Original Article

Oral Antifungal Therapy: Emerging Culprits of Cutaneous Adverse Drug Reactions

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Abstract

Introduction: Antifungals are one of the most widely used drugs in dermatology practice for dermatophytosis. Oral antifungal therapy against superficial dermatophytosis is generally associated with a low incidence of adverse events in an immunocompetent population. However, lately, cutaneous adverse drugs reactions (CADRs) have been reported with varying incidence rates in the patients on oral antifungal therapy with many uncommon morphological patterns. The present, observational study was conducted over a period of 4 months to report the cases which presented with antifungal therapy-associated CADRs. **Materials and Methods:** It was an observational, prospective study carried out at a tertiary care center in Western India over a period of 4 months. All patients diagnosed with superficial dermatophytic infections (clinically and fungal hyphae seen on 10% potassium hydroxide mount) started on oral antifungal therapy, presenting with cutaneous manifestation other than the primary dermatophytosis were included. The incidence of CADRs due to oral antifungal agents and the percentage of each clinical type of the CADR observed was calculated. **Results:** The incidence of CADRs due to antifungal drugs was 8.3 per 10,000 patients. In total, 35 cases were reported out of 4,208 cases of dermatophytosis. Terbinafine was the most common causative drug, accounting for nearly 83% of cases, followed by itraconazole for 14% cases, and griseofulvin for 2.8% of cases. **Conclusion:** The role of systemic antifungals must not be overlooked in any patient with a CADR and should be reported as a trend indicator.

Keywords: *Cutaneous adverse drug reactions, generic drugs, lupus erythematosus-like reaction, oral antifungals*

Introduction

Oral antifungal therapy against superficial dermatophytosis is generally associated with a low incidence of adverse events in an immunocompetent population.[1] Lately, cutaneous adverse drugs reactions (CADRs) have been reported in patients on oral antifungal agents with many uncommon morphological patterns, such as symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), acute generalised exanthematous pustulosis (AGEP), lupus-like reaction, drug rash with eosinophilia and systemic symptoms (DRESS), Steven Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) spectrum, and many other cutaneous manifestations. The present study was conducted to report such cases.

Objectives

The aim of this study was to detect the incidence and evaluate the trend of cutaneous adverse events in patients on oral antifungals.

Materials and Methods

It was a prospective observational study conducted at dermatology outpatient department of a tertiary care hospital in Western India. Cases were recruited over a period of 4 months, and followed up till the complete resolution of their CADRs.

Treatment naive patients diagnosed with superficial dermatophytic infections, confirmed by a positive 10% potassium hydroxide mount by a dermatologist, started on oral antifungal therapy, presenting with any CADR as suggested in reference source[2] after starting antifungal therapy were included in the study.

Also, those patients who had been prescribed oral antifungals from outside the study site, without any concurrent topical or oral medication, were included irrespective of 10% KOH positivity. We excluded

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patients who were on multiple antifungal agents, those not giving consent, and those with a history of concomitant medications at the time of prescribing antifungal or prior to 1 month of onset of CADR.

The study was conducted after obtaining the permission from institutional review board. After informed written consent, all the patients, fulfilling the above criteria, on standard antifungal therapy regimen [Table 1],[3,4] presenting with signs suggestive of CADR,[2] developed after starting the oral antifungal agent were included in the study. The choice of antifungal drug was made by criterion sampling on the basis of number of body areas involved by dermatophytosis. The patient's demographic data, clinical photographs, details of the antifungal drug prescribed including the molecule, generic or branded, dosage, concurrent antihistaminic drug, duration of onset, and type of CADR were recorded.

Baseline investigations; viral serology for dengue, chikungunya, hepatitis B, C virus; and case-specific laboratory investigations were done in every patient presenting with a CADR.

The suspected drug was withdrawn, and based upon the clinical severity, treatment was given either in the form of supportive antihistamines or systemic corticosteroids.

The incidence of CADRs due to oral antifungal agents and the percentage of each type of the CADR observed were calculated. The data analysis was carried out considering the age distribution of the CADR, the type of CADR noted, association with generic/branded nature of the drug, and relation with the dosage of the drug prescribed. The time taken for the resolution of lesions as well as the treatment given was also analyzed.

Table 1: Protocol for prescribing oral antifungals

Itraconazole	Extensive involvement
Terbinafine	Minimum two areas along with involvement of nails
Fluconazole	Single area
Griseofulvin	Tinea capitis

Table 2: A summary of different CADR patterns

Molecule	Type of CADR	Number of cases	Remarks
Terbinafine	Lupus-like reaction	1	ANA titer: ++, negative anti-dsDNA and anti-histone antibodies, normal s. complement levels Biopsy: superficial perivascular dermatitis
	AGEP	5	
	SDRIFE	6	
	Maculopapular rash	10	
	Urticaria	1	
	Pityriasis Rosea-like rash	1	
	SJS/TEN	2	
	FDR	1	
Itraconazole	Maculopapular rash	7	
Griseofulvin	DRESS	1	

CADR = Cutaneous adverse drugs reaction, AGEP = Acute generalised exanthematous pustulosis, SDRIFE = Symmetrical drug-related intertriginous and flexural exanthem, SJS = Steven Johnson syndrome, FDR = Fixed drug reaction, DRESS = Drug rash with eosinophilia and systemic symptoms, ANA = Antinuclear antibody

Results

Overall, 35 cases of CADR due to oral antifungal agents were recorded over a period of 4 months, from a total population of 4,208 patients having dermatophytosis and meeting the prescription criteria as per our inclusion criteria (from a total OPD of 14,400 patients having dermatophytosis) giving an incidence of 8.3 per 10,000 patients. Maximum CADRs were recorded with terbinafine, followed by itraconazole and griseofulvin [Table 2 and Figure 1]. The ratio of CADRs due to branded and generic medicines was found to be nearly equal. In 27 patients, terbinafine was found to be the most common culprit drug [Table 3] and found to be associated with various benign CADRs such as maculopapular rash, SDRIFE [Figure 2], Pityriasis rosea like rash, fixed drug eruption (FDE), Urticaria, as well as severe cutaneous adverse reactions, such as AGEP [Figure 3], SJS/TEN [Figure 4], and lupus-like reaction [Figure 5].

Seven cases of itraconazole-induced rash and one case of griseofulvin-induced DRESS [Figure 6] were recorded.

In all the cases of maculopapular rash, complete blood count and liver and renal function tests were within normal limits. A negative serology for viral infections (dengue, chikungunya, hepatitis B, C) was done to rule out other etiologies of the rash.

Suspected antifungal agent was withdrawn in all cases. About 68.57% cases responded to drug withdrawal and institution of supportive antihistaminic drugs alone, whereas in the remaining cases, additionally, systemic steroid had to be started in tapering doses.

Discussion

CADR caused by a drug is any undesirable change in the structure or function of skin, its appendages, or mucous membranes and it encompasses all adverse events related to drug eruption; regardless of etiology.[5] CADRs, lately, have been reported with a varying incidence in patients on oral antifungal agents, such as terbinafine, griseofulvin, and itraconazole [Table 4].

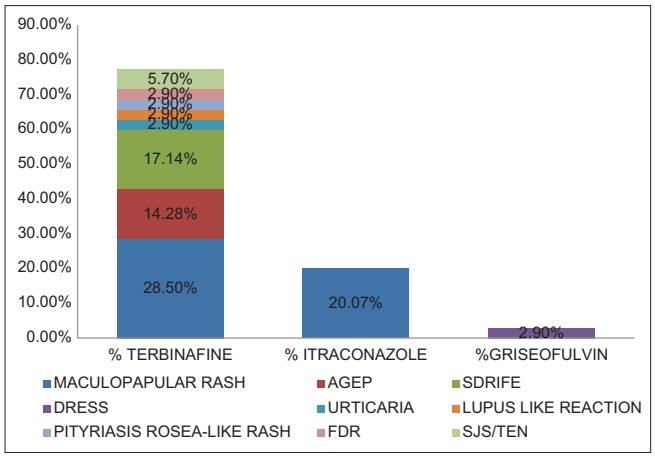

Figure 1: Chart: drug-wise distribution of various cutaneous adverse drug reactions

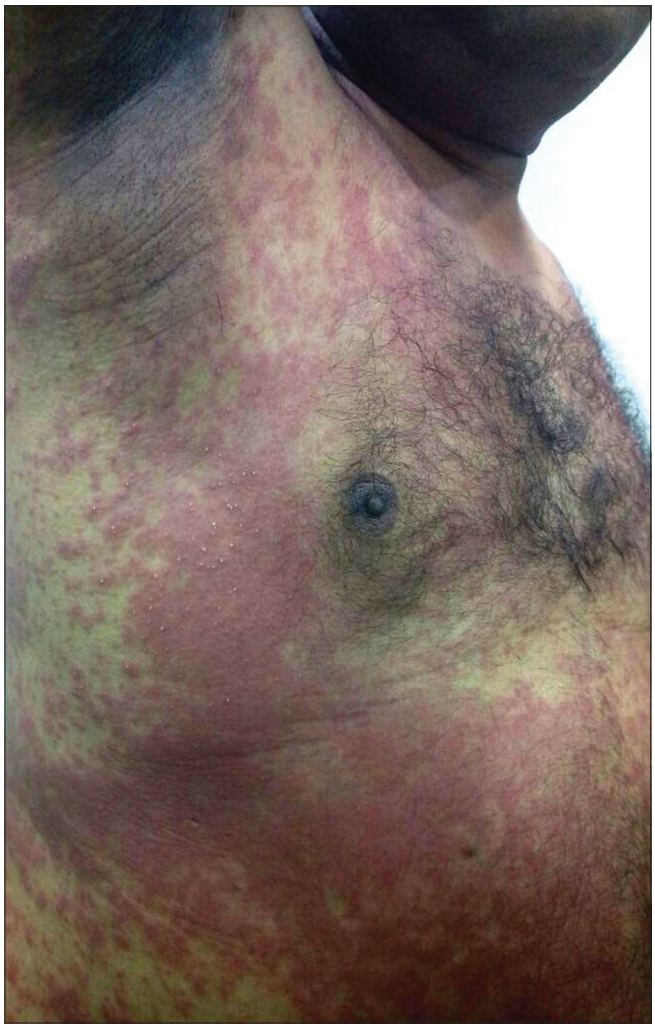

Figure 3: Acute generalised exanthematous pustulosis: Erythematous flexural rash with multiple pustules overlying the background erythema

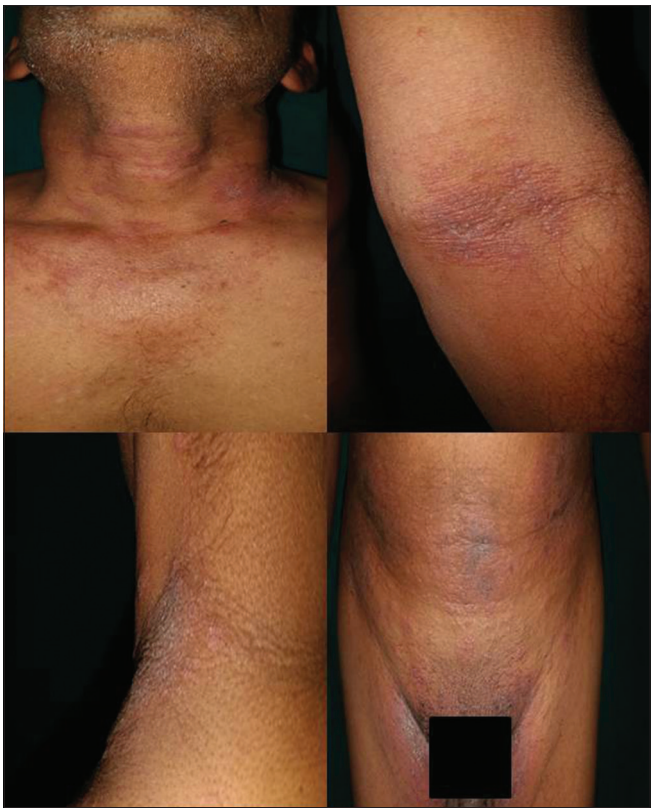

Figure 2: Terbinafine-induced SDRIFE: Erythematous, maculopapular rash with flexural predilection

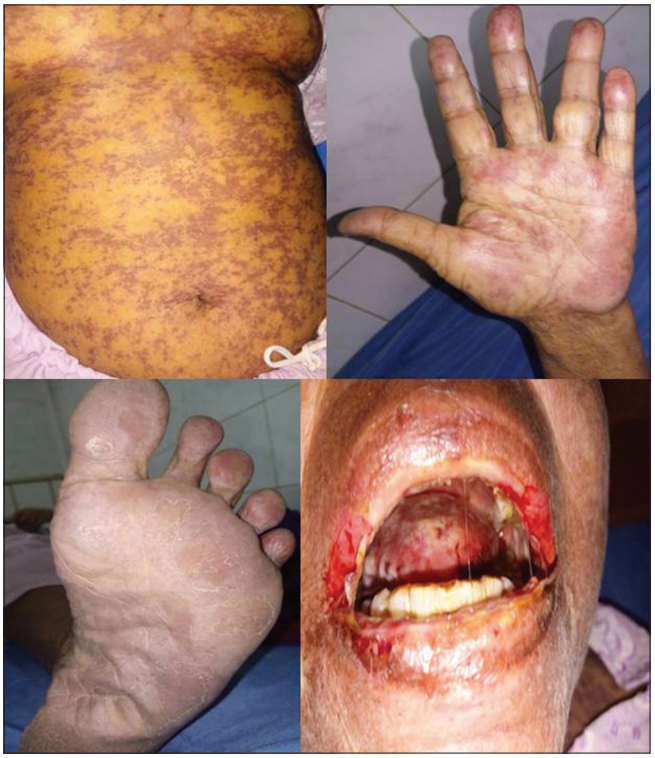

Figure 4: Toxic epidermal necrolysis: dusky, erythematous, rash over the abdomen, palms, soles with erosions over lips and in oral cavity

Cutaneous side effects have been reported in 2% of the patients on terbinafine therapy with many morphological patterns. These include pruritus, rash, urticaria, erythema multiforme, cutaneous lupus, and psoriasis.[6] In a survey by Babu *et al*., terbinafine was well tolerated by the patients, with only 12% patients

Table 3: Drug wise data-demographic distribution and duration of onset and resolution

	Total number of cases	Mean duration of onset (days)	Mean duration of resolution with treatment (days)	Mean age (years)	Females	Males
Terbinafine	27	12.87	6.57	36.57	13	14
Itraconazole	7	6.29	4.94	34.64	2	4
Griseofulvin	1	6.25	21	43	1	0

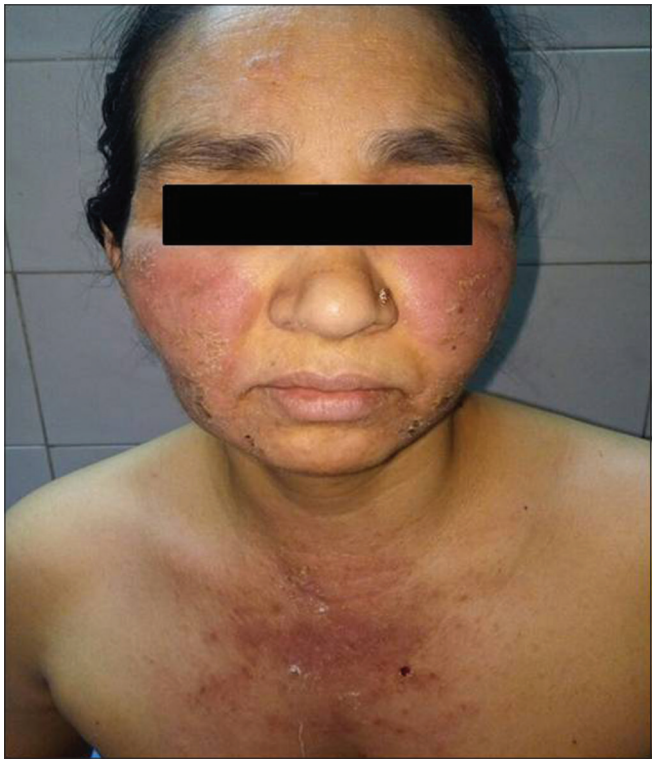

Figure 5: Lupus-like reaction from terbinafine: Erythematous, scaly maculopapular rash over malar area and anterior chest

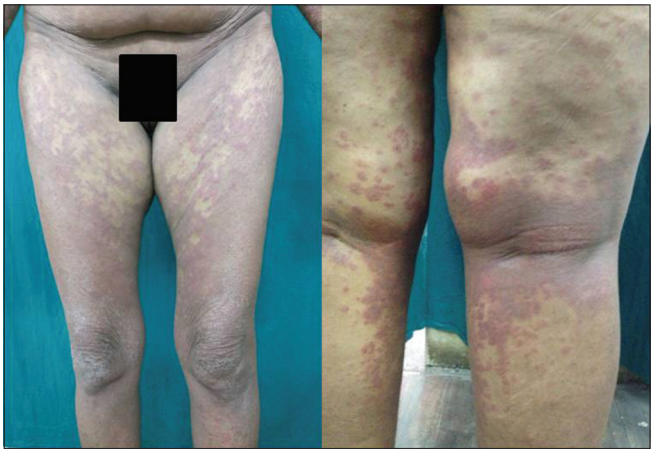

Figure 6: Griseofulvin-induced drug rash with eosinophilia and systemic symptoms: Purpuric rash over both the lower limbs

reporting adverse effects of which 1.8% were CADRs in the form of pruritus.[3]

Terbinafine has been associated with pustular eruptions, and AGEP. It is the most common antifungal agent associated with AGEP. To date, there have been at least 15 cases of AGEP induced by terbinafine reported in the literature.[7]

A few cases of SDRIFE have already been reported in the literature attributed to terbinafine. The latency period usually ranges from a few hours to a few days after exposure to the offending agent.[8] In our study, the earliest developing SDRIFE was over 4 days, and the latest developing by 7 days after ingestion of drug.

Total 31 cases of terbinafine-induced subacute cutaneous lupus erythematosus (SCLE) representing 26% of all cases of drug-induced SCLE were reported. It has been postulated that terbinafine with its lipophilic and keratophilic properties may change the configuration of nuclear antigens and induce antinuclear antibodies (ANAs) formation, resulting in terbinafine-induced SCLE. It also enhances the cytotoxic reaction dependent on anti-Ro antibodies and keratinocyte damage typical of SCLE.[9] In our patient, clinical features along with a low positive ANA titre were consistent with SCLE. The symptoms resolved within 10 days of stopping terbinafine. However, patient was later lost to follow-up.

Cutaneous rash has been reported with itraconazole in 2% cases. Maculopapular rashes subsided on cessation of itraconazole. Urticarial reaction, pruritus, angioedema, SJS/TEN and AGEP, and FDE have been reported in literature.[10] Mean duration of onset in our cases of maculopapular rash developing while on itraconazole therapy was 5 days.

The medical literature has multiple case reports of other forms of drug hypersensitivity to griseofulvin, including serum sickness like reaction, AGEP, FDE, SCLE, TEN, and DRESS.[11,12] We have reported the case of a 43-year-old female patient with confluent purpuric rash over the axillae, groins, popliteal fossae, thighs, and both legs associated with pruritus, mild fever, bilateral inguinal lymphadenopathy. A diagnosis of griseofulvin-induced DRESS was considered after detailed investigation and the patient's symptoms subsided after 3 weeks of oral corticosteroid therapy in tapering doses.

In our studies, 17 out of 35 patients had taken generic antifungal, whereas the rest were found to be on branded antifungals. The results of our case series remained inconclusive in this regard.

In a study conducted in 2002, the cumulative incidence rates of CADRs to terbinafine, itraconazole, and griseofulvin

Table 4: Comparison of terbinafine, itraconazole, griseofulvin, and fluconazole with various studies

Drug	Proportion in various studies (%)	Proportion in our study (%)
Terbinafine[1]	12	4.15
Itraconazole[2]	2	1.11
Griseofulvin[3]	1.11	0.43
Fluconazole[3]	6.66	0.00

[1]Babu P R, 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;62:395-9, [2]Grayson ML *et al*. Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs. 7th Ed. CRC Press; 2017, [3]Tejashwani, Patel D, Bhuptani N. An observational study of cutaneous adverse drug reactions in tertiary hospital. Int J Res Dermatol 2018;4:254-8.

was found to be 2.9, 1.3, and 2 per 10,000 patients, respectively.[13]

Also, from the cases of terbinafine-induced ADRs reported in literature,[6,14] most of the patients were reported to have been prescribed terbinafine at a dose of 250 mg daily, whereas the cases we have reported have been variably prescribed terbinafine at 250 and 500 mg/day. Likewise itraconazole-induced rash has been reported at dose of 400 mg/day, which is the standard dose for onychomycosis, whereas in our patient, itraconazole had been prescribed at 200 mg/day for tinea cruris. The dose of griseofulvin in our patient was 500 mg/day. This suggests a greater likelihood of idiosyncratic CADRs to oral antifungals rather than a dose-dependent toxicity profile. A major contributing factor to ADRs with antifungal agents relates to drug distribution, metabolism, and excretion due to genetic variation in key genes. Less is known regarding the key genes that interact with antifungal agents, resulting in idiosyncratic (type B) ADRs.[15]

Conclusion

The myriad CADR patterns observed with oral antifungal drugs, which are usually considered as relatively safe drugs, makes it necessary for dermatologists to appropriately counsel their patients regarding these CADRs while prescribing these drugs. Moreover, review of the literature suggests a relative paucity of CADRs reported with oral antifungal agents. An increasing trend of CADRs to antifungals is observed. Terbinafine is the most common culprit drug. The data on the relationship of CADRs to the dose suggest that most of these reactions are idiosyncratic in nature. The data on the role of generic or branded medications remains inconclusive in our study.

To conclude, the role of systemic antifungals must not be overlooked in any patient with a CADR and should be reported as a trend indicator.

Limitations

The limitations of this study are that only the KOH-positive cases and treatment-naive patients on oral antifungals referred from other dermatologists have been included in the study; hence, few patients in whom oral antifungal was started, only on basis of clinical presentation, have been missed. Histopathological study was not carried out in all the patients. The role of adjuvants, drug vehicles, and antihistaminic drugs has not been evaluated in our study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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