

## Original Research Article

# Comparative clinical effectiveness and safety of super bioavailable itraconazole and conventional itraconazole in management of dermatophytosis: a retrospective data analysis

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## ABSTRACT

**Background:** A newer itraconazole formulation i.e., super bioavailable itraconazole has been launched recently in India which is claimed to overcome all the pharmacokinetic challenges faced with conventional itraconazole. The present retrospective data analysis was undertaken to evaluate the effectiveness and safety of super bioavailable itraconazole in comparison with conventional itraconazole in the treatment of dermatophytosis in Indian patients.

**Methods:** The present multi-centric, retrospective data analysis was done at 12 dermatological centers across India from July 2020 to December 2020. Medical records of patients of dermatophytosis, who were prescribed with either super bioavailable itraconazole 50 mg twice daily for four weeks or conventional itraconazole 100 mg twice daily for four weeks were included in the study.

**Results:** 56% patients (n=30) in super bioavailable itraconazole group achieved complete clearance of their symptoms (cured) compared to only 34% patients (n=17) in conventional itraconazole group and this difference was statistically significant (p=0.02). Significantly more patients achieved complete clearance of their lesions in super bioavailable itraconazole-37 patients (69%) compared to conventional itraconazole group-25 patients (49%) at the end of 4 week therapy (p=0.04). The difference in total symptom score ( $\Delta$ TSS) in super bioavailable itraconazole group was more (5.81) as compared to conventional itraconazole group (4.75) (p=0.09). Both the treatment were well tolerated.

**Conclusions:** From the findings of the present study, super bioavailable itraconazole was more effective with similar safety profile as compared to conventional itraconazole in the treatment of dermatophytosis.

**Keywords:** Super bioavailable itraconazole, Dermatophytosis, Effectiveness, Safety, Conventional itraconazole

## INTRODUCTION

Itraconazole is commonly used systemic antifungal for the treatment of dermatophytosis in India.<sup>1</sup> It has various challenges like dependency on gastric acid for its dissolution, less bioavailability, inter and intra-patient variability, that is, fluctuations in absorption, dependency on food, reduction in absorption when co-administered

with gastric acid reducing drugs like proton pump inhibitors (PPIs).<sup>2</sup>

A newer itraconazole formulation that is, super bioavailable itraconazole has been launched in European countries and Australia in 2019 and recently in India which is approved by Drug Controller General of India. It is claimed to overcome all the pharmacokinetic challenges faced with conventional itraconazole. Super

bioavailable itraconazole have been claimed to have the benefits of increased bioavailability, no food interaction, less inter-subject variability, no reduction in absorption with concomitant use of PPI not seen with other gastric acid lowering agents, which are seen with conventional itraconazole.<sup>2-4</sup> All these benefits can be anticipated to improve the clinical outcomes as well as the patient compliance.<sup>5</sup>

However, there is no published evidence of super bioavailable itraconazole in the treatment of dermatophytosis in Indian patients. Therefore, the present retrospective data analysis was undertaken to evaluate the effectiveness and safety of super bioavailable itraconazole in comparison with conventional itraconazole in the treatment of dermatophytosis in Indian patients.

## METHODS

The present multi-centric, retrospective data analysis was done at 12 dermatological centers across India from July 2020 to December 2020. Medical records of patients of

dermatophytosis, who were prescribed either super bioavailable itraconazole 50 mg twice daily for four weeks or conventional itraconazole 100 mg twice daily for four weeks were included in the study. Only those records were included for analysis whose complete clinical evaluation over 4 weeks treatment period was available. After screening 120 medical records for completeness of mandatory parameters described above, medical records of 105 patients were finally included for analysis (Figure 1).

### Inclusion criteria

Medical records of patients of either gender and >18 years of age who were diagnosed with recalcitrant dermatophytic infection, recurrent or relapsing infection were included in this study.<sup>6</sup>

### Exclusion criteria

Data of patients with history of onychomycosis and naïve tinea infections were excluded from the analysis.

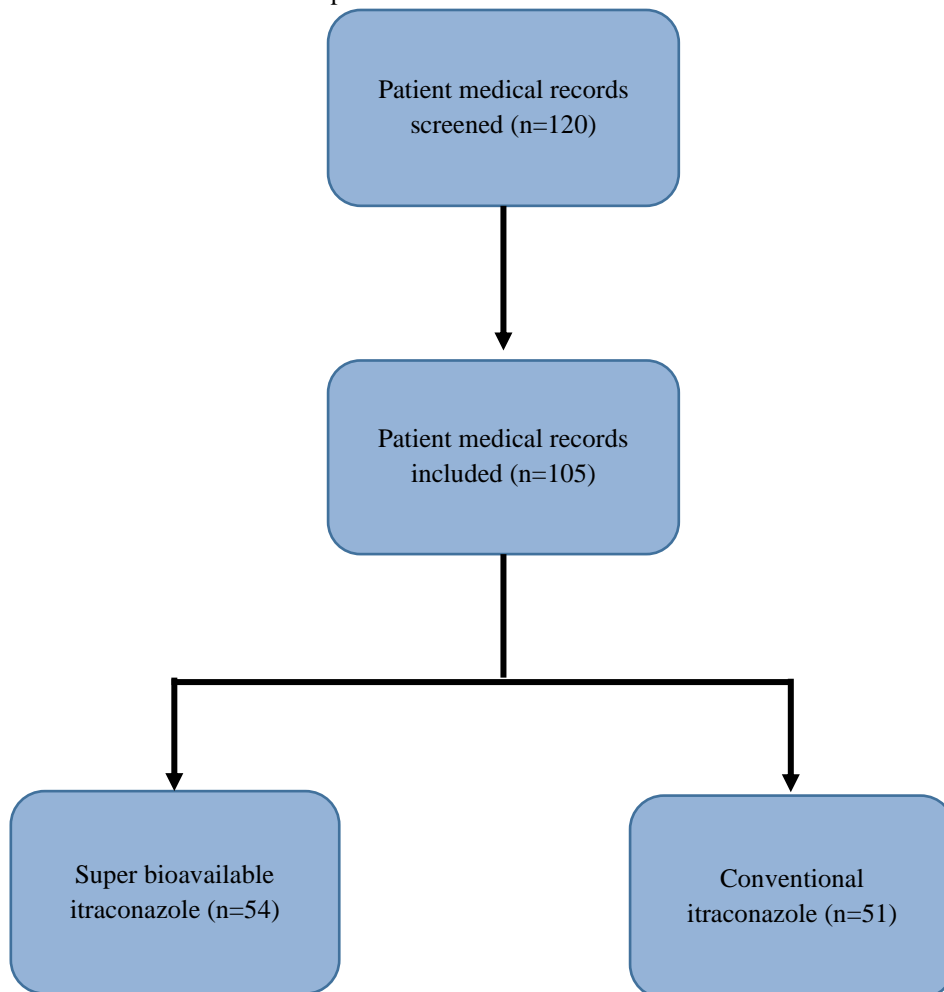


Figure 1: Screening of medical records of the patients for present study.

**Table 1: Scoring system used for clinical evaluation in patients of dermatophytosis in the present study.**

Parameters	Particulars	Score
Symptom score	Erythema	0- absent,
	Pruritus	1- mild,
	Scaling	2- moderate, 3- severe
Extent of lesion score	Body surface area (BSA)	0- absent
		1- mild/BSA 1-2%
		2- moderate/BSA 3-10%
		3- severe/BSA>10%

### Effectiveness evaluation

As per the medical records total symptom score included scoring of erythema, scaling and pruritus along with extent of lesions in the form of body surface area (BSA) involvement in both the treatment groups. Each symptom/sign and BSA was scored on 4 point scale (0 to 3) which were recorded at baseline and at the end of therapy which was 4 weeks. The details of the scoring system are depicted in Table 1.

#### Primary effectiveness endpoint

Primary effectiveness end point was percentage of patients achieving complete cure at the end of treatment (4 weeks), which was defined by complete disappearance of symptoms and lesions in both groups.

#### Secondary effectiveness endpoints

Secondary effectiveness end points were percentage of patients achieving following parameters at the end of treatment (4 weeks) in both groups; remarkable improvement: clearance of symptoms by 75-99%; improvement: clearance of symptoms by 51-75%; failure: clearance of symptoms by  $\leq 50\%$ ; difference/improvement in total symptom score ( $\Delta TSS = TSS$  at baseline minus TSS at 4 weeks).

### Safety evaluation

Safety evaluation was done by assessing the adverse events (AEs) in medical records during the treatment period in both the groups.

### Statistical analysis

Descriptive statistics were utilized to analyze the effectiveness and safety in both the treatment groups. Quantitative variables were expressed in terms of mean and standard deviation. Categorical variables were across both the treatment groups were analyzed by unpaired t-test. Statistical analyses was done using SPSS software version 19.0. P value  $< 0.05$  was considered to be statistically significant.

## RESULTS

Out of total 105 patients, 54 patients were prescribed with super bioavailable itraconazole 50 mg and 51 patients with conventional itraconazole 100 mg.

### Baseline characteristics

Mean age, sex distribution in both the groups were comparable at baseline. Most common diagnosis in both the treatment groups was *Tinea corporis* et *cruris*, followed by *Tinea corporis* and *Tinea cruris*. Majority of the patients in both the groups had severe lesions ( $>10\%$  BSA involvement). The mean total symptom score in both the treatment groups was comparable (Table 2).

### Effectiveness analysis

56% patients (n=30) in super bioavailable itraconazole group achieved complete clearance of their symptoms (cured) compared to only 34% patients (n=17) in conventional itraconazole group and this difference was statistically significant ( $p=0.02$ ) (Figure 2).

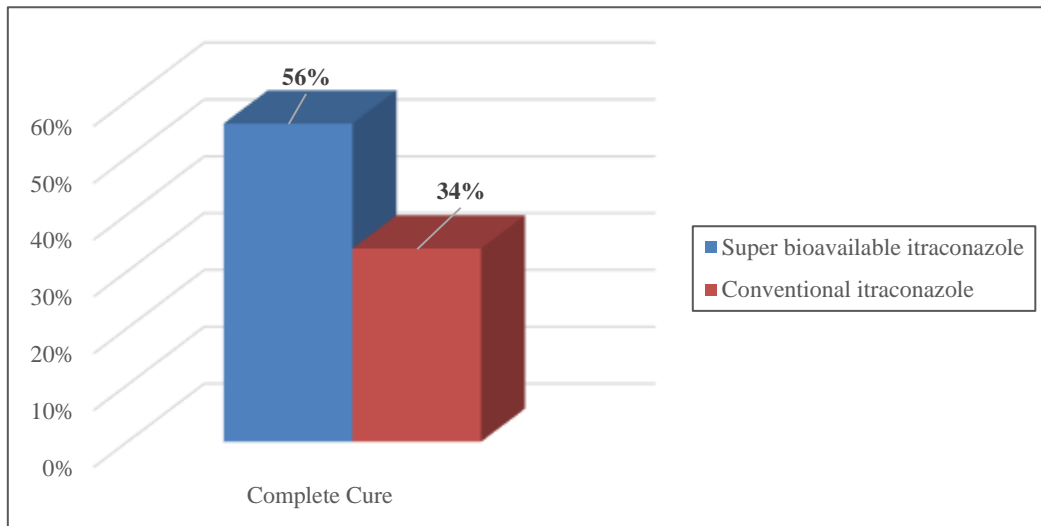
17% of patients (n=10) in super bioavailable itraconazole group achieved remarkable improvement compared to 25% patients (n=12) in conventional itraconazole group. 4% of the patients (n=2) in conventional itraconazole group did not show any improvement in their symptoms after 4 weeks of treatment. The difference in these parameters on both treatment groups was not statistically significant ( $p>0.05$ ) (Figure 3).

Significantly more patients achieved complete clearance of their lesions in super bioavailable itraconazole in super bioavailable itraconazole group-37 patients (69%) compared to conventional itraconazole group-25 patients (49%) at the end of 4 week therapy ( $p=0.04$ ) (Figure 3).

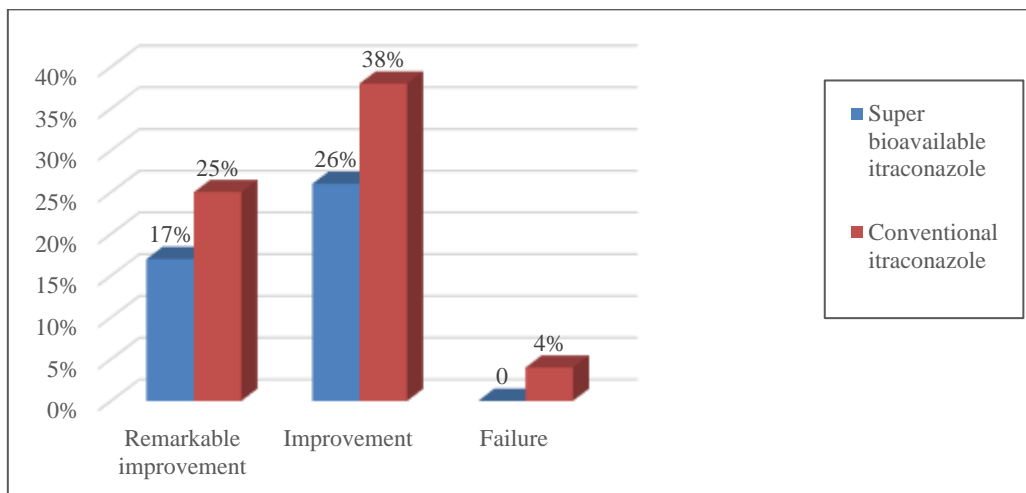
The difference in total symptom score ( $\Delta TSS$ ) in super bioavailable itraconazole group was more (5.81) as compared to conventional itraconazole group (4.75) ( $p=0.09$ ) (Figure 4).

**Table 2: Baseline characteristics of patients.**

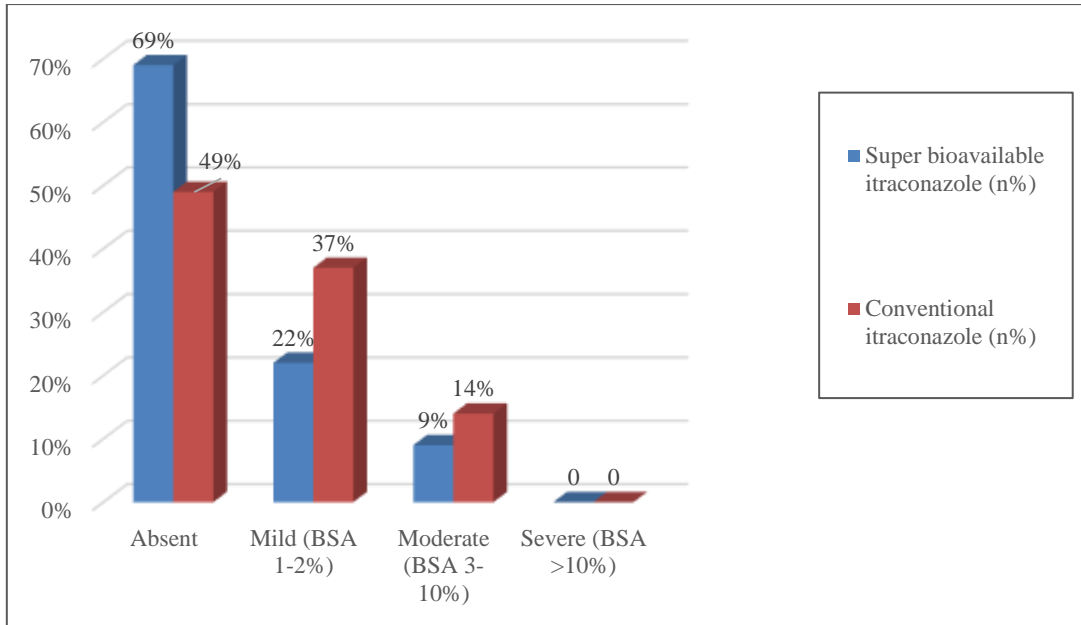
Parameters	Category	Super bioavailable itraconazole (n=54) (%)	Conventional itraconazole (n=51) (%)	P value
<b>Age (mean±SD)</b>		33.11±10.49	34.32±11.29	0.631
<b>Sex N (%)</b>	Male	32 (59.25)	30 (58.82)	0.582
	Female	22 (40.25)	21 (41.17)	0.614
<b>Diagnosis</b>	Tinea cruris et corporis	24 (44.4)	22 (43.13)	0.472
	Tinea corporis	15 (27.7)	14 (27.45)	0.558
	Tinea cruris	10 (18.5)	11 (21.5)	0.518
	Tinea corporis et facie	3 (5.5)	2 (3.92)	0.239
	Tinea facie	2 (3.7)	2 (3.92)	1
<b>% BSA involved</b>	Mild (1-2% BSA)	9 (16.6)	8 (15.6)	0.381
	Moderate (3-10%)	20 (37)	19 (37.2)	0.459
	Severe (>10%)	25 (46.2)	24 (47)	0.682
<b>Total symptom score</b>		6.22±1.56	6.14±1.78	0.44



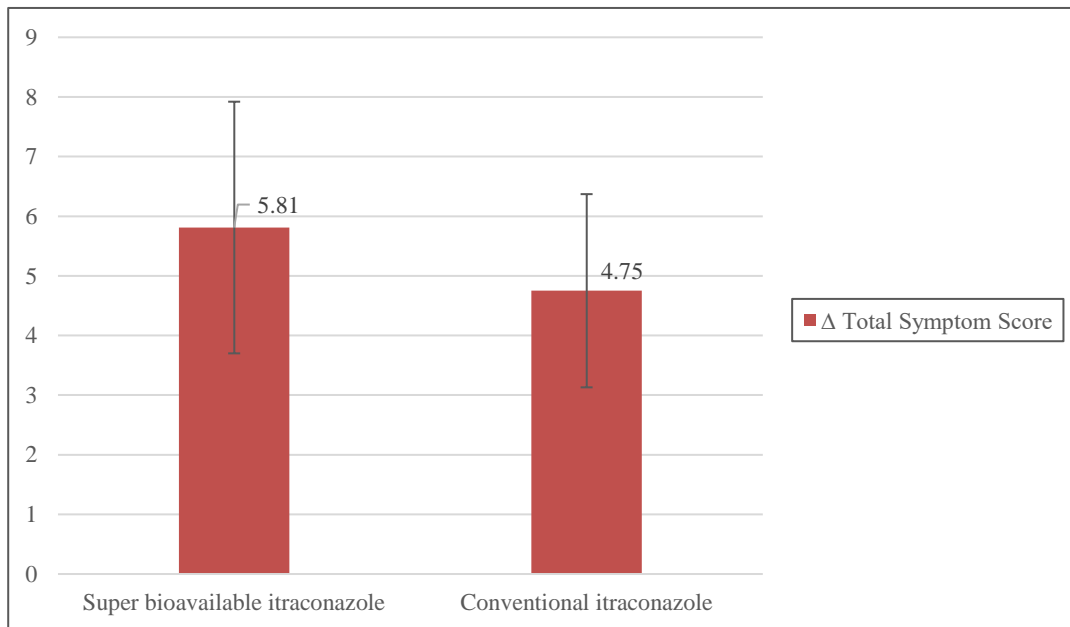
**Figure 2: Percentage of patients achieving complete cure in both the treatment groups at the end of therapy which is 4 weeks.**



**Figure 3: Outcomes of patients in both the treatment groups at the end of therapy which is 4 weeks.**



**Figure 4: Body surface area score in the patients of present study at the end of therapy.**



**Figure 5: Difference in total symptom score ( $\Delta$ TSS) in both the treatment groups of present study.**

### Safety analysis

Both the treatment were well tolerated. Only 3 patients (1 in super bioavailable itraconazole group and 2 in conventional itraconazole group) reported gastrointestinal (GI) adverse events. The adverse events were of mild intensity and none of the patient in both the groups discontinued the therapy. The compliance to therapy in both the group was excellent.

### DISCUSSION

The prevalence of dermatophytosis in India has increased sharply over the past few years, particularly the recalcitrant cases.<sup>7</sup> Owing to change in clinical presentation, there have been changes in management of dermatophytosis which include increased dose and duration of antifungal therapy, combination of systemic and oral antifungal drugs.<sup>7</sup> This holds true particularly for itraconazole which is commonly used systemic antifungal

in the treatment of dermatophytosis.<sup>8</sup> Its inherent pharmacokinetic characteristics have been one of the major limitation and are frequently overlooked in clinical practice.<sup>9</sup> Super bioavailable itraconazole is devoid of all these pharmacokinetic issues. However, there are no published studies on comparative effectiveness and safety of conventional and super bioavailable itraconazole, especially in Indian patients of dermatophytosis.

In the present study 30 patients (56%) achieved complete clearance of symptoms in super bioavailable itraconazole group as compared to 17 (34%) patients in conventional group. A randomized clinical trial was conducted in patients of onychomycosis to evaluate efficacy and safety of super bioavailable (50 mg twice daily for 12 weeks) and conventional itraconazole (100 mg, 2 capsules once daily for 12 weeks). It was found that clinical cure rate, mycological cure rate and therapeutic cure rate (percentage of patients achieving both clinical and mycological cure rate) were higher in super bioavailable itraconazole group as compared to placebo and this difference was highly statistically significant ( $p=0.001$ ). Whereas, in conventional itraconazole, barring mycological cure rate there was no statistically significant difference as compared to placebo ( $p=0.08$ ).<sup>10</sup>

Better cure rates in super bioavailable itraconazole can be attributed to its pharmacokinetic advantages as compared to conventional itraconazole. Itraconazole being a lipophilic molecule and a weak base is ionized in gastric acid and is dependent on gastric acid for its dissolution. This leads to its erratic absorption, high intra, inter-subject variability, reduction in absorption when co-administered with gastric acid reducing agents like PPIs. Apart from this, major site of absorption of itraconazole is small intestine, whereas in conventional form less amount reaches the small intestine and the bioavailability of conventional itraconazole is only around 55%.<sup>11,12</sup> Super bioavailable itraconazole is consistently released and available for absorption throughout the small intestine.<sup>2,13</sup> This ensures increased bioavailability of itraconazole and consequently the concentration at site of action is also increased with very less fluctuations (inter and intra-patient variability is less).<sup>14</sup> Moreover, it was found in a clinical study that co-administration of PPI does not hamper the absorption of super bioavailable itraconazole, rather it moderately increases the absorption of latter.<sup>4</sup>

Attainment of high concentration at site of action is single most important predictor of outcome of antifungal therapy.<sup>8</sup> Itraconazole is a lipophilic drug, therefore its excretion in sebum and concentration achieved in stratum corneum is important, particularly in patients with recalcitrant dermatophytosis.<sup>11</sup> In an unpublished Indian study, the sebum concentration of conventional itraconazole and super bioavailable itraconazole was compared in healthy volunteers (unpublished data, 2020). It was found that sebum concentration of itraconazole was significantly more in super bioavailable itraconazole

group (11.6% more in 7 day drug administration) as compared to conventional itraconazole ( $p=0.01$ ). Thus, higher drug concentration achieved at target site can aid in extensive eradication of fungus from the lesions, as was evident from higher mycological cure rate in patients who received super bioavailable itraconazole in a clinical trial.<sup>10</sup> Thus high concentration achievement in sebum might be responsible for better improvement on total symptom score ( $\Delta$ TSS) in super bioavailable itraconazole group in the present study.

The relapse rates couldn't be evaluated in the present study owing to its retrospective study design. In a randomized clinical trial, relapse rates were less in patients of onychomycosis who received super bioavailable itraconazole as compared to conventional itraconazole.<sup>10</sup> This supports the notion that super bioavailable itraconazole aids in complete eradication of the dermatophytes. Less relapse rate is a welcome sign, especially in India where prevalence of recalcitrant dermatophytosis including relapse and recurrent cases are increasing alarmingly.<sup>15</sup>

In the present study, both the treatments were well tolerated. In a comparative clinical cohort study by Lindsay et al safety and efficacy of high dose super bioavailable itraconazole and itraconazole solution (both 200 mg twice daily) was evaluated in hematopoietic stem cell transplant patients as a prophylaxis against invasive fungal infections. Even in such high concentration (3-4 times the dosage used in present study), adverse effects in super bioavailable itraconazole were less as compared to itraconazole solution. Only 11% of the patients in super bioavailable itraconazole group had mild derangements in liver function test (LFTs), whereas 27% patients in itraconazole solution group had mild LFT derangements and 7% patients had moderate LFT derangements.<sup>16</sup>

Due to its retrospective design there were certain limitations in the present study which might have impacted the results of the study. These include prescription of topical antifungal to all the patients, small sample size, no mycological examination, short duration of study and no data on relapse rates. Long term clinical trials are warranted to compare and validate the results of the present study.

## CONCLUSION

To the best of our knowledge, the present study is first real world evidence on clinical effectiveness and safety of super bioavailable itraconazole versus conventional itraconazole in treatment of dermatophytosis in India. From the findings of the present study, patients treated with super bioavailable itraconazole showed greater improvement in total symptom score. More number of patients in this group achieved remarkable improvement and complete clearance of lesions as compared to conventional itraconazole. Thus, super bioavailable itraconazole can serve as a potent therapeutic choice to

effectively tackle the current menace of recalcitrant dermatophytosis in India.

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## REFERENCES

1. Sardana K, Khurana A, Singh A, Gautam RK. A pilot analysis of morphometric assessment of itraconazole brands using dermoscopy and its relevance in the current scenario. *Indian Dermatol Online J.* 2018;9(6):426-31.
2. Abuhelwa AY, Foster DJR, Mudge S, Hayes D, Upton RN. Population pharmacokinetic modeling of itraconazole and hydroxyl itraconazole for oral SUBA-itraconazole and Sporanox capsule formulations in healthy subjects in fed and fasted states. *Antimicrob Agents Chemother.* 2015;59(9):5681-96.
3. Australian Product Information. Lozanoc (itraconazole) capsules. Available at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2014-PI-01749-1&d=202009031016933>. Accessed 15 March 2021.
4. Lindsay J, Mudge S, Thompson G. Effects of food and omeprazole on a novel formulation of super bioavailability itraconazole in healthy subjects. *Antimicrob Agents Chemother.* 2018;62(12):01723-18.
5. Sardana K, Mathachan SR. Super bioavailable itraconazole and its place and relevance in recalcitrant dermatophytosis: Revisiting skin levels of itraconazole and minimum inhibitory concentration data. *Indian Dermatol Online J.* 2021;12(1):1-5.
6. Rajagopalan M, Inamadar A, Mittal A, Miskeen AK, Srinivas CR, Sardana K, et al. Expert consensus on the management of dermatophytosis in India (ECTODERM India). *BMC Dermatol.* 2018;18:6.
7. Kandhari S, Prabhat P, Rengarajan M, Dogra S, Nayak C, Banerjee D, et al. Consensus on Management of Dermatophytosis and Vulvovaginal Infections in Non- Pregnant and Pregnant Females. *J Gynecol Obstetr.* 2020;8(6):195-210.
8. Mahajan H, Dhoot D, Barkate H. Clinical assessment of itraconazole in dermatophytosis (CLEAR Study): a retrospective evaluation. *Int J Sci Stud.* 2020;8(2):1-5.
9. Prentice AG, Glasmacher A. Making sense of itraconazole pharmacokinetics. *J Antimicrob Chemother.* 2005;56(1):17-22.
10. NIH U.S. National Library of Medicine. Fact sheet: Study comparing SUBA™-Itraconazole with SPORANOX® (itraconazole) in the treatment of onychomycosis. Available at: <https://clinicaltrials.gov/ct2/show/NCT00791219?term=suba+itraconazole&draw=2&rank=4>. Accessed on 21 February 2021.
11. Brouwers J, Geboers S, Mols R, Tack J, Augustijns P. Gastrointestinal behavior of itraconazole in humans - Part 1: Supersaturation from a solid dispersion and a cyclodextrin-based solution. *Int J Pharm.* 2017;525(1):211-7.
12. Label. Fact sheet: Sporanox®(Itraconazole) capsules. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/020083s048s049s050lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020083s048s049s050lbl.pdf). Accessed on 22 February 2021.
13. Abuhelwa AY, Mudge S, Hayes D, Upton RN, Foster DJR. Population in vitro-in vivo correlation model linking gastrointestinal transit time, pH, and pharmacokinetics: itraconazole as a model drug. *Pharm Res.* 2016;33(7):1782-94.
14. Cauwenbergh G, De Greef H, Heykants J, Woestenborghs R, Rooy PV, Haeverans K. Pharmacokinetic profile of orally itraconazole in human skin administered. *J Am Acad Dermatol.* 1988;18:263-8.
15. Verma S, Madhu R. The great Indian epidemic of superficial dermatophytosis: an appraisal. *Indian J Dermatol.* 2017;62(3):227-36.
16. Lindsay J, Sandaradura I, Wong K, Arthur C, Stevenson W, Kerridge I. Serum levels, safety and tolerability of new formulation SUBA-itraconazole prophylaxis in patients with haematological malignancy or undergoing allogeneic stem cell transplantation. *J Antimicrob Chemother.* 2017;72(12):3414-9.

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