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Original Article

Clinical Assessment of Itraconazole in Dermatophytosis (CLEAR Study): A Retrospective Evaluation

Harshal Mahajan[1], Dhiraj Dhoot[2], Hanmant Barkate[3]

[1]Assistant Manager, Medical Services, Glenmark Pharmaceuticals Ltd., Mumbai, Maharashtra, India, [2]Senior Manager, Medical Services, Glenmark Pharmaceuticals Ltd., Mumbai, Maharashtra, India, [3]Vice President, Medical Services, Glenmark Pharmaceuticals Ltd., Mumbai, Maharashtra, India

Abstract

Introduction: The recent prevalence of dermatophytosis in India ranges from 36.6 to 78.4%. Itraconazole is commonly used systemic antifungal to treat dermatophytosis.

Objective: The objective of the present study was to evaluate the effectiveness and safety of itraconazole given 100 mg twice daily for the treatment of dermatophytosis.

Materials and Methods: The present retrospective questionnaire-based survey was done, wherein dermatologists and general physicians were given survey questionnaire. Data analysis up to 4 weeks of treatment with itraconazole was considered for this study. Efficacy evaluation was considered as percentage of patients achieving clinical cure.

Results: A total of 150 doctors completed the survey involving 1100 patients. Out of 1100 patients, 341 patients (31%) responded well to topical therapy alone and were considered as clinically cured as per medical records. In remaining patients who did not respond well to topical monotherapy, itraconazole was found to be added in 652 patients as 100 mg twice daily for 4 weeks. Of these, 456 patients (70%) responded well to therapy in 4 weeks and were considered as clinically cured. Among the topical antifungals coprescribed with itraconazole, luliconazole was most commonly prescribed (49%). On comparison of clinical cure rates in patients who received topical antifungal monotherapy (31%) and itraconazole cotherapy (70%), it was found that itraconazole cotherapy was better and the difference between the two therapies was statistically significant (P = 0.001).

Conclusion: From the findings of the present analysis, clinical cure rates obtained with itraconazole were more than satisfactory. Although the standard duration of therapy ranges from 1 to 2 weeks, long-term treatment is warranted and that is with topical antifungals and other supportive measures.

Key words: Clinical cure, Dermatophytosis, Efficacy, Itraconazole

INTRODUCTION

Superficial fungal infections are caused by dermatophytes, non-dermatophytic molds, and commensal yeasts.[1] According to published literature, the global prevalence rate of superficial mycotic infection has been found to be 20–25%.[2] The recent prevalence of dermatophytosis in India ranges from 36.6 to 78.4%.[3] Hot and humid climate in the tropical and subtropical countries like India makes dermatophytosis a very common superficial fungal infection.[1,4]

Although usually painless and superficial, these fungi can behave in an invasive manner, causing deeper and disseminated infection and should not be neglected.[5] The lesions may become widespread and may have significant negative social, psychological, and occupational health effects and can compromise the quality of life significantly.[6]

Various antifungal agents, both topical and systemic, have been introduced into clinical practice for effectively treating

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Corresponding Author: Dr. Harshal Mahajan, Corporate Enclave, Medical Services, Glenmark Pharmaceuticals Ltd., Andheri (East), Mumbai, Maharashtra, India.

dermatophytic conditions. The commonly used drugs include azoles, allylamines, and griseofulvin.[7]

Itraconazole is orally administered triazole antifungal. It is commonly used systemic antifungal among the commercially available antifungal agents.[7] Itraconazole acts by inhibiting fungal 14-α-demethylase enzyme, which causes deficiency of ergosterol synthesis and accumulation of methyl precursors which ultimately leading to disruption of fungal cell membrane.[8] Efficacy of itraconazole against dermatophytic infections is very well proven.[9]

Intrinsic pharmacokinetic properties of itraconazole make its absorption erratic, with significant inter- and intra-individual differences in absorption and thus bioavailability, food and drug interactions, etc. Lately, quality of itraconazole has been topic of debate, which is considered to affect the bioavailability of the molecule.[10] Thus, it becomes imperative to test the clinical effectiveness and safety of itraconazole in dermatophytosis so that the technological advancement claims in manufacturing process actually translate into patient benefit, in the real-world experience.

To the best of our knowledge, the present study is first of its kind to analyze the effectiveness and safety of itraconazole in such a large number of patients with dermatophytosis.

MATERIALS AND METHODS

The present retrospective study was carried out at 150 centers across India using a pretested questionnaire. The questionnaire was designed to assess the effectiveness and safety of itraconazole 100 mg twice daily in the treatment of superficial fungal infections. The survey period was from July 2018 to July 2019. Patients with chronic dermatophytosis were not considered for this analysis. Dermatologists and general physicians involved in the management of superficial fungal infections with itraconazole 100 mg were identified through "SCRIP intelligence" database. Among these, 150 doctors who were maintaining the patients' clinical record were selected across four zones (East, South, West, and North) each by convenient sampling to have uniform representation of population across country.

Each doctor was given survey questionnaire booklet containing survey forms. These questionnaire booklets were collected after the end of survey period and data from all the patients were assessed to evaluate the effectiveness and safety of itraconazole 100 mg. Data analysis up to 4 weeks of treatment with itraconazole was considered for this study. Ethics committee approval was obtained before the start of the study.

Efficacy evaluation was considered as percentage of patients achieving clinical cure. All adverse events (AEs) were assessed for severity. Multiple occurrences of the same AE were only counted once for each patient. Statistical analysis was done for comparing cure rates of topical antifungal monotherapy and itraconazole-based combination antifungal therapy using Fisher's exact test. $P < 0.05$ was taken as statistically significant.

RESULTS

A total of 1100 survey forms were analyzed. Males (657) outnumbered females (443), with a male:female ratio of 1.48. On analyzing the age-wise distribution, it was found that all the age groups had almost equal number of patients, except in >60 years age group [Table 1].

On analyzing the diagnosis, it was found that tinea corporis was encountered in 33% of the patients followed by tinea cruris (29%) and tinea cruris et corporis (28%) [Figure 1].

Effectiveness Evaluation

Out of 1100 patients, 341 patients (31%) responded well to topical therapy alone and were considered as clinically cured as per medical records. In remaining patients who did not respond well to topical monotherapy, itraconazole was found to be added in 652 patients as 100 mg twice daily for 4 weeks. Of these, 456 patients (70%) responded well to therapy in 4 weeks and were considered as clinically cured. Among the topical antifungals coprescribed with itraconazole, luliconazole was most commonly prescribed (49%) [Table 2]. Evaluation of effectiveness parameters is mentioned in detail in Figure 2.

On analyzing clinical cure rates and demographic parameters in the patients, it was found that males and females had almost same clinical cure rates, while in age groups, clinical cure rates reduced with progression of age [Figure 3].

On comparison of clinical cure rates in patients who received topical antifungal monotherapy (31%) and itraconazole cotherapy (70%), it was found that

Table 1: Sex distribution in patients of the present study

Demographic parameter	*n* (%)
Sex	
Male	657 (60)
Female	443 (40)
Age (in years)	
21–40	401 (36)
41–60	388 (35)
>60	311 (29)

itraconazole cotherapy was better and the difference between the two therapies was statistically significant ($P = 0.001$) [Figure 4].

Safety Evaluation

Adverse effects were encountered in 71 patients (10.9%), of which gastrointestinal upset was most commonly encountered adverse effect, seen in 55 patients (8.4%) [Table 3].

DISCUSSION

Superficial dermatophytosis is no longer a simple, cutaneous fungal infection that is easily amenable to treatment. It has evolved into a chronic and recurrent, difficult-to-treat infection which affects the physical and the social well-being of the affected patients. Widespread resistance to conventional doses of antifungals with increasing clinical failure rates warrants the search for an effective first-line antifungal drug that brings about rapid clinical and mycological cure in dermatophytosis.[11]

Itraconazole is a triazole antifungal drug which is increasingly being used as a first-line drug for dermatophytosis, but it is being given for longer periods as compared to before.[12,13]

Table 2: Topical antifungal drugs prescribed monotherapy and in combination with itraconazole in the patients who were clinically cured

Molecule	Topical monotherapy (%)	Coprescribed with itraconazole (%)
Ciclopirox	43 (13)	78 (17)
Terbinafine	32 (9)	26 (6)
Luliconazole	120 (35)	221 (49)
Amorolfine	34 (10)	36 (8)
Sertaconazole	65 (19)	64 (13)
Eberconazole	47 (14)	31 (7)
Total	341	456

Table 3: Safety evaluation in patients of the present study who were prescribed with itraconazole

Category	Subcategory	*n* (%)
Adverse event	Gastrointestinal intolerance	55 (8.4%)
	Headache	11 (1.7%)
	Pedal edema	5 (0.8%)
	Total	71 (10.9%)
Patient adherence	Good	521 (80%)
	Average	72 (11%)
	Poor	59 (9%)

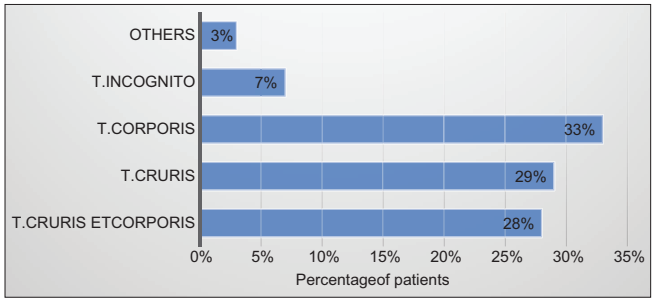

Figure 1: showing diagnosis in patients of the present study

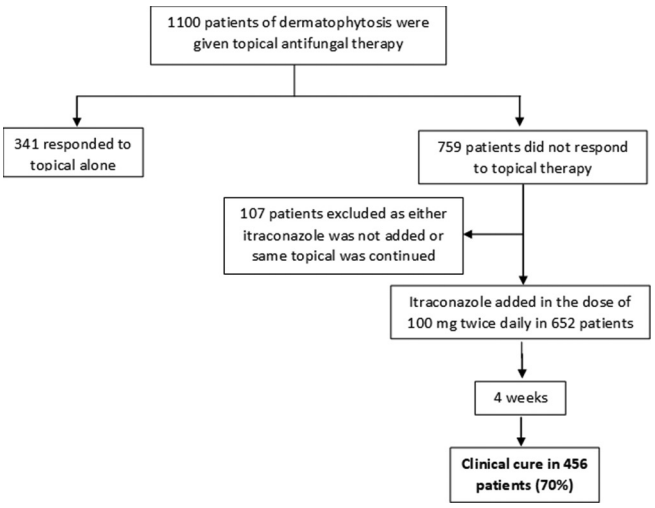

Figure 2: Effectiveness evaluation in patients of the present study

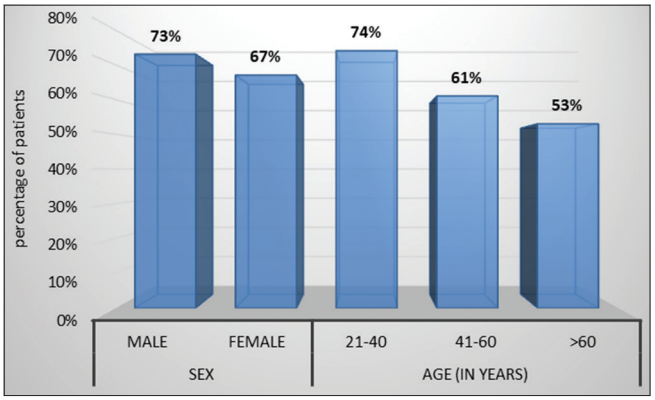

Figure 3: Age and sex wise distribution of clinical cure rates

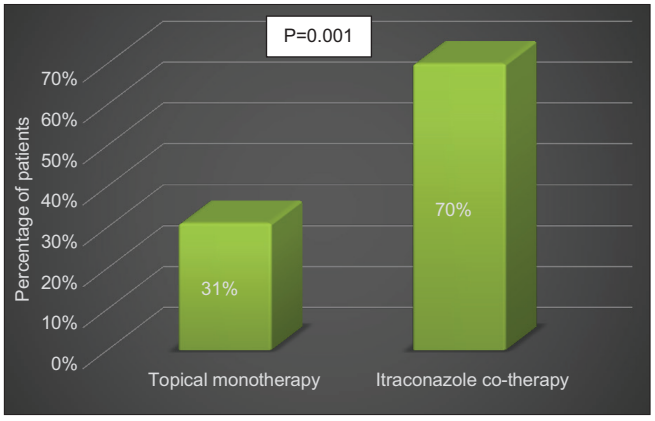

Figure 4: Comparison of clinical cure rates in patients who received topical monotherapy and itraconazole co-therapy

Conventional dose for itraconazole is 200 mg/day for 1–2 weeks, but in the current scenario in India, it is widely used beyond 4 weeks.

We conducted this survey to find out the effectiveness and safety of itraconazole in patients with dermatophytosis. In our analysis, it was found that itraconazole is being commonly used for all variants of dermatophytosis along with different drugs as combination. In recently published article by Ardeshna *et al.*, recalcitrant recurrent dermatophyte infections were successfully treated by a combination of itraconazole and isotretinoin.[12] In addition, role of anti-histamines, salicylic acid, and moisturizers has been suggested in consensus statement by Rajagopalan *et al.*[3]

The results of our analysis suggest that itraconazole achieves clinical cure in much shorter duration. In our analysis, 70% of the patients achieved clinical cure within 4 weeks of itraconazole-based combination therapy. This is similar to an earlier analysis in patients of dermatophytosis who also found itraconazole to have higher cure rates.[14]

Recently published literature cites the rise of trichophyton mentagrophytes, as the most common cause of dermatophytosis in India.[15] It is characterized by significant inflammatory lesions and is intrinsically less sensitive to conventional antifungal agents.[15] Among the commercially available systemic antifungal drugs, itraconazole is the commonly prescribed drug for the treatment of dermatophytosis.[7] One of the reasons for such upper hand of itraconazole in the class of systemic antifungals might be attributed to the fact that it has found to have better MIC values, as compared to other systemic antifungal agents, in a clinical analysis.[16]

Itraconazole can cause gastric upset, headache, taste alteration, and jaundice, and rarely, it can cause hypokalemia, torsade de pointes, and heart failure.[13] However, in our analysis, side effects such as gastrointestinal upset, headache, and pedal edema were seen.

Most of the dosage forms of systemic antifungal drugs mentioned in dermatology textbooks, however, have been found to be non-effective in the therapy of the dermatophytosis in India. Duration of treatment mentioned in the Western literature is not applicable to treat dermatophytosis in a tropical country like India.[15] Even in our analysis, only 70% of the patients achieved clinical cure within 4 weeks although all patients were prescribed topical antifungal.

In the current scenario, combination therapy is the need of hour in the management of dermatophytosis. Topical antifungal drugs are preferred with systemic since they provide high concentration of the drug at the site of action. Different classes of topical and systemic AFAs may be combined. Although eberconazole and sertaconazole have the advantage of anti-inflammatory activity,[5,17] in our analysis, luliconazole was the most commonly used topical antifungal.

It is a general convention that two drugs can be synergistic when they act through different mechanisms of actions to produce enhanced common end effect.[18] Still, some researchers believe that drug delivery of both the drugs to their site of action is more important than mechanism of action to achieve the synergistic effect.[19] Systemic along with topical therapy will ensure their optimal concentration in the stratum corneum along with deeper layers of skin for effective antifungal action. These can be the attributable factor for enhanced cure rates observed in the present study with itraconazole and concomitant luliconazole therapy.

This has been corroborated by the findings of the present study, i.e., satisfactory clinical cure rates obtained in patients with concomitant topical luliconazole therapy. It has also been cited in the literature that combination therapy of systemic and topical antifungal drugs should be used in the treatment of recalcitrant dermatophytosis.[20]

This analysis has certain limitations. Due to the retrospective design, the possibility of selection bias cannot be ruled out. Treatment with other antifungals such as topical agents, anti-histamines, and other drugs may have impacted the final outcome. Long-term combination and comparative studies to address the shortcomings of the present analysis are warranted.

CONCLUSION

From the findings of the present analysis, clinical cure rates obtained with itraconazole were more than satisfactory. Although the standard duration of therapy ranges from 1 to 2 weeks, long-term treatment is warranted and that is with topical antifungals and other supportive measures. Consequently, with regard to the treatment of dermatophytosis, counseling is indeed the cornerstone of therapy. Systemic treatment provided in a systematic manner, based on the clinical response seen in patients, will definitely yield a good therapeutic outcome. Furthermore, the duration of treatment needs to be individualized, with complete cure considered as the end point.

REFERENCES

1. Gupta C, Tripathi K, Tiwari S, Rathore Y, Nema S, Dhanvijay AG. Current trends of clinicomycological profile of dermatophytosis in Central India.

IOSR J Dent Med Sci 2014;13:23-6.
2. Havlickova B, Czaika V, Friedrich M. Epidemiological trends in skin mycoses worldwide. Mycoses 2008;52:2-15.
3. 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.
4. Falahati M, Akhlaghi L, Lari AR, Alaghehbandan R. Epidemiology of dermatophytoses in an area South of Tehran, Iran. Mycopathologia 2003;156:279-87.
5. Bristow I, Spruce M. Fungal foot infection, cellulitis and diabetes: A review. Diabet Med 2009;26:548-51.
6. Jerajani H, Janaki C, Kumar S, Phiske M. Comparative assessment of the efficacy and safety of sertaconazole (2%) cream versus terbinafine cream (1%) versus luliconazole (1%) cream in patients with dermatophytoses: A pilot study. Indian J Dermatol 2013;58:34-8.
7. Sahoo A, Mahajan R. Management of tinea corporis, tinea cruris, and tinea pedis: A comprehensive review. Indian Dermatol Online J 2016;7:77-86.
8. Lestner J, Hope W. Itraconazole: An update on pharmacology and clinical use for treatment of invasive and allergic fungal infections. Expert Opin Drug Metab Toxicol 2013;9:911-26.
9. Bhatia A, Kanish B, Badyal DK, Kate P, Choudhary S. Efficacy of oral terbinafine versus itraconazole in treatment of dermatophytic infection of skin-a prospective, randomized comparative study. Indian J Pharmacol 2019;51:116-9.
10. 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;9:426-31.
11. Rengaswamy M, Chellam J, Ganapati S. Systemic therapy of dermatophytosis: Practical and systematic approach. Clin Dermatol Rev 2017;1:S19-23.
12. Ardeshna K, Rohatgi S, Jerajani H. Successful treatment of recurrent dermatophytosis with isotretinoin and itraconazole. Indian J Dermatol Venereol Leprol 2016;82:579-82.
13. Donckar P, Pande S, Richarz U, Garodia N. Itraconazole: What clinicians should know? Indian J Drugs Dermatol 2017;3:4-10.
14. Shakya N, Jha M, Dangol A, Shakya S, Shah A. Efficacy of itraconazole versus terbinafine for the treatment of tinea cruris. Med J Shree Birendra Hosp 2012;11:24-6.
15. Verma S, Madhu R. The great Indian epidemic of superficial dermatophytosis: An appraisal. Indian J Dermatol 2017;62:227-36.
16. Dabas Y, Xess I, Singh G, Pandey M, Meena S. Molecular identification and antifungal susceptibility patterns of clinical dermatophytes following CLSI and EUCAST guidelines. J Fungi (Basel) 2017;3:17.
17. Moodahadu-Bangera LS, Martis J, Mittal R, Krishnankutty B, Kumar N, Bellary S, *et al*. Eberconazole--pharmacological and clinical review. Indian J Dermatol Venereol Leprol 2012;78:217-22.
18. Tallarida R. Drug synergism: Its detection and applications. J Pharmacol Exp Ther 2001;298:865-72.
19. Vakil V, Trappe W. Drug combinations: Mathematical modeling and networking methods. Pharmaceutics 2019;11:208.
20. Hay R. Therapy of skin, hair and nail fungal infections. J Fungi (Basel) 2018;4:99.

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