broad spectrum of medically important fungi *in vitro* has been described in previous papers [14,16,17,18]. It is highly active against *Trichophyton*, *Epidermophyton*, and *Microsporum* species *in vitro*, with MICs ranging from 0.001 to 0.01 µg/ml. So far there are limited data on the comparative study on combination of systemic and topical versus monotherapy with systemic antifungal treatment. Therefore, the present study aim to investigate the efficacy and safety of 250 mg terbinafine oral along with Itraconazole and topical 1% Terbinafine cream for patients suffering from chronic dermatophytic infection.

2. MATERIALS AND METHODS

This study was carried out in the Dermatology Out-patient Clinic, Adesh Hospital of Adesh University, Bathinda, India. The patients were examined clinically and mycologically before the start of therapy and end of treatment.

2.1 Study Design

Cross sectional study has been conducted, in which Male and female patients (n=210 in total) aged 10–60 years were recruited over the period from June to September and advised to have treatment with both

oral and topical Terbinafine treatment along with Itraconazole. Terbinafine 1% cream twice a day and 250 mg tablet once daily in the evening after a meal for upto 4-6 weeks or according to the improvement of infection. In severe cases and patients with relapsed infection also advised to take Itraconazole 100 mg/day after meal for upto 4-6 weeks along with Terbinafine.

Every patient advised to report after 2 weeks and after investigations and improvement, patient again recommended medicine for another 2 weeks followed by a 1 week post treatment observation period. For topical therapy patients were instructed to thoroughly clean and dry the skin and then to rub the terbinafine 1% cream gently into all affected areas twice daily till the infection finished. The most severe lesion was chosen as the target lesion for assessment of efficacy. Patients were urged not to apply any other creams, lotions, or ointments to their lesions during the course of the study.

2.2 Mycological Examinations

Skin scrapings were taken for microscopy and culture. All patients with a clinical diagnosis of *Tinea* confirmed by the detection of fungal hyphae on a potassium hydroxide (KOH) wet mount were eligible to be included in the study. Specimens (scrapings) were placed on a slide with a drop of 10% KOH and examined immediately under the microscope for hyphae and spores. Also specimens were inoculated into Sabouraud's agar plates. Patients were advised to purchase Terbinafine tablets (250 mg, 7 tablets each week) and Itraconazole 100 mg/day of the same manufacture and after purchased medicines were cross checked by clinician.

The primary efficacy criterion was negative culture through microscopy at the end of the study. Secondary efficacy criteria were total clinical signs and symptoms score and clinical response. The severity of seven clinical signs and symptoms-erythema, scaling, vesiculation, pruritis, pustules, exudation and crusting-was recorded at baseline and at each study visit on a 4-point scale: 0 absent; 1 mild; 2 moderate; 3 severe. Clinical response was categorized as either effective or ineffective treatment. Effective treatment was defined as negative microscopy and culture with mild or no residual erythema and/or scaling and/or pruritis and no other clinical signs. Treatment outcomes that did not meet these definitions were classified as ineffective.

2.3 Final Evaluation

In addition a final examination was planned 4 weeks after treatment initiation to assess complete cure of the patients. The criterion for mycological cure was that samples should be negative by both microscopy and culture. The subjective clinical criteria were considered improvements in the appearance of the cutaneous skin with a marked reduction in the signs and symptoms of infection. Cure was evaluated by clinical cure (≥85% skin clearing), mycologic cure (negative microscopy of KOH samples and negative culture) and complete cure at follow up (mycologic cure and complete skin clearing). Safety and tolerability were assessed by adverse event (AE) rates based on patient information, answers to investigator questions, and physical examinations.

2.4 Ethical and Consent Disclaimer

All patients gave written informed consent and the research project was approved by the Institutional Ethical Committee of Adesh University, Bathinda.

3. RESULTS AND DISCUSSION

The incidence of chronic dermatophytic infections of skin significantly increased from last few years and also proven difficult to treat. The climatic conditions of Malwa region of Punjab are favorable for high prevalence of dermatophytes during June to September because of hot and humid environment. The oral therapy is usually reserved for more severe infections and will lead to better mycological clearance. Therefore, the present study included the topical (1% cream) and oral terbinafine drug (250 mg) treatment along with Itraconazole in *Tinea* infections at a dermatology clinic of Adesh hospital in Northern India.

During the period of study, total 210 patients treated with topical (1% cream) and oral terbinafine drug (250 mg) treatment in *Tinea* infections along with Itraconazole. Of theses, 40% (n=84) were male while 60% (n=126) were female with mean age group was 35 years. On the contrary Dabas et al. [19] reported a high prevalence among males (64%) and the mean age of patients was 31.2 years. The erythema (28.57%) and pruritis (21.42%) were the most common diagnosed symptoms. The 57.14% patients investigated with the moderate severity of *Tinea* infection, whereas 15.71% patients showed severe infections, in which older aged female patients reported more severe infections (Table 1). The age group 10-20 years showed less (8.57%) susceptibility of infection followed by 12.86% for older age of 51-60 year of patients. In addition the most common age groups were ranging from 21 to 50 years which showed 22.86% to 30% infections of cutaneous soft tissues. The infections were more frequent among these groups because of more active involvement in

Table 1. Summary of patient demographics for treatment with terbinafine

Characteristics				
Age (Year)	**Male**	**Female**	**Total**	**Percentage**
10-20	12	06	18	08.57
21-30	36	27	63	30.00
31-40	09	45	54	25.71
41-50	15	33	48	22.86
51-60	12	15	27	12.86
Total (M/F)	84	126	210	40/60
Severity of *Tinea*				
Mild	25	35	60	28.57
Moderate	56	64	120	57.14
Severe	03	30	33	15.71
Duration of *Tinea* infection (in months, mean±SE)				5.5±0.8
Main presenting symptoms/signs				
Itching	84	126	210	100
Erythema	26	32	60	28.57
Scaling	04	10	14	06.70
Vesiculation	Nil	02	02	0.95
Pruritis	21	37	58	27.62
Pustules	01	01	02	0.95
Exudation	20	25	45	21.42
Crusting	12	19	31	14.76

the agriculture activities. Similarly, housewife females residing in the villages had more infections as compared to working women (Table 1), because in villages housewife involved in farming activities. The other factors that aided the dermatophytes infections included the unhygienic living standards, which were specifically common among the low socio-economic and high population densities. Similarly during the diagnosis about 2% patients acquired infection by using unclean blade for shaven underarms and river water usage. The sportsman and Army personnel acquired infection for more physical activities and contact with soil. After delivery 2.86% females were also observed for dermatophytes infections. Whereas 29.05% patients showed chronic groins area infections followed by 17.14% of abdomen as well as all over the body (Table 2). In addition, about 5.7% infections of dermatophytes were also reported in which whole family members were infected due to one person carrying the infection and then distributed to other family members. The pathogenesis of dermatophytes infection involves complex interaction between the host, environment and other agents. The other predisposing factors which could produce severe widespread dermatophytosis are *diabetes mellitus*, lymphomas, immunocompromised status, older age [20]. Some body parts are more prone to the dermatophytes infections in which excess sweating, maceration, and alkaline pH favor the growth of the fungus such as intertriginous areas like web spaces and groins. The suitable condition favor the infection of dermatophytes to progress through adherence followed by penetration which mediated by proteases, serine-subtilisins and fungolysin, which causes digestion of keratin network into oligopeptide or amino acid [20,21].

3.1 Combination of Therapy

In the present study about 70% patients reported 100% cure, whereas 30% patients had slight improvements. Further treated with combination of both terbinafine (250 mg/day for 2–4 weeks) and itraconazole (100 mg/day for 2–4 weeks) were advised. It was observed that 4 weeks of combination therapy resulted in effective treatment and patients responded well (Table 3). The total follow up for all these patients was upto 4-6 weeks. Fluconazole was used earlier but nowadays restricted because it is a fungistatic drug and potency is less than terbinafine which is a fungicidal drug. However to some patients when fluconazole 150 mg every other day was given along with terbinafine 250 mg/day response was good. All age male and female patients responded similar ways and there was no sex differentiation reported among the 210 patients in response of Terbinafine.

The monotherapy with itraconazole or fluconazole was less effective and also require long-term treatment. In most of patients relapse occurred with itraconazole and fluconazole after six months treatment. On the contrary Lachapelle et al. [22] conducted comparative trial between itraconazole

Table 2. Dermatophytes infection on the different body parts

Area affected	Male (84)	Female (126)	Total	Percentage
Groin area (*Tinea cruris*)	24	37	61	29.05
Abdomen	16	18	34	16.20
Arms	20	16	36	17.14
Underarms	-	10	10	04.76
Chest/under breast	08	13	21	10.00
Face (*Tinea faciei*)	03	03	06	02.86
All over body (*Tinea corporis*)	13	23	36	17.14
After delivery	-	06	06	02.86

Table 3. Treatment of dermatophytes infection through combination of therapy

Variable	Terbinafine 250 mg OD	*Itraconazole 100 mg BD	**Fluconazole 150 mg EOD
Age	21-60	21-60	21-60
Sex (%M/F)	84/126	25/38	05/15

**Combination therapy of Terbinafine and Itraconazole.*

*** Combination therapy of Terbinafine and Fluconazole, when patients failed monotherapy with Terbinafine*

100 mg/day and ultramicronized griseofulvin 500 mg/day for *Tinea corporis* or *Tinea cruris*, which showed significantly better mycological cure and clinical outcome as compared to monotherapy with itraconazole after 2 weeks. Similarly another study comparing terbinafine with griseofulvin (both 500 mg daily for 6 weeks) for *Tinea corporis* and reported about 87% mycological cure rate with terbinafine and 73% with griseofulvin [23]. Henceforth, in a double-blinded study between griseofulvin (500 mg/day) and itraconazole (100 mg/day) reported that itraconazole is better for treatment of *Tinea* infections [24]. Further Bell-Syer et al. [25] reported that topical therapy is less effective than oral antifungals for the treatment of *Tinea pedis*, and oral treatment is generally given for 4–8 weeks. The efficacy of oral terbinafine and itraconazole were found to be similar as compared to griseofulvin.

3.2 Antifungal Therapy in Pregnancy and Lactation

Antifungal therapy in pregnancy and lactation is demanding, because of a lack of research on efficacy and safety. In pregnancy Terbinafine is a category B drug and also there is no clear cut guideline available for managing dermatophytic infection based upon risk-benefit ratio [26]. The topical azole drugs are considered as safe for fungal skin infections during pregnancy and lactation. Therefore, the pregnant and lactating females reported during the studies treated with Itraconazole 100 mg twice a day instead of terbinafine. Kaplan et al. [27] stated that Fluconazole is also used in the treatment of fungal diseases in infants and has a good safety profile. Therefore, there is no need to interrupt breastfeeding when a mother is treated with fluconazole.

3.3 Relapse of Infection

The topical and oral terbinafine for 4 weeks appears to be the treatment of choice, in the present study about 20% patients reported relapse of infection. The many patients discontinue treatment when the clinical signs and symptoms resolve therefore shorter duration of treatment with topical and oral terbinafine also resulted in the relapse. Therefore, all the patients were advised not to stop medicine before 4 weeks whether infection was negative. But when Terbinafine was combined with Itraconazole treatment results were more effective. Also when oral therapy was combined with topical treatment results were markedly improved. If mycological cure is delayed, the risk of relapse is greater [28]. Similarly, in the present study observed that chronic dermatophytosis and persistent dermatophytosis that runs a chronic course with episodes of remission and exacerbation. Chronicity can be considered in terms of duration and recurrences of infection and more common in older age patients [28].

Moriarty et al. [29] also advised topical therapy for the treatment of *Tinea corporis*, *cruris* and *pedis* and also enlist the failure of therapy because of common reasons such as poor adherence to treatment, relapse of the infection, development of drug resistance, misdiagnosis, and infection with rare species. Therefore such patients should be advised to a higher center for appropriate treatment and management of *Tinea* infections and also suggested short term use of topical hydrocortisone for inflamed lesions. The use

of topical steroid increases the bioavailability of topical antifungals particularly imidazole groups and also for the better symptomatic relief in the early inflammatory stage [30]. Topical steroid may be benefit to patients with initial improving in symptoms and inflammation lesions but such practice should be strongly discouraged because of frequent misuse by patients who finally end up with *Tinea incognito* and sometimes also lead to corticosteroid-induced cutaneous atrophy and telangiectasia [31]. Topical antifungals (sertaconazole or luliconazole) with potent anti-inflammatory may be a better option than an antifungal-steroid combination action [20].

3.4 Safety and Efficacy of Terbinafine

The data collected so far appear to suggest that no high adverse effects of terbinafine 250 mg tablet. Only 5% patients reported headache, nausea and vomiting, which was very minor. Similarly for topical terbinafine 2.0% females reported hyper pigmentation of the skin. Terbinafine has good oral bioavailability (70–80%) and absorption is not affected by food. It is also highly lipophilic and achieves high concentrations in the *stratum corneum*, sebum and nail. In addition terbinafine also extensively metabolized in the liver, and 15 different metabolites have been reported which are subsequently excreted in urine (80%) and feces (20%) [32].

All the patients had effective treatment with terbinafine 1% cream and applied twice daily for 7 days and resulted in the 85% cure rate in terms of reduction in the total signs and symptoms score and further continued for 2 weeks resulted in 100% cure. The efficacy monitored by both investigators and patients as 'very good' or 'good' and within 2 weeks *Tinea* infection subsides and area was clear of fungi. Newland and Abdel-Rahman [18] reported that once-daily terbinafine upto 7 to 14 days resulted in 84% to 94% mycological cure rates, whereas clinical cure rates ranges from 75% to 84% with overall efficacy rates measured was 65% to 83%. Similarly, topically terbinafine also showed statistically higher mycological cure rates than 2% ketoconazole cream for 2-week course [33,34]. Currently available topical antifungal therapies resulted in the relief of clinical symptoms but relapse rates also reported to be greater. Therefore, terbinafine 1% cream reduced the duration of infectivity by achieving quick mycological cure rate and higher symptomatic relief, which may have resulted in the reduction of transmission of the disease within the family and in communal bathing places. The terbinafine cream absorption rates are not different significantly between children and adults. Korting et al. [14] reported mycological cure rate of 91.4% with 1 week twice-daily treatment with 1% terbinafine cream and same range observed (88%) in the vehicle-controlled study [35]. On the contrary, Evans et al. [36] and Bergstresser et al. [37], investigated dermatophytes cure with clotrimazole 97.2% and 82.5%, respectively. However, most patients were required to apply an azole cream 2–3 times daily for upto 4 weeks to cure the infection. While terbinafine has a fungicidal mode of action along with quick clinical and mycological response. It has also been shown to penetrate rapidly into the *stratum corneum* and to maintain high tissue levels for several weeks after discontinuation of treatment [38].

In addition along with treatment therapy all the patients were encouraged to change clothing more frequently, use absorbent powders and deodorants to decrease perspiration. Loose-fitting cotton clothes are advisable to let the flow of air comfortably. The patients were also advised not to share garments, towels, hairbrushes, combs and shaving blades which carried viable spores and spread infection to other family members. Undergarments, socks, and caps should be regularly washed and dried in the sun and ironed.

4. CONCLUSION

Nowadays the cutaneous dermatophytosis treatment has become difficult due to modern life style and complex environmental conditions. Among numerous options for antifungal drugs, the topical and oral terbinafine for 4 weeks appears to be the treatment of choice for dermatophytes infection. In case of severe dermatophytes infection the choice is still debatable. Therefore in present study the combination of both terbinafine (250 mg/day for 4–6 weeks) and itraconazole (100 mg/day for 4–6 weeks) appear to be most effective treatment for the control of severe dermatophytosis. Nevertheless, proper dose and duration of drug intake to prevent relapse of infection still remains elusive. Therefore further study is underway for molecular identification of different dermatophytes along with antimicrobial susceptibility testing so that better treatment with short interval of time should be recommended to the patients.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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