



Original Research Article

Clinical assessment of Super bioavailable Itraconazole 50 mg in dermatophytosis (Clear 50)

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ABSTRACT

Introduction: Super bioavailable itraconazole (SBITZ) is a newer formulation of itraconazole which is recently launched in India. But there is no published clinical evidence of SBITZ in the management of dermatophytosis in Indian patients.

Materials and Methods: A Real world retrospective data analysis was conducted with 346 dermatologists across India to assess the response of Indian patients with dermatophytosis who were prescribed super bioavailable itraconazole 50 mg twice a day for 4 weeks.

Results: Out of 4625 patients' data, 2743 were included for final analysis. Mean age of patients was 36.17±12.05 years with male preponderance. Most of the patients were diagnosed as T. cruris. At the end of treatment, 51% of patients achieved complete clinical cure while 46% achieved clinical improvement (>50% symptom clearance) and 3% were labelled as clinical failure. About 70% patients achieved clearance in body surface area. Mean total symptom score (TSS) was reduced to 0.74±1.1 from 7.29±1.73 while mean BSA score was reduced from 1.96±0.83 to 0.38±0.65 (p<0.05). Similar type of improvements were seen in naïve, recurrent and chronic dermatophytosis patients. A total of 61 adverse effects (AE) were reported from 56 patients. All the AEs were mild to moderate in nature and did not require discontinuation of therapy.

Conclusion: Patients treated with super bioavailable itraconazole showed greater improvement in clearance of symptoms as well as lesions. Additionally, it showed significant improvement in naïve, recurrent and chronic patients enabling its placement in armamentarium of management of all types of dermatophytosis.

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1. Introduction

Dermatophytosis is one of the commonest dermatological disorder in India and itraconazole is commonly used systemic antifungal in its management because of higher sensitivity.¹ But itraconazole has some pharmacokinetic challenges like dependency on fatty food and gastric acid for its absorption and dissolution, less bioavailability, fluctuations in absorption, decreased absorption when co-administered with acid lowering agents, etc.² Super

bioavailable itraconazole (SBITZ) is a newer formulation of itraconazole which is approved across the world and has been recently launched in India. It is claimed to overcome all these challenges faced with conventional itraconazole.^{2–4} Moreover, all these benefits may be anticipated to improve the clinical outcomes as well as the patient compliance.⁵

However, there is no published clinical evidence of SBITZ in the management of dermatophytosis in Indian patients. Hence a real world study was conducted with dermatologists across India to assess the response of Indian patients with dermatophytosis who were prescribed super

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bioavailable itraconazole.

2. Materials and Methods

2.1. Patients and definitions

We performed a retrospective review of all patients presented in dermatology OPD and diagnosed with dermatophytosis during September 2020 and February 2021 at 346 centers. The diagnosis was identified according to physical signs and symptoms as per available medical records. Only those patients' records requiring systemic therapy as SBITZ 50 mg twice a day were included. Exclusion criteria included (a) Missing key data; (b) Medical records of those patients in whom treatment plan was changed during the treatment period of 4 weeks. This study was approved by the Ethics Committees (Suraksha Ethics Committee Reg. no. ECR/644/Inst/MH/2014/RR-17).

Naïve patients were defined as first episode of dermatophytosis with duration of <6 weeks. When the patient had suffered from dermatophytosis for ≥ 6 months, with or without recurrence, in spite of being adequately treated it was termed as chronic dermatophytosis. Re-occurrence of the disease (lesions) within 6 weeks after completion of the treatment was defined as recurrent dermatophytosis.⁶

2.2. Therapeutic methods

A total of 4625 patients' data was analyzed. All the patients were treated with SBITZ along with other commonly used topical anti-fungal.

2.3. Outcome assessments

The primary outcome was treatment response evaluated at the end of 4 week. Therapeutic outcome was classified into three levels: (a) Complete clinical cure – Resolution of all attributable clinical symptoms and physical findings associated with clinical diagnosis (Fungal score of 0); (b) Clinical improvement – Resolution of at least some clinical symptoms and physical findings associated with clinical diagnosis (Improvement in fungal score by >50%); (c) Clinical failure – Stable disease or progression of clinical symptoms and physical findings associated with clinical diagnosis (Improvement in fungal score by <50% or no change in score or deterioration of score). Improvement in body surface area (BSA) was also evaluated as an exploratory endpoint.

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. 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 i.e. 4 weeks. The details of the scoring

system are depicted in Table 1.

Table 1: Assessment scoring system

Parameter	Particulars	Score
Total Symptom score	Erythema Pruritus Scaling	Each symptom was rated from 0 to 3 0-absent 1-mild 2-moderate 3-severe
Lesion extent score	Body Surface area (BSA)	0-absent 1-mild/BSA 1-2% 2-moderate/BSA 3-10% 3-severe/BSA>10%

2.4. Assessment of adverse events

Data of adverse events were collected and timing and reasons were captured.

2.5. Statistical analysis

Baseline demographic and clinical characteristics are presented as percentages, mean with standard deviations (SD). Efficacy of treatment responses was estimated by percent change.

3. Results

3.1. Basic clinical characteristics

Out of 4625 patients' data, 2743 met the criteria and were included for final analysis. Out of 2743, 1600 were male (58.33%) and 1083 were females (39.48%) with average age of 36.17 ± 12.05 years. Out of 2743 patients, 33.6% of patients were diagnosed as tinea cruris, 28.1% as tinea corporis, 23.7% as tinea corporis et cruris, 8.9% as tinea faciei and 3.2% as multisite infection and 2.3% as other forms of dermatophytosis. All the patients have received some form of topical anti-fungal therapy along with SUBA itraconazole 50 mg. The demographics and baseline parameters of the study patients are listed in Table 2.

3.2. Treatment response

The primary treatment response outcome was evaluated at the end of 4 weeks following therapy with SBITZ. At the end of treatment, 1404/2743 patients (51%) achieved complete clinical cure, 1252 patients (46%) achieved clinical improvement and 87 patients (3%) were labelled as clinical failure. Response to treatment is shown in Figure 1.

In terms of BSA, data of 2337 patients was available. Of the 2337 patients, 70% (1634) achieved complete improvement in BSA while 30 % (703) had BSA score of 1-3 as shown in Figure 2.

Mean total symptom score (TSS) was reduced to 0.74 ± 1.1 from 7.29 ± 1.73 while mean BSA score was reduced from 1.96 ± 0.83 to 0.38 ± 0.65 . These improvements were statistically significant ($p < 0.05$) as shown in Figure 3.

Table 2: Baseline demographic characteristics

Characteristics	N	Percentage
N	2743	100
Male	1630	59.42
Female	1113	40.58
Age years (SD)	36.17±12.05	
Types of dermatophytosis		
T. Cruris	922	33.61
T. Corporis	773	28.18
T. Faciei	246	8.97
Corporis et cruris	650	23.70
Multisite dermatophytosis	89	3.24
Other dermatophytosis	63	2.30
Presentation		
Naïve	1314	47.90
Chronic	972	35.44
Recurrence	457	16.66
Mean TSS	7.29±1.73	
Mean BSA	1.96±0.83	

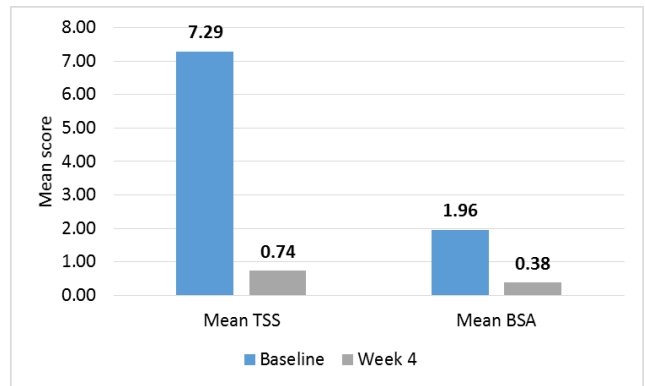


Fig. 3: Improvement in mean TSS and mean BSA scores

Similar improvements were seen on subgroup analysis. In Naïve patients, mean TSS was reduced to 0.64 ± 0.95 from 6.38 ± 1.79 . This improvement was statistically significant ($p < 0.05$). In chronic and recurrence group, mean TSS was reduced to 0.87 ± 1.17 & 1.23 ± 1.30 from 6.66 ± 1.66 & 7.09 ± 1.62 respectively ($p < 0.05$) as shown in Figure 4.

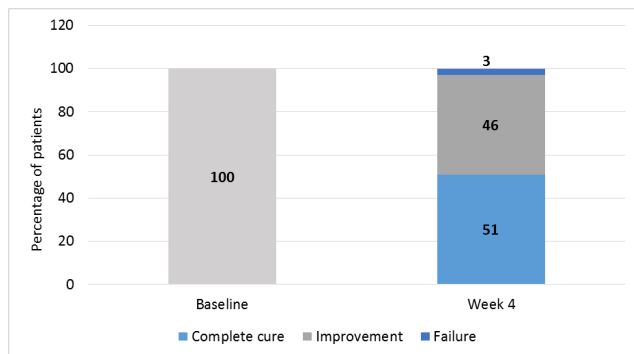


Fig. 1: Clinical response to treatment

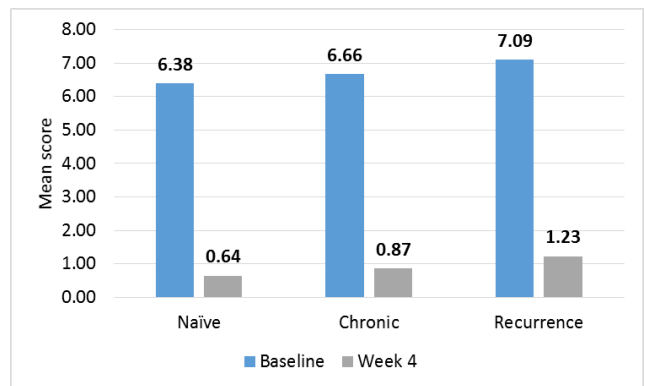


Fig. 4: Mean TSS improvement in naïve, chronic and recurrence patients

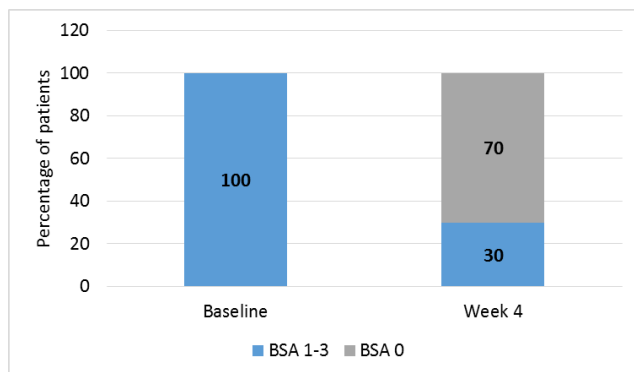


Fig. 2: Improvement in BSA

3.3. Adverse events

A total of 61 adverse effects (AE) were reported from 56 patients. Details of AE are depicted in Table 3. All the AEs were mild to moderate in nature and did not require discontinuation of therapy. In 5 patients, lack of efficacy was noted after 4 weeks of treatment.

4. Discussion

The goal of treatment in dermatophytosis is complete symptom control. Due to the change in clinical presentation, there has been change in management of dermatophytosis in terms of combination of systemic and oral antifungal drugs, etc.^{2,7} Though itraconazole is commonly prescribed systemic anti-fungal in combination therapy, its inherent

Table 3: Total no. of AE

Adverse effects	No. of AE
GI disturbances	24
Lack of efficacy	12
Headache	7
Nausea	6
Vomiting	3
Itching	4
Others	5

pharmacokinetic characteristics have been one of the key limitations and are frequently overlooked in clinical practice.⁸ SBITZ is devoid of all these pharmacokinetic issues. However, there is no published literature on its real world effectiveness and safety in dermatophytosis.

Results of this analysis reported here indicated that the use of SBITZ in the management of dermatophytosis appeared to be generally safe and well-tolerated, with few AE. In relation to efficacy, SBITZ continued to be associated with a decrease in TSS during treatment phase, as well as with an improvement in overall disease severity as measured by BSA. In the present study, we analyzed the response on two domain; clearance of symptoms and clearance of lesions. In first domain i.e. clearance of symptoms, 51% of the patients achieved complete clearance while 46% achieved improvement. Only 3% showed clinical failure. On the basis of clearance of lesions i.e. improvement in BSA, 70% of the patients achieved complete clearance of the lesions. Similar improvement was seen in reduction of mean TSS which was reduced to 0.74 ± 1.1 from 7.29 ± 1.73 . Additionally, mean BSA score was reduced from 1.96 ± 0.83 to 0.38 ± 0.65 . Both the improvements were statistically significant ($p < 0.05$). Moreover, SBITZ was found to be statistically significant in improvements of all types of dermatophytosis infections like naïve infection, recurrent and chronic infections.

These better cure rates in SBITZ can be attributed to its pharmacokinetic advantages as compared to conventional itraconazole. Itraconazole is dependent on gastric acid for its dissolution leading to erratic absorption and high intra and inter-subject variability. Secondly, site of absorption of itraconazole is small intestine, whereas in conventional form, less amount reaches the small intestine and hence the bioavailability of conventional itraconazole is only around 55%.^{9,10} Inversely, SBITZ is consistently released and available for absorption throughout the small intestine,^{2,11} ensuring increased bioavailability and less inter and intra-patient variability.¹² Moreover, as per one report, co-administration of proton pump inhibitor (PPI) does not hamper the absorption of SBITZ, rather increasing its absorption moderately.⁴

The safety profile demonstrated by SBITZ was favorable. Only 2% of the patients were reported with adverse effects (AE). In a report by Lindsay et al., only 11% of the

hematopoietic stem cell transplant patients reported AE with super bioavailable itraconazole which is not in concordance with our results.¹³ In our study, there were no serious AEs reported. All of the AEs were mild to moderate in severity, and no discontinuation was reported by any of the patients.

Patient adherence to therapy is known to be low in medical practice. Adherence can be compromised by many factors such as patient frustration due to a lack of clinical response or delayed response and by general dissatisfaction with the treatment experience or the occurrence of adverse events. In the current study, only 0.43% patients showed lack of response to treatment. But other factors like favorable tolerability profile, continued reduction in symptom score, and steady improvement in BSA in terms of extent of lesion suggested that use of an effective systemic agent like SBITZ might have had an impact on patient adherence to therapy. Improvement levels support this notion, considering that about 97% of all patients were in improvement category.

Due to its retrospective design, there were certain limitations in the present study which might have impacted the results of our study. These include prescription of topical antifungal to all the patients, non-availability of mycological examination report, non-comparison with conventional itraconazole and no data on relapse rates. Long term clinical trials are warranted to validate the results of the present study.

5. Conclusion

To the best of our knowledge, the present study is first real world evidence on clinical effectiveness and safety of super bioavailable itraconazole in the management of dermatophytosis in India. From the findings of the present study, patients treated with super bioavailable itraconazole showed greater improvement in clearance of symptoms as well as lesions. Additionally, it showed significant improvement in naïve, recurrent and chronic patients enabling its placement in armamentarium of management of all types of dermatophytosis. Thus, super bioavailable itraconazole can serve as a potent therapeutic choice to effectively tackle the current menace of dermatophytosis in India.

6. Acknowledgements

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7. Source of Funding

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8. Conflicts of Interest

There are no conflicts of interest.

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