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Original Research Article

A multicenter, retrospective study to evaluate the effectiveness, safety, and utilization patterns of super bioavailable itraconazole 50 mg in superficial dermatophytic infections

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ABSTRACT

Background: Objectives of the study were to assess the clinical characteristics of patients with superficial dermatophytic infections, and to evaluate the safety and effectiveness of super bioavailable (SB) itraconazole 50 mg.
Methods: In this cross-sectional observational study, data of patients with superficial dermatophytic infections treated as per physician's discretion was collected retrospectively from 71 centers across India between April 2021 and March 2022. Patient's demographics, prescribing patterns of SB-itraconazole, and clinician-rated effectiveness and safety were evaluated.
Results: Of 432 analyzed patients, 72.22% (n=312) had new infections, 27.77% (n=120) had recalcitrant/recurrent infections. Majority of the patients were males (66%) and aged 21-40 years (72.45%). *Tinea corporis* (27.08%) was the most common fungal infection followed by *Tinea cruris* (20.60%). SB-itraconazole was most commonly prescribed with water (63.88%; n=276); majority (55.8%) of the patients received SB-itraconazole post-meals. Majority of the patients achieved clinical (naïve: 71.47%; recalcitrant: 79.17%) cures within 4 weeks. The efficacy was excellent/good in 71.95% of patients who received SB-itraconazole as the first choice over conventional itraconazole for overall benefits as per the clinician's global assessment; and in 87.22% of patients who received concomitant acid-lowering drugs. Most (83.33%) patients reported excellent/good compliance with SB-itraconazole. The clinicians' rated this newer formulation of itraconazole (SB-itraconazole) as excellent/good in efficacy (83.33%) and safety (79.17%) for most patients.
Conclusions: SB-itraconazole was effective and safe in patients with superficial dermatophytic infections. The effectiveness of SB-itraconazole was similar with high response rates for naïve and recalcitrant cases. Further, the efficacy was excellent/good in most patients receiving SB-itraconazole as the first choice over conventional itraconazole, or who received concomitant acid-lowering drugs.

Keywords: SUBA, Super bioavailable itraconazole, Superficial dermatophytic infections

INTRODUCTION

Superficial dermatophytic infections are very common in the general population affecting about 20-25% of the global population. These infections are most common in tropical and subtropical countries such as India.[1-3] Trichophyton has appeared to be the main causative organism for these infections in India.[4,5] The clinical

presentation of dermatophytic infection varies like *Tinea pedis*, *Tinea corporis*, and *Tinea cruris*, and these lesions may overall negatively impact the societal well-being of the patients.[6,7]

In the recent years, the clinical profile, disease severity, and therapeutic landscape have remarkably changed along with increased cases of recurrent or recalcitrant dermatophytosis in India.[5,8]

The preferred systemic drugs for the management of dermatophyte infections include terbinafine and itraconazole.[9] For naive and recalcitrant *Tinea pedis*, extensive lesions of *Tinea corporis*, and recalcitrant cases of *Tinea cruris* and *Tinea corporis*, a systemic and topical antifungal combination therapy is recommended.[9] Itraconazole is a preferred systemic agent for recalcitrant cases of dermatophyte infections.[9,10] Itraconazole exerts antifungal properties through inhibition of fungal cytochrome P450 (CYP)3A isoenzymes.[11,12] Itraconazole is formulated as drug coated pellets to increase the absorption profile, however, inconsistency in the palletization profile leads to inconsistent bioavailability. In addition, the erratic absorption profile causes wide fluctuations in blood concentration.[13]

Furthermore, the prescription patterns of itraconazole may also result in the varied bioavailability. The co-administration of an acidic beverage with itraconazole enhances the bioavailability of itraconazole, particularly in patients receiving acid lowering drugs.[14,15] Also, itraconazole capsule administration shortly after meal may yield optimal bioavalability.[16]

To overcome these challenges with conventional itraconazole formulation, a new 'super bioavailable' (SB)-itraconazole formulation was developed.[5,6] SB-itraconazole has a solid dispersion of a uniform non-pellet drug formulation in a polymeric matrix, which is pH-independent that improves the dissolution and intestinal absorption of itraconazole, subsequently resulting in greater bioavailability. In India, Intas Pharmaceuticals Limited introduced the SB-itraconazole at a dose of 50 mg post approval by the apex drug regulator 'Drugs Controller General of India (DCGI)'.[13,17] The 50 mg SB-itraconazole is reported to be therapeutically equivalent to 100 mg conventional itraconazole.[12]

Several factors such as drug resistance, adherence, dosage forms, drug interactions, co-morbid conditions, or altered pharmacokinetic profiles are known to affect the clinical outcomes in superficial dermatophytic infections and understanding these may help identify the optimal management strategies.[9,18]

Hence, we conducted the current study to evaluate the demographic details of patients with superficial dermatophytic infections, the prescription patterns of SB-itraconazole and its safety and efficacy in these patients.

METHODS

Study design

The retrospective study to capture the utilization pattern of Super Bioavailable itraconazole in superficial dermatophytic infections-2 (RETRO SB-2) was a retrospective, observational, cross-sectional study conducted at 71 centers across India between April 2021 and March 2022. The patients of superficial dermatophytic infections who were treated with SB-itraconazole in a real world clinical set up were only included in this study and accordingly there was no specific exclusion criterion. Data of these patients were collected from hospitals, clinics and healthcare institutes. The data on age, sex, clinical diagnosis, treatment history, treatment compliance, safety and effectiveness of SB-itraconazole was captured and filled by the clinicians retrospectively. Patients were selected based on the treating physician's discretion. For the purpose of this study, no additional interventions or investigations were performed.

Study endpoints

The study endpoints included various demographic details like age and gender wise distribution, type of *Tinea* infections, comorbid conditions, utilization pattern of SB-itraconazole. The efficacy (clinical cure) and safety outcomes, patient compliance with medication and clinician's global assessment for SB-itraconazole on safety and efficacy were also evaluated.

Sample size and statistical analysis

In this real-world study, patients' data was collected retrospectively without any predetermined sample size. The study did not test any hypothesis and only the observations from patient's records were analyzed. The data collected from all the centres across India were compiled and statistical analysis was performed using Microsoft excel (Microsoft Corporation, USA). A descriptive statistical analysis was performed for the demographic and baseline characteristics at Lambda Therapeutic Research Ltd., Ahmedabad, India. For categorical data, frequency and percentage were used, and for continuous data, count, mean, median, minimum, and maximum were presented. Graphical presentation of data was done using bar chart as appropriate.

Ethical statement

The study protocol presents less than minimal risk based on the "ethical guidelines for biomedical research on human participants" by Indian Council of Medical Research (ICMR), and, hence, the study falls under 'exemption' category from the ethics committee approval.[19] The study was approved by the Bio-smart independent ethics committee, Ahmedabad, India. The informed consent from patients was not feasible owing to

the retrospective design of the study. The anonymized data of the patients were analyzed.

RESULTS

A total of 432 patients were included in this study. Of these, new infections were reported in 72.22% (n=312) patients while 27.78% (n=120) patients had recalcitrant/recurrent infections. The majority (65.51%, n=283) of patients were males, and belonged to the age group of 31 to 40 years (39.35%, n=170) (Table 1). Recent history of corticosteroid usage was reported in 23.38% (n=101) patients.

Table 1: Patient characteristics (n=432).

Parameter	All patients N (%)
Age group (years)	
<10	11 (2.55)
11 to 20	27 (6.25)
21 to 30	143 (33.1)
31 to 40	170 (39.35)
41 to 50	64 (14.81)
51 to 60	13 (3.01)
>60	4 (0.93)
Gender	
Men	283 (65.51)
Women	149 (34.49)
Comorbidities	
Chronic kidney disease	33 (7.64)
Hypochlorhydria	40 (9.26)
Malignancy	101 (23.38)
Pregnancy	53 (12.27)
Diabetes	170 (39.35)
Other	35 (8.1)
Dermatophytic infections	
New infections	312 (72.22)
Recalcitrant/recurrent infections	120 (27.78)

SD: Standard deviation

Tinea corporis (n=117, 27.08%) followed by *Tinea cruris* (n=89, 20.60%) were the most common type of fungal infections (Figure 1). *Tinea corporis* was reported most in the age group of 31 to 40 years (n=53/117, 45.30%) followed by 21 to 30 years (n=35, 29.91%) and 41 to 50 years (n=15, 12.82%).

SB-itraconazole prescription pattern

Of 432 patients, SB-itraconazole was prescribed with water in 63.89% (n=276) patients, lemon juice in 15.74% (n=68) patients, aerated drinks in 13.19% (n=57) patients and buttermilk in 5.09% (n=22) patients; details for remaining 9 patients were not specified. SB-itraconazole was taken after meal in 241 (55.79%) patients and before a meal in the remaining 191 (44.21%) patients. In a total of 126 (29.17%) patients, SB-itraconazole was given before meal and with water. The most commonly co-prescribed topical antifungal drug was luliconazole (39.58%, n=171/432) followed by sertaconazole (8.80%, n=38/432); amorolfine (n=36, 8.33%), terbinafine (n=28, 6.48%), eberconazole (n=25, 5.79%), ketoconazole (n=21, 4.86%) and ciclopirox (n=14, 3.24%) were the other co-prescribed topical antifungal agents.

Efficacy of SB-itraconazole

Clinical cure

Clinical cure, defined as patients clinically free from signs and symptoms of fungal infection, was reported with SB-itraconazole treatment in majority of the naïve (71.47%) and recalcitrant (79.17%) patients at 4 weeks (Figure 2).

SB-itraconazole when prescribed as the first choice over conventional itraconazole

The efficacy of SB-itraconazole when prescribed as a first choice over conventional itraconazole was reported as excellent/good in 71.95% of the patients.

Other parameters

The clinician's global assessment of efficacy was 'excellent' in 37.27% patients. Similarly, in 34.49% patients, clinician's global assessment of safety was 'excellent'. Most (83.33%) patients had good to excellent compliance with SB-itraconazole (Table 2). In patients who had taken SB-itraconazole with water, lemon juice, or aerated drink, the efficacy was recorded as 'excellent' in 44.57% (n=123/276), 25% (n=17/68), and 21.05% (n=12/57) patients, respectively. In patients receiving SB-itraconazole after meal, the efficacy was reported as 'excellent' in 31.95% (n=77/241) patients and in 43.98% (n=84/191) patients receiving SB-itraconazole before a meal. In patients receiving SB-itraconazole before meal and with water, 54.76% (n=69/126) patients reported the efficacy to be 'excellent' (Table 2). Of 101 patients with recent history of corticosteroid usage, in about half (46.53%, n=47/101) of the patients' efficacy was reported as 'excellent'. The efficacy was excellent/good in 87.22% (n=116/133) patients who received concomitant acid lowering drugs, and in 86.67% (n=91/105) patients when SB-itraconazole prescribed to minimize food interaction. Among the patients who were co-prescribed topical luliconazole; around 88% shown 'excellent/good' efficacy by clinician's global assessment (Table 2).

Safety of SB-itraconazole

In the present study, common adverse events were gastrointestinal disturbances, rash, and headache; most of which were mild in nature. The incidence of patients experiencing severe nausea, vomiting, diarrhea, abdominal pain, rash, and headache were 1.85%, 1.62%, 2.31%, 2.78%, 3.47% and 5.79%, respectively.

Table 2: Treatment outcomes.

Parameter	Response, N (%)			
	Excellent	Good	Fair	Poor
Clinician's global assessment of efficacy, N=432	161 (37.27)	199 (46.06)	63 (14.58)	9 (2.08)
Clinician's global assessment of safety, N=432	149 (34.49)	193 (44.68)	71 (16.44)	19 (4.4)
Compliance with SB-itraconazole, N=432	158 (36.57)	202 (46.76)	66 (15.28)	6 (1.39)
Efficacy with respect to SB-itraconazole taken with water, lemon juice, aerated drink, and before/after meal status				
With water, N=276	123 (44.57)	121 (43.84)	29 (10.51)	3 (1.09)
With lemon juice, N=68	17 (25)	36 (52.94)	13 (19.12)	2 (2.94)
With aerated drink, N=57	12 (21.05)	31 (54.39)	12 (21.05)	2 (3.51)
Before meal, N=191	84 (43.98)	79 (41.36)	23 (12.04)	5 (2.62)
After meal, N=241	77 (31.95)	120 (49.80)	40 (16.6)	4 (1.66)
Before meal and with water, N=126	69 (54.76)	48 (38.1)	7 (5.56)	2 (1.59)
Efficacy in patients with recent history of corticosteroid usage, N=101	47 (46.53)	37 (36.63)	15 (14.85)	2 (1.98)
Efficacy of SB-itraconazole when prescribed to patients on acid lowering drugs, N=133	58 (43.61)	58 (43.61)	14 (10.53)	3 (2.26)
Efficacy of SB-itraconazole when prescribed to minimize food interaction, N=105	36 (34.29)	55 (52.38)	12 (11.43)	2 (1.9)
Efficacy in patients who received concomitant topical antifungal agents				
Luliconazole, N=171	62 (36.26)	88 (51.46)	17 (9.94)	4 (2.34)
Sertaconazole, N=38	18 (47.37)	16 (42.11)	4 (10.53)	-
Amorolfine, N=36	20 (55.56)	11 (30.56)	4 (11.11)	1 (2.78)
Terbinafine, N=28	12 (42.86)	11 (39.29)	4 (14.29)	1 (3.57)
Eberconazole, N=25	7 (28)	14 (56)	4 (16)	-
Ketoconazole, N=21	9 (42.86)	10 (47.62)	2 (9.52)	-
Ciclopirox, N=14	7 (50)	3 (21.43)	3 (21.43)	1 (7.14)

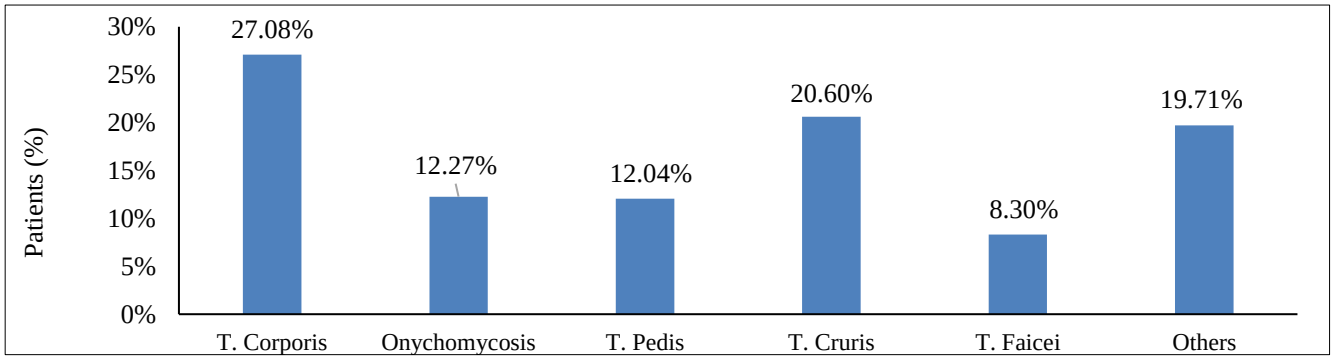

Figure 1: Type of fungal infection (N=432).

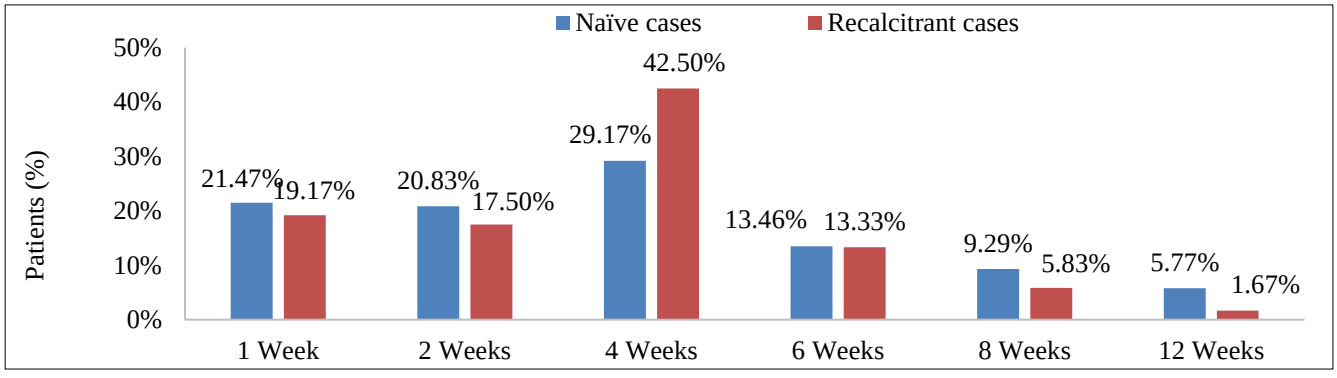

Figure 2. Proportion of patients achieving clinical cure.

DISCUSSION

Itraconozole has been one of the most commonly used antifungal agent for the dermatophytic infections, but the variability in bioavailability, inconsistent pharmacokinetic profile and therapeutic concentration have hampered its clinical effectiveness in real-wolrd scenario. A new SB-itraconazole formulation has been developed to overcome these challenges. The use of SB-itraconazole has been reported in several indications with a limited data on dermatophytosis. The current multicenter study reported the real-world clinical profile for patients of superficial dermatophytic infections, who were treated with SB-itraconazole. The study reported that most of the patients were superficial dermatophytic infection naïve whereas a few cases of recalcitrant infections were also seen. Clinical cure was reported within 4 weeks in majority of the patients with naïve and recalcitrant infections. The current study also evaluated the effects of administration modes of SB-itraconazole, and effects of concomitant antifungal agents used.

In our study, majority of the patients were males, similar to as reported in previous studies in patients with superficial dermatophytic infection.[20-22] The low incidence of dermatophytic infections in females could be attributed to the comparatively low reporting of female patients to hospitals due to the social stigma, especially in the rural areas of our country.[23] However, isolated reports have also shown contrasting results with female prepondrance as seen in a study by Das and colleagues in India.[5]

Majority of the patients in this study were aged between 21 to 40 years, which is consistent with earlier reports from India. In a study of 260 patients with dermatophytic infections from India, 95 patients were aged between 16-40 years.[23] Das and colleagues reported that 61% of the patients with dermatophyte infection were young adults (18–40 years of age).[5]

Among superficial dermatophytic infections, *Tinea* infections are the most common.[20] In our study, *Tinea corporis* followed by *Tinea cruris* were the most common lesions. These findings are consistent with previous reports from India.[20,23] *Tinea pedis* was reported in about 12% of the patients in our study. However, *Tinea pedis* is reported to be the common site of infection in western countries, which could be due to the extensive use of shoes and socks in these countries, leading to perspiration and maceration.[23,24]

Itraconazole is amongst the most commonly used agent in the treatment of dermatophytic infections.[6,25] SB-itracoazole has shown improved bioavailability profile, less inter-patient variability, and improved efficacy and safety profiles versus conventional itraconazole.[13,20,26-28] Several previous studies have reported a higher effectiveness with SB-itraconazole versus the conventional itraconazole for the treatment of superficial dermatophytic infections.[17,20,22,29] Shenoy et al compared the efficacy and safety of SB-itraconazole (n=26) versus conventional itraconazole (n=33) in an open-label, randomized, double-arm clinical trial. In patients receiving SB-itraconazole, a clinical cure was reported within 4 weeks in about 65.38% of the patients including the naïve as well as recalcitrant cases. Our study also reported similar results with majority (73.61%) of the patients achieving clinical cure in naïve (75.32%) as well as recalcitrant (79.17%) cases, within 4 weeks of SB-itraconazole treatment. Overall, our study demonstrated excellent/good efficacy in most patients who received SB-itraconazole as first choice over conventional itraconazole for overall benefits. In addition to the clinical studies, real-world studies have also evaluated the effects of SB-itraconazole in dermatophytic infections. In a multi-centric, retrospective study, Mahajan et al reported complete clearance of symptoms in 56% of the patients receiving SB-itraconazole.[17] In a real world retrospective data analysis study by Ghate et al in 2743 patients, a complete clinical cure rate was reported at 51%, with 46% patients showing clinical improvements at 4 weeks with SB-itraconazole for superficial dermatophytic infections.[22]

The widespread usage of antifungal agents have led to an increase in the recalcitrant/recurrent dermatophytosis.[3] In India, the increased cases of recalcitrant/recurrent dermatophytosis is alarming.[30] Further, the irrational use of steroid-antifungal-antibacterial durgs in India results in a new entity of steroid modified tinea, leading to recalcitrant cases.[17,31] In these patients, the traditional treatments are not effective and a combination of topical and systemic antifungal agents remains the most commonly used therapeutic approach.[32] In the study, majority of the patients were newly diagnosed whereas about 1/3rd of the patients had recalcitrant/recurrent infections. A recent history of corticosteroid usage was observed in 23.38% of the patients in our study, which is consistent with 23.1% reported in the study by Shenoy et al.[29] Overall, our study demonstrated that the effectiveness of SB-itraconazole was similar with high response rates for both treatment naïve and recalcitrant cases.

Most of our study participants also received other concomitant antifungal agents; luliconzaole being the most common. Sardana and colleagues have reported a potential synergy for itraconazole and other common antifungal agents such as luliconazole and ketoconazole in recalcitrant dermatophytic infections.[33]

A population pharmacokinetic modeling study in healthy adults in fed and fasting states reported 173% bioavailability with 21% less variability for SB-itraconazole versus conventional itraconozole.[27] A decrease of 40% to 60% in the absorption of conventional itraconazole has been reported in the fasting state as compared with the fed state.[16,34] The effect of food on the bioavailability of SB-itraconazole was evaluated in an open-label, randomized, crossover bioavailability study in healthy adults by Lindsay et al. The authors reported a slightly higher bioavailability of SB-itraconazole in a

fasting state as compared with fed state.[35] These results confim that presence of food is not required to increase the solubility of itraconazole from the novel SB formulation.[35]

In the present study, the responses to the questionnaire were filled by the clinicians themselves. The clinicians' global assessments of the efficacy and safety of SB-itraconazole were 'good' to 'excellent' in most of the patients. Studies have reported a poor medication compliance with antifungal agents.[19] In our study, the compliance was 'good' to 'excellent' in 83.33% cases with SB-itraconazole. The limitations of our study include the retropective nature and unavailablity of data on relapse rate.

CONCLUSION

This real-world retrospective data analysis study confirms that SB-itraconazole is effective in patients with superficial dermatophytic infections in India. This study reported that tinea corporis is the most common fungal infection in India. As per the clinician's global assessment, majority of the patients who received SB-itraconazole as the first choice over conventional itraconazole for overall benefits had excellent/good efficacy. SB-itraconazole was most commonly prescribed with water, and majority of the patients received SB-itraconazole post-meals. The clinical cure was achieved in majority of the patients within 4 weeks of SB-itraconazole treatment. The clinicians' rated SB-itraconazole as excellent/good in efficacy and safety for most patients and the compliance to SB-itraconazole was also excellent/good in most patients. These details regarding the prescription patterns of SB-itraconazole and the real-world experience related to effectiveness, safety, and compliance of this newer super bioavailable formulation of itraconazole may facilitate the clinicians for optimal decision making in the management of superficial dermatophytic infections in India. Large scale, long-term clinical trials may yield more robust data to validate the findings of the current study.

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Ethical approval: The study was approved by the institutional ethics committee

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