RESEARCH ARTICLE

An open label, single arm, pilot study to evaluate the safety, tolerability, and efficacy of daily fluconazole 150 mg in subjects suffering from Tinea cruris and Tinea corporis [version 1; peer review: awaiting peer review]

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Abstract

Background: Dermatophytes are the most common superficial fungal infections worldwide and are treated with prescribed regimens of terbinafine and itraconazole, or with weekly doses of fluconazole. Dermatologists are increasingly encountering treatment failures, and experts suggest that standard treatment regimens are not applicable anymore. We planned an open-label study to evaluate the results of fluconazole 150 mg daily for 8 weeks in patients with tinea cruris and tinea corporis.

Methods: Patients were enrolled from the La'Mer Clinic, Mumbai, India. We included adult subjects with uncomplicated dermatophytosis confirmed by microscopic examination of skin scrapings. Pregnancy, poor renal function, and recent exposure to anti-fungal therapy were exclusion criteria. Patients were reviewed on days 14, 28 and 56. The treating doctor scored the severity of erythema, scaling, and pruritus on a four-point scale: absent, mild, moderate, and severe. Of 107 subjects screened, 100 were finally included in the study. Eleven were lost to follow up and one subject withdrew consent.

Results: The site of disease was body alone in 29, groin alone in 7, and both body and groin in 64 cases. At 5 weeks, 98%, 100%, and 97% of patients had no scaling, erythema, and pruritus, respectively. Skin scrapings showed 100% mycological cure. In one patient the alanine transaminase level rose from 54.9 to 100.2 U/L, and qualified as a grade 1 adverse event not requiring intervention. No other significant adverse events were noted.

Conclusions: Our results suggest that fluconazole 150 mg daily for eight weeks effectively treats dermatophytosis. This regimen is safe and well-tolerated even in patients with co-morbidities. Fluconazole is

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about eight times less expensive than itraconazole or terbinafine and may be the preferred therapy.
Registration: The trial was registered with Clinical Trials Registry, India (Registration number CTRI/2020/06/026110) on 24 June 2020.
FDC Company, India, provided financial support for the study.

Keywords
Dermatophytes, skin infections, fungal infections, Tinea capitis, antifungal agents, itraconazole, terbinafine, tropical diseases, erythema, scaling, pruritus

This article is included in the Pathogens gateway.

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Introduction

Dermatophytes are the commonest superficial fungal infections worldwide. They include three genera of fungi: *Trichophyton*, *Epidermophyton*, and *Microsporum.*[1] Treatment of localized lesions involves the use of topical antifungals such as luliconazole, sertaconazole, clotrimazole, terbinafine and others, or oral agents such as itraconazole, terbinafine, and griseofulvin.[2] Oral agents effective against dermatophytes include the azoles (*e.g.*, itraconazole, fluconazole) and the allylamines (terbinafine). The azoles act at the fungal P-450 pathway to prevent the formation of ergosterol, an important biomembrane lipid.[3]

However, practicing dermatologists are increasingly encountering treatment failures, and reports of recalcitrant dermatophytosis have begun to appear in the literature. Yamada *et al.*,[4] showed in 2017 that as many as 17% of Trichophyton strains showed reduced susceptibility to terbinafine. Monod and Mehul[5] reviewed the literature to show that mutant strains of Trichophyton were responsible for this decreased sensitivity. Poojary *et al.*,[6] noted a sudden unexplained surge of difficult-to-treat dermatophytosis in India, and experts gradually have come to suggest that standard treatment regimens are probably not applicable anymore.[7,8]

Fluconazole has traditionally not been used routinely in the treatment of dermatophytosis.[1,7] There are increasing reports of inadequate response to therapy, relapses, recurrence and resistance to available antifungal drugs like terbinafine, itraconazole and griseofulvin. We therefore planned a study to determine the results of fluconazole therapy in cases of dermatophytosis. Using fluconazole 150 mg daily for 8 weeks, we evaluated clinical parameters and mycological cure rates in patients with tinea cruris and tinea corporis.

Methods

Ethics

Written informed consent was taken from subjects prior to their inclusion in the study. This study was approved by the Vision Independent Ethics Committee, Mumbai (independent Government-approved Ethics Committee), per its letter dated 13 June 2020. The study was registered with the Clinical Trials Registry – India on 24 June 2020 (registration number CTRI/2020/06/026110).

Study design

This research was a prospective, open label, single-center, non-comparative study.

Study population

We enrolled 100 patients with dermatophytosis (tinea cruris and tinea corporis) visiting the outpatient department of La'Mer Clinic, Mumbai, considering this number to be adequate for a pilot study. All the subjects were enrolled after they gave written informed consent. The first patient was enrolled on 22 July 2020 and the last subject was enrolled on 24 August 2021.

Inclusion and exclusion criteria

We included subjects with dermatophytosis confirmed by fungal hyphae in a 10% potassium hydroxide (KOH) preparation of skin scraping. Subjects were aged 18 to 65 years old.

We excluded patients with secondarily infected or eczematized lesions, and those who had received any type of oral or topical anti-fungal therapy within 14 days prior to baseline visit. We also excluded patients who were immunosuppressed, had a creatinine clearance < 30 ml/minute, patients who were pregnant or lactating, and those with any severe medical comorbidity. Diabetes was not an exclusion criterion unless it was uncontrolled.

Intervention

All patients were administered fluconazole 150 mg daily for 8 weeks.

Measurements

In the screening visit ("Visit 1", day -4 to day 1) patients were examined and baseline full blood counts, renal function tests, liver function tests and urine physical, chemical and microscopy studies were carried out. Urine pregnancy tests were conducted in female patients. Fluconazole therapy was started in eligible subjects on the day of enrolment ("Visit 2"). They were then reviewed clinically and microbiologically on days 14 $\pm$ 2, 28 $\pm$ 2, and 56 $\pm$ 2 ("Visit 3", "Visit 4", and "Visit 5").

Clinical review consisted of a subjective evaluation of three parameters: erythema, scaling, and pruritis. The treating doctor (GDS) scored the severity of each parameter on a four-point scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Mycological review consisted of examination of a 10% KOH preparation of a skin scraping under direct microscopy. The result of the examination was reported as absent or present for fungal hyphae. Fungal culture was not carried out.

Patients received an investigational product compliance diary card on which they were advised to record medication intake and adverse events. The treating doctor (GDS) reviewed diary entries at every visit.

On the final visit (day 56), the treating doctor also carried out a urine analysis and blood examination for full blood count, renal function tests and liver function tests.

Alterations of aminotransferase levels were graded according to the criteria described by the US Department Of Health And Human Services per their 2017 document.[9]

Data analysis
The data were analyzed by simple mathematical calculation of response rates.

Results
Demographics
Of 107 subjects screened, 100 were finally included in the study (Figure 1). Of these, 11 were lost to follow up and one subject withdrew consent. The mean age was 40 years old (SD 11.6). A total of 46 of the 107 subjects were female.

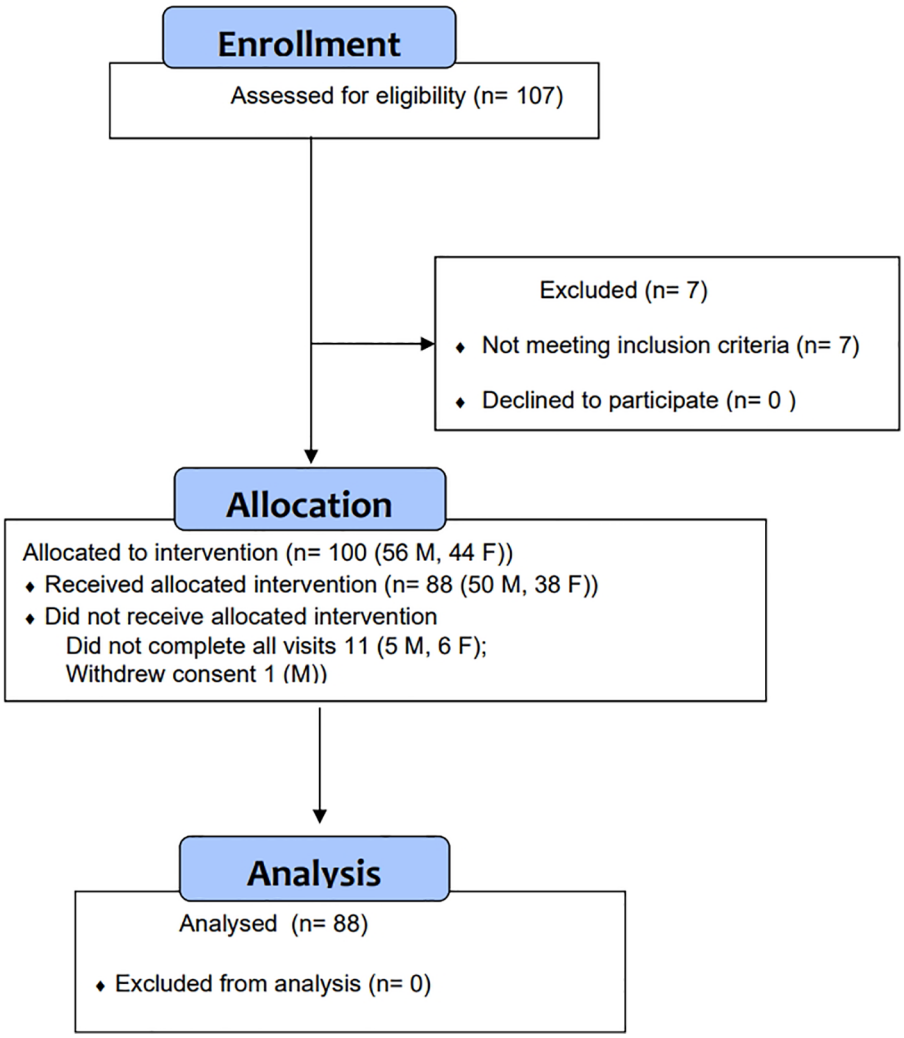


Figure 1. CONSORT 2010 flow diagram of study patients.

Table 1. List of comorbidities. CAD, coronary artery disease.

Comorbidity	Number
Allergic Asthma	1
Diabetes	3
Hypertension	9
Diabetes & Hypertension	2
Diabetes, Hypertension & CAD	3
Hypertension & CAD	1
Hypothyroidism	3

Twenty two patients had comorbidities, of which the commonest were diabetes and hypertension (Table 1).[10]

The site of disease was body (Tinea corporis) alone in 29, groin (Tinea cruris) alone in 7, and both body and groin in 64 cases.

Response to treatment

Scaling, erythema, pruritus, and mycological results improved over the 5 visits, as shown in the charts below.

Scaling

Scaling was present in all patients at enrolment. The number of patients with severe scaling, and the severity of scaling decreased with treatment. At 5 weeks, 86 of 88 patients had no scaling; the other two had mild residual scaling (Figure 2).

Erythema

Erythema was present in 97 of the 100 patients at enrolment. By the end of the fifth visit the erythema had disappeared in all cases (Figure 3).

Pruritus

Pruritus was present in all patients at enrolment. By the end of the fifth visit the pruritus had disappeared in 97% of cases (Figure 4).

Thus, the overall clinical cure rate was 97%, with two patients having mild residual scaling, and three having mild pruritus.

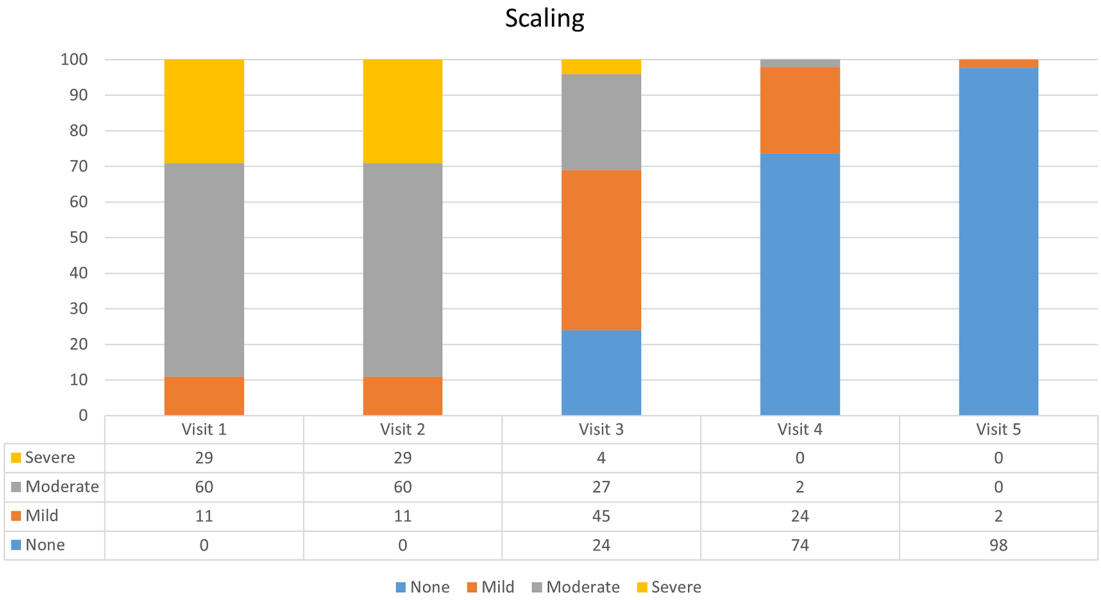
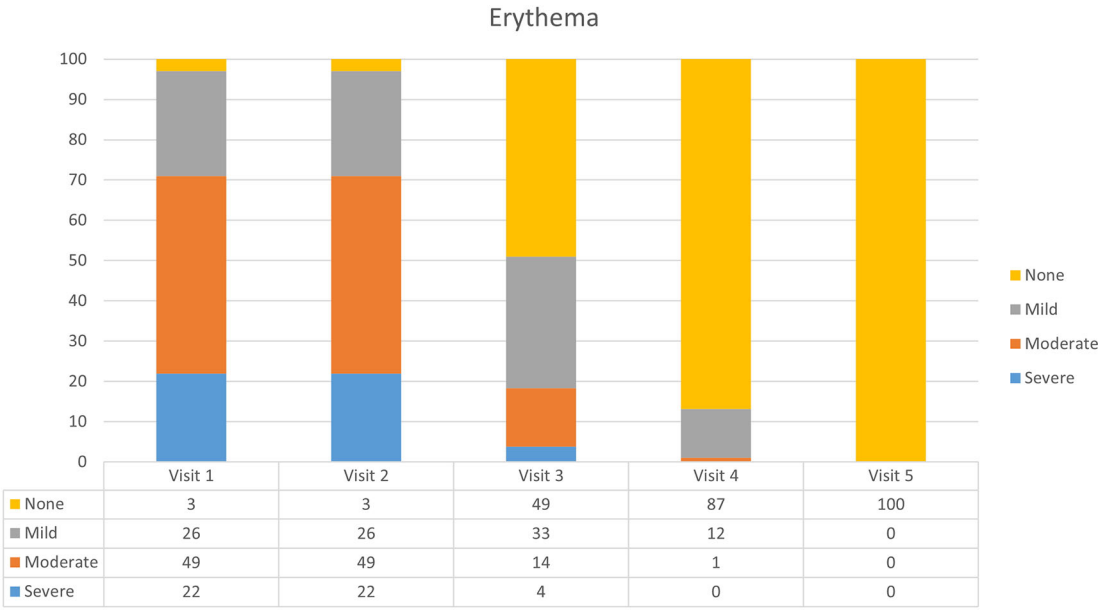
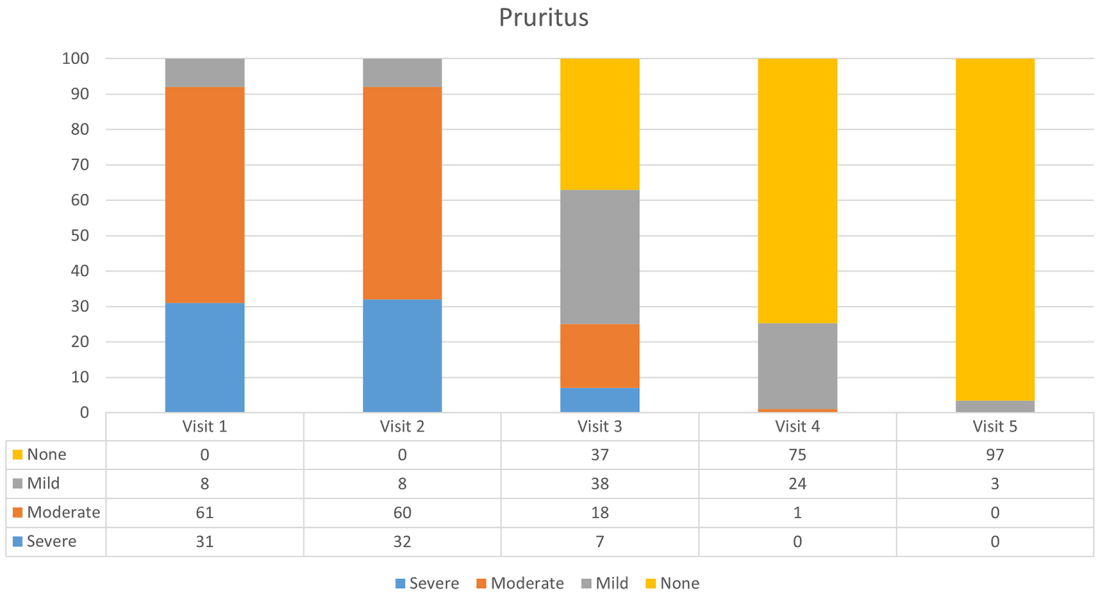


Figure 2. Progress of the scaling parameter over time. The numbers are percentages of the total number of patients available for assessment.



	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
None	3	3	49	87	100
Mild	26	26	33	12	0
Moderate	49	49	14	1	0
Severe	22	22	4	0	0

Figure 3. Progress of the erythema parameter over time. The numbers are percentages of the total number of patients available for assessment.



	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
None	0	0	37	75	97
Mild	8	8	38	24	3
Moderate	61	60	18	1	0
Severe	31	32	7	0	0

Figure 4. Progress of the pruritus parameter over time. The numbers are percentages of the total number of patients available for assessment.

Mycological cure

Skin scrapings were examined for fungal hyphae on visits 1, 3, 4 and 5. By the fifth visit, mycological cure was 100% (Figure 5).

Adverse events

One patient had an elevation of serum creatinine to 1.22 mg/dl (laboratory normal 0.67-1.17). This change did not reach the threshold to be considered an adverse event.

Mild elevations of liver enzymes were noted in a few patients between visit 1 and visit 5. (Table 2). Six patients, none with comorbidity, had alanine aminotransferase (ALT) levels above the upper limit of normal. In five, the levels just barely

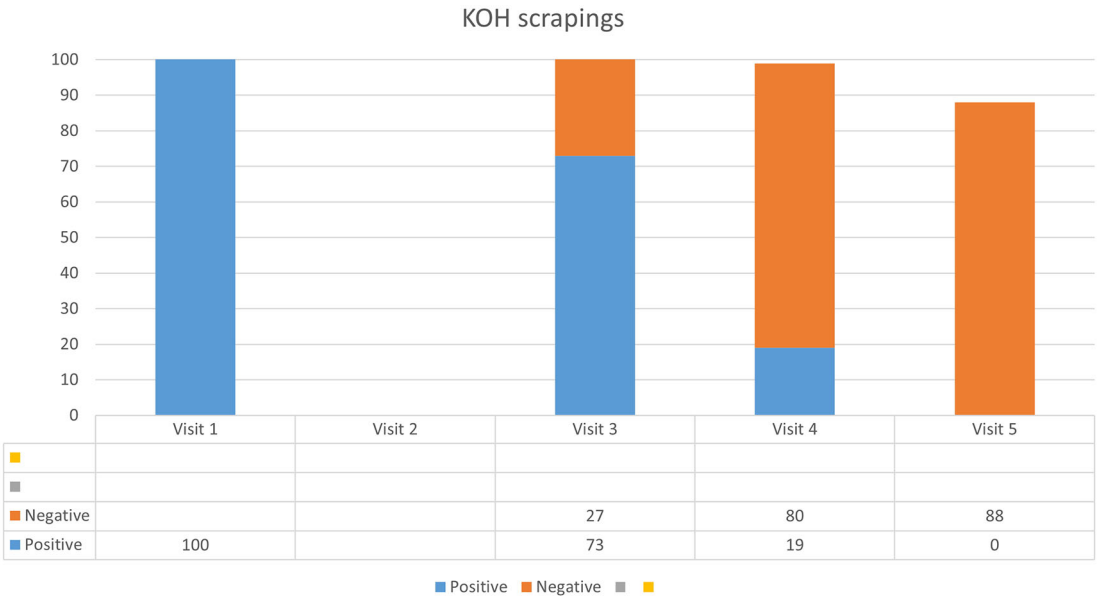


Figure 5. Progress of the skin microscopy over time. The numbers are percentages of the total number of patients available for assessment. KOH, potassium hydroxide.

Table 2. Changes in liver enzymes with treatment.

Patient nos.[a]	Serum ALT (Lab normal 5–45 U/L)	Serum AST (Lab normal 5–40 U/L)
2[b]	54.9 → 100.2	37.7 → 43.1
12[b]	40.7 → 64.9	21.8 → 49.2
23[b]	26.3 → 58.6	27.8 → 40.4
40[c]	No change	30.8 → 41.8
52[d]	No change	15.6 → 51.9
77[b]	40.9 → 47.0	36.0 → 40.4
88[b]	24.0 → 61.2	18.7 → 46.6
97[b]	39.7 → 58.9	21.8 → 53.7

[a]In no other patient did the change meet the threshold to be considered an adverse event; [b]Patients had no comorbidity; [c]hypertension; [d]diabetes. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

exceeded the upper limits of normal and did not reach the threshold for being considered Grade 1 adverse events. In one, the ALT level rose from 54.9 to 100.2 U/L, and qualified as a grade 1 adverse event only,[9] not requiring intervention. Eight patients, two with comorbidity, had mild elevations of serum aspartate aminotransferase levels. The changes did not meet the criteria for being considered adverse events (Table 2).

Discussion

Dermatophytosis affects 20-25% of the world's population.[11] The prevalence is likely much higher in India[12] and is certainly increasing to alarming, almost panicky levels.[8,13]

The burden of recalcitrant dermatophytosis is growing in India, with an estimated 3-10% of cases being difficult-to-treat.[1,7,14–16] Almost every major dermatological conference has begun to devote an entire session to the discussion of dermatophytosis.[14] Reports are also appearing from other parts of the world about the worrying increase in resistance.[11,17]

The emergence of recalcitrant tinea is almost certainly encouraged by the non-adherence to the treatment regimen and shorter duration of the regimen.[16,18] A species shift to *Trichophyton indotineae* is another likely cause of the observed recalcitrance.[19] Taking in consideration the significant number of recalcitrant cases, one of us (DGS) decided to conduct a trial of daily dose fluconazole for patients with dermatophytosis.

Response to fluconazole

This study shows that at present one may expect a reliable response to oral fluconazole in a 150 mg daily dose regimen lasting five weeks. While there are several reports of the efficacy of weekly fluconazole for dermatophytosis,[20] there is a paucity of literature regarding the daily use of fluconazole in dermatophytosis, and the clinicians have been discouraged from its use for treating this condition. The usual recommended dose is 150 mg once a week. At this dose the cure rates vary from 64%[21] to about 90%.[22,23] On the other hand, the daily dosing ensures that the drug concentrations consistently exceed the minimum inhibitory concentrations (MICs) required to kill the fungus. This result should come as no surprise: fluconazole is among the triazoles that is known to be effective in treating dermatophytosis. Indeed, members of an expert panel recently indicated that fluconazole and terbinafine were their preferred systemic choice of antifungal agents for children.[13]

Fluconazole is about eight times less expensive than itraconazole or terbinafine, therefore if the therapeutic effect is similar fluconazole may be the preferred therapy, as it is likely to ensure patient compliance for a long time. Considering that nearly 70% of infections occur in the low and very low income socioeconomic groups,[24] cost becomes a critical factor in deciding the medication.

It is also worthy of note that fluconazole accumulates in the stratum corneum[25] and its levels are very high when compared to other azoles.[26] The *in vitro* MIC_{90} levels of fluconazole are 16–32 micrograms/ml,[27,28] depending on the species. In the stratum corneum the tissue concentrations of fluconazole are more than the MICs for most dermatophytes, and the drug is eliminated 2–3 times more slowly than from the blood.[29] Daily doses of fluconazole achieve levels of 66 micrograms/gram, about three times as high as levels after weekly doses,[25] which explains why daily fluconazole is so effective in the treatment of dermatophytosis. Sardana *et al.*,[26] and others reviewed the literature on the pharmacokinetics of antifungal agents, and stated that the distribution of itraconazole and terbinafine, being highly lipophilic, depended on the presence of sebum. Though itraconazole and terbinafine achieved MIC_{90} inhibition at lower levels in laboratory studies, these drugs also achieved lower levels in the skin.[30] Standard antifungal sensitivity test (AFST) methods involving *in vitro* and animal data are unreliable for predicting clinical outcomes, and there is the suggestion that fluconazole might be the preferred drug, especially for sites that secrete less sebum or in persons with intrinsically dry skin (such as diabetics).[26] Khurana *et al.*,[31] in a recent review, pointed out that the 60–90 hour elimination half-life of fluconazole would be insufficient antifungal cover if the drug was given once weekly. We believe that it is likely that these properties of fluconazole provide a strong rationale for a daily dose regimen.

Safety

Several studies have shown that fluconazole is well tolerated at daily doses of up to 1,600 mg.[23,32–36] Hepatotoxicity is described, but rare, and in most cases is self-limiting. Mild elevations in serum aminotransferase levels occur in up to 5% of patients. These patients are asymptomatic and do not require discontinuation of the medication.[37] In our cases none of the patients developed any significant adverse effect. The drug was well-tolerated even in patients who had existing comorbidities. Except in one patient, the transaminases remained stable, and showed a minimal elevation in only about 5% of patients.

Cross-reactivity of fluconazole with other azoles is unlikely, but fluconazole should nevertheless be used with caution in patients who have had adverse effects from itraconazole and related compounds.[37] It is good to remember that fluconazole inhibits the cytochrome P450 enzyme CYP 3A4, and may cause interactions with drugs that are metabolized by this enzyme, though it is a less potent inhibitor of the pathway than are itraconazole and posaconazole.[38]

Conclusions

Our results suggest that fluconazole in a dose of 150 mg daily for eight weeks effectively treats dermatophytosis, with a clinical efficacy of 97% and a mycological cure rate reaching 100%. The eight-week daily dose regimen is safe and well-tolerated, even in patients with co-morbidities. In view of the severe concerns about the applicability of existing recommendations for dermatophytosis, dermatologists should consider this regimen as first-line therapy. There is also a need for a large comparative study with itraconazole and terbinafine.

Strengths and weaknesses

This study evaluates the efficacy of an inexpensive and safe drug, fluconazole, in the management of a major health disorder. The enrolled patients were carefully evaluated, and an attempt was made to ensure that the readings were as objective as was possible. Patients were also examined microbiologically to corroborate the clinical findings.

In a single center private clinic, it was not feasible to carry out fungal cultures due to financial limitations. However, we did not encounter any case that would require us to ask for fungal culture and anti-fungal sensitivity tests. Additionally, even expert panels do not recommend cultures except in recalcitrant cases.[13]

We also were not able to blind the measurement of the clinical responses to the drug.

Data availability

Underlying data

Harvard Dataverse: Replication Data for: FLUCONAZOLE_150. https://doi.org/10.7910/DVN/P7DLSU.[10]

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