Brief Report

Comparative Efficacy and Safety of Super-Bioavailable Itraconazole-130 mg Once Daily in Obese and Non-Obese Patients of Glabrous Tinea

Abstract

Background: Obesity is considered one of the risk factors for dermatophytosis and warrants systemic therapy. Itraconazole is the most commonly used antifungal, but owing to pharmacokinetic challenges, super-bioavailable itraconazole (SITZ) was approved globally, recently. For the management of dermatophytosis in obese patients, there are mixed opinions regarding the dosing of systemic antifungals. **Materials and Methods:** This study was conducted to compare the efficacy and safety of SITZ-130 mg once daily in glabrous tinea or dermatophytosis in obese and non-obese patients for a total duration of 10 weeks on 87 eligible patients. Efficacy and safety assessments were done at weeks 3 and 6 with follow-up at week 10 for relapse. The primary objective was to assess the proportion of patients achieving complete cure at week 6 with the assessment of safety, clinical, and mycological cure rates as secondary objectives. **Results:** Out of 87 patients, 80 were considered for analysis. At week 6, 22/35 (63%) and 33/45 (73%) patients in obese and non-obese groups were completely cured ($P = 0.47$). Similarly, there was no statistically significant difference for mycological and clinical cure in both the groups ($P = 0.17$ and $P = 0.61$, respectively). Four patients in the obese group (18% of completely cured), while one patient in the non-obese group (3% of completely cured), relapsed within 4 weeks of completion of treatment ($P = 0.14$). The therapy was well tolerated by both groups, with only one patient in the non-obese group experiencing pruritus. **Conclusion:** SITZ-130 mg once daily achieved desired and similar clinical response in obese patients as of non-obese patients suffering from dermatophytosis, and hence, a higher dose may not require in obesity.

Keywords: *Dermatophytosis, efficacy, obesity, super-bioavailable itraconazole*

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Introduction

With an astonishing prevalence rate of 37–74% and an increase in resistant cases, dermatophytosis has epidemic proportions in India.[1] Obesity has been recognized as one of the major risk factors for this transformation,[1-4] among many other risk factors. These modifications have led to the present care of dermatophytosis evolving into a combination therapy that includes itraconazole, the most widely prescribed systemic antifungal drug along with topical antifungal.[5] However, a more recent itraconazole formulation (ITZ), super-bioavailable itraconazole (SITZ), was recently approved by the Central Drugs Standard Control Organisation (CDSCO) in India due to pharmacokinetic challenges of conventional formulation of itraconazole, such as food dependency and the need for an acidic environment for optimal absorption, etc.[6]

Obesity is defined by the WHO as a body mass index (BMI) of at least 30 kg/m^2, and overweight is defined as a BMI between 25 and 29.9 kg/m^2. In obesity, the pharmacokinetics of lipophilic drugs like ITZ is altered in tissue distribution and clearance, which results in varying practices of dosing regimens.[7,8] As a result, higher dosages of ITZ have been practiced in severe fungal infections worldwide, especially in obese patients.[1,9,10] Payne *et al.* had also mentioned to use a double dose of ITZ in obese patients with dermatophytosis.[11] In a recently published experimental rat model study, skin concentrations for all doses of SITZ in obese and non-obese rats were within the minimum inhibitory concentration (MIC) range, suggesting that a higher dose may not be necessary.[12]

Currently, there are no clinical data on SITZ in obese patients with dermatophytosis.

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Secondly, ITZ follows non-linear pharmacokinetics and hence is recommended as once daily (OD).[13,14] With these objectives, this clinical study was planned to compare the efficacy and safety of SITZ-130 mg OD in the management of glabrous tinea in overweight and obese patients.

Materials and Methods

This analysis was the subgroup analysis of the original three-arm clinical study (Clinical Trials Registry India, registration number CTRI/2021/11/038275), which was carried out across seven centers in India with prior approval from the ethics committee for respective centers between December 2021 and August 2022. Out of 261 enrolled patients, 87 patients in SITZ-130 mg OD group were considered for this analysis.

After informed consent, all the randomized patients diagnoses were confirmed on clinical and direct microscopy under 10% potassium hydroxide examination (KOH mount). Fungal culture was not done. Additionally, liver function tests (LFTs) were also recorded at baseline. The study duration was of 10 weeks with 6 weeks of treatment phase and 4 weeks of observation period for relapse, if any. Following the active treatment phase, patients with complete cures were not prescribed any antifungal medication and were asked to follow up in case of any recurrence. The complete consort diagram is shown in Figure 1.

For this analysis, all the patients in the SB-130 group were divided into two groups: Group I comprised overweight and obese patients (BMI ≥25 kg/m^2), and Group II, non-obese patients (BMI <25 kg/m^2). All received SITZ-130 mg OD, after food along with an emollient. Patients were refrained to use any other anti-fungal medication.

The primary endpoint was to compare the percentage of patients achieving a complete cure (clinical cure plus mycological cure) at the end of the treatment period from baseline in both the groups. Clinical cure was defined as the absence of any signs and symptoms [Lesion Severity Score of 0 or 1 (in case of pruritus)] and complete clearance of area involved (Area Severity Score of 0). Mycological cure was defined as negative KOH at the end of 6 weeks.

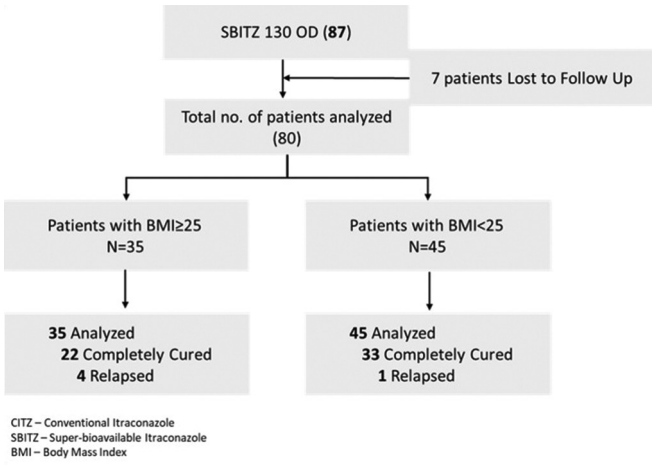

Figure 1: Consort diagram

Baseline variables were presented as numbers and percentages, and as mean with standard deviations (SDs) depending on the distribution of data. The difference in the proportion of patients with Lesion and Area Severity Scores (based on improvement criteria) was analyzed using unpaired *t* test with a significance level set at 0.05, as appropriate. Cure rates and relapse rates were compared by Fisheropriate. and All *P* values were two-tailed. When appropriate, 95% confidence intervals were calculated. The denominator for the calculation of the relapse rate was the number of patients who had achieved cure. All statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, IL, USA) and Microsoft Excel.

Results

Patients

Of the 87 patients, seven were lost to follow-up and hence were not considered for analysis. Out of 80 patients, 45 were found to have BMI <25 and 35 patients had BMI of ≥25. All of the baseline characteristics are presented in Table 1, and most of the patients presented with ≥3 lesions and of ≥6 weeks of disease duration.

Treatment response

At week 6, 55/80 patients were completely cured while 12 failed to treatment, giving an overall cure rate of 58.75%. Thirteen patients showed clinical improvement (>50% improvement in LSS and ASS). Thus, the cure rates in obese and non-obese groups were 63% (22 of 35 patients) and 73% (33 of 45 patients), respectively [Table 2]. This difference was not statistically significant (P = 0.47). For mycological cure, 29 patients (83%) in the obese group achieved mycological cure, while 42 (93%) patients in the non-obese group achieved the same (P = 0.17).

The mean LSS of 9.53 ± 2.18 reduced to 1.23 ± 1.83 (87% reduction) in the obese group, while it reduced from 9.35

Table 1: Demographic information of patients in both the groups

	Obese patients	Non-obese patients	*P*
n	35	45	
Male; *n* (%)	18 (51)	25 (55)	
Female; *n* (%)	17 (49)	20 (45)	
Age; mean (SD) Years	39.66 (11.78)	35.33 (12.27)	0.11
BMI; mean (SD)	28.01 (3.51)	21.81 (2.31)	<0.05
Mean LSS (SD)	9.53 (2.18)	9.35 (1.82)	0.68
Mean ASS (SD)	2.39 (0.69)	2.43 (0.54)	0.77

SD=Standard Deviation, BMI=Body Mass Index, LSS=Lesion Severity Score, ASS=Area Severity Score

Table 2: Efficacy assessment at week 6

Complete cure rate at week 6					
	Obese patients		Non-obese patients		*P*
n	35		45		
Completely cured	22		33		0.47
Clinical improvement	8		5		
Clinical failure	5		7		
Efficacy scores in terms of mean LSS and ASS at week 6					
	Obese patients		Non-obese patients		*P*
n	35	CI	45	CI	
Mean LSS (SD)	1.23 (1.83)	0.62–1.83	1.47 (2.34)	0.84–2.23	0.61
Mean ASS (SD)	0.71 (0.69)	0.48–0.94	0.58 (0.81)	0.33–0.82	0.45

LSS=Lesion Severity Score, ASS=Area Severity Score, CI=Confidence Interval (95%)

± 1.82 to 1.47 ± 2.34 (84% reduction) in the non-obese group. SITZ-130 mg OD was found to be statistically significant in reducing LSS at the end of therapy ($P < 0.05$) from baseline in both the groups. But on intergroup comparison, no statistically significant difference was seen at week 6 ($P = 0.61$), as shown in Table 2. Significant lesion clearance was also seen in both the groups at week 6. The mean ASS of 2.39 ± 0.69 and 2.43 ± 0.54 reduced to 0.71 ± 0.69 (70% reduction) and 0.58 ± 0.81 (76% reduction) in obese and non-obese groups, respectively ($P = 0.45$). Clinical improvement in obese and non-obese groups is shown in Figure 2.

Four patients in the obese group (18% of completely cured), while one patient in non-obese group (3% of completely cured), relapsed within 4 weeks of completion of treatment, which was not statistically significant ($P = 0.14$).

Safety

Both the groups tolerated therapy very well with only one patient in the non-obese group reported to have pruritus. Additionally, no derangements in liver enzymes were noted at the end of treatment in both the groups.

Discussion

In recent times, dermatophytosis has been on the rise in India, with an increase in the case of difficult-to-treat, recurrent, and recalcitrant dermatophytosis. While multiple factors, such as global warming, overuse of corticosteroids, and lifestyle changes, are considered to be responsible for this havoc, obesity in recent times has emerged as one of the neglected but important aggravating factors.[15] Though, in one of the articles, it was recommended to use a double dose of ITZ in obese patients, studies are lacking regarding the efficacy of ITZ even at regular dose.[11] With this objective, analysis was done to evaluate the efficacy and safety of SITZ-130 mg OD in obese and non-obese patients of dermatophytosis.

In our study, out of 80 patients, 35 patients had BMI ≥25 kg/m2 (six patients had BMI <30 kg/m2 and 29 had ≥30 kg/m2), thus accounting for 44% of total enrolled patients.

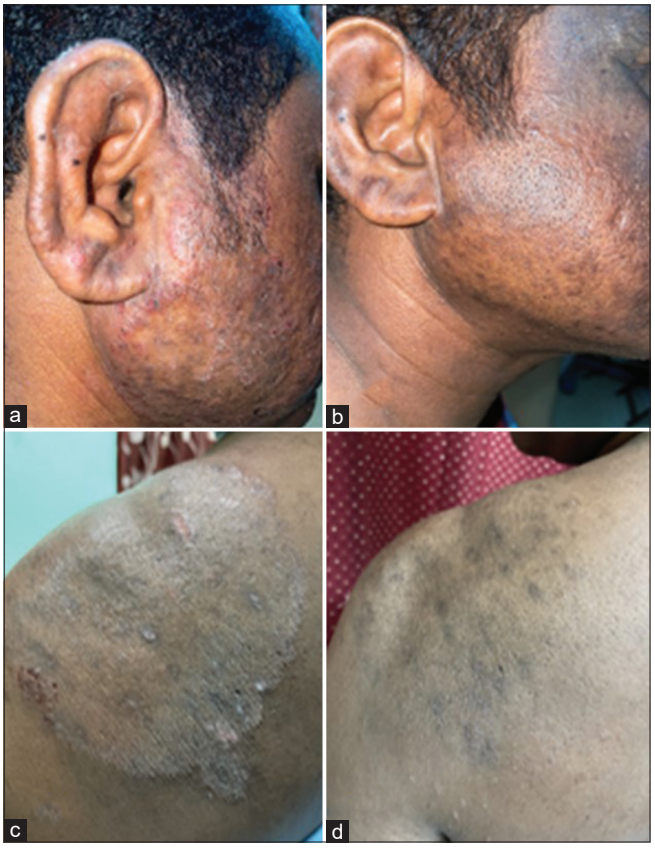

Figure 2: Clinical cure with SITZ-130 mg OD; (a and c) – before treatment (b and d) – after treatment with SITZ-130 mg OD in obese and non-obese patients, respectively; Photo courtesy – Dr Manjunath Shenoy

This suggests that high percentage of overweight and obese patients in our study had dermatophytosis. Many articles concluded that obesity was associated with an increased incidence of dermatophytosis.[2,16,17]

Multiple factors have been suggested to explain the possible mechanism behind this. Firstly, obesity may make the skin more vulnerable to fungal growth. Warm and humid conditions are critical for fungal growth and its survival. Obese patients have layers of subcutaneous fat with deep skin folds causing profuse sweating. This leads to trapped moisture and warmth, providing an ideal condition for

the colonization of the dermatophytes.[18,19] Secondly, the increased adipose tissue itself may further contribute to the increased risk for infection.[20-22] Recently, it has been perceived that adipose tissue participates actively in immunity by producing a variety of cytokines like leptin and adiponectin.[21,22] Leptin is a pro-inflammatory cytokine, which activates poly-morphonuclear neutrophils and T lymphocytes, thus regulating the activation of monocytes and macrophages.[21,22] Obese patients often show leptin resistance, making them more vulnerable to infection.[20]

In spite of the increased risk for the development of dermatophytosis, cure rate in obese and non-obese patients was 63% and 73%, respectively, in our study, with no statistically significant difference between the two. Additionally, there was no statistical difference for achieving mycological cure rate, clinical cure rate, and even relapse rates, suggesting that a higher dose of ITZ was not required for optimal results in obese patients. This is not in accordance with the suggestion from Payne *et al*. who recommended to use a double dose of ITZ in obese patients.[11] In the recently published ITART (Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) Task Force against Recalcitrant Tinea) guidelines, authors concluded that, owing to non-linear pharmacokinetics, high dose of ITZ >200 mg daily may result in decreased clearance and eventually toxic levels.[14,23]

This is the first clinical comparative analysis on SITZ-130 mg OD in obese and non-obese patients with dermatophytosis. Small sample size remained the major limitation along with duration of treatment. Hence, a comparative clinical study with larger sample size and for longer duration is warranted.

Conclusion

From the results, it was concluded that obesity posed as one of the risk factors for dermatophytosis. Additionally, SITZ-130 mg OD achieved desired and similar clinical response in obese patients as of non-obese patients suffering from dermatophytosis, and hence, a higher dose may not require in obesity.

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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

Dhiraj Dhoot is an employee of Glenmark Pharmaceuticals Ltd. Rest of authors do not have any conflict of interest.

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