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ITRACONAZOLE 200MG DAILY FOR 16 WEEKS FOR TREATMENT OF CHRONIC DERMATOPHYTOSIS IN DIFFERENT LOCATION IN THE BODY: OPEN LABELED CLINICAL TRIAL

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ABSTRACT

A brief mono- antifungal regimen is no longer adequate to successfully clear fungus and stop it rising again. With the exponential rise in refractory dermatophytoses, this demand keeps growing. The study's objective was to assess the efficacy of long course oral itraconazole monotherapy in treating chronic dermatophytosis. This is an open-labeled trial performed on 85 patients with chronic dermatophytosis in different parts of the body between June 2023 to July 2024. For sixteen weeks, patients received 200mg of itraconazole daily. Response was assessed clinically using clinic outcome score. Results reveal the mild itch persist in 5 (0.07%) of patients and moderate itch in 1 (0.01%). Erythema had vanished completely in 76 (90.54%), mild in 5 (0.07%) and moderate in 2 (0.03%). only one patient shows active border. Extent of lesions dropped significantly from 2.25 \pm 0.67%. to 0.01 \pm 0.003%. The overall clinical score dramatically decreases from 24.80 \pm 6.27 to 0.04 \pm 0.20. The clinical outcome score was classified as cure in 68 (91.89%), partial cure in 6 (0.08%), and none was considered failure. In conclusion, itraconazole in a dose of 200mg daily for as long as 16 weeks is an effective regimen in eradicating dermatophytosis in different part of the body.

KEYWORDS: Chronic, Dermatophytosis, Itraconazole, Monotherapy. Long-term therapy.

INTRODUCTION

Cutaneous fungal infection "dermatophytosis" is a common dermatologic problem. It severely compromises one's social, mental, and professional well-being.^[1] Recent Research indicates that the frequency of dermatophytosis in the general population is rising to almost affect 25% of the world's population (-). Multiple factors like global warming, great people displace, socioeconomic difficulties, and increasing pet contact make the current epidemic dermatophytosis widely distributed all over the globe (-). Furthermore, mycoses that are exceedingly hard to cure initially arose in South Asian nations before rapidly propagating to other nations, including Iraq. This make simple treatable superficial infection turned into widespread, persistent, and resistant atypical mycoses (-).

Itraconazole is the most widely used medication among systemic antifungals for the treatment of dermatophytosis. Itraconazole is prescribed in textbooks at a dose of 100 mg daily for two to four weeks. However, using it at standard dosages and durations is increasingly associated with treatment failure due to partial response, relapses and possibility of development

of drug resistance. At the same time, using higher doses carries the risk of inducing adverse effects.

Multi-recent publication concludes that this regimen is no longer effective in clear dermatomycosis. These findings imply that the new guideline needs to be amended to face this epidemic by selecting sufficient dose with enough duration to completely eradicate fungus and prevent it from recure again.^[4]

Recently published study by Khurana etal, 2022 conclude that duration of dermatophytosis treatment is positively correlated to drug efficacy. They found duration to achieve a cure vary from 2 to 20 weeks. In the era of recalcitrant dermatophytosis, a paucity of data about adequate duration and appropriate dose of itraconazole to manage tinea, prompt us to conduct the current investigation aiming to assess the efficacy of intermediate dose (200mg) oral itraconazole in a long course (16 weeks) as monotherapy for treating chronic dermatophytosis at different parts of the body.

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PATIENTS AND METHODS

This open, non-blinded trial involved eighty-five patients with chronic dermatophytosis of different parts of the body who attend dermatology outpatient clinic at Mosul General Hospital in Mosul, Iraq, between June 2023 to July 2024. Ethical clearance of the current investigation was approved by the Ninevah Health Directorate's Research Ethics Committee. Additionally, the patients who are eligibles for study were recruited after signing an informed permission form.

Inclusion criteria 1. All naive cases of dermatophytosis. 2. Positive cases with fungal hyphae on potassium hydroxide (KOH) test. 3. Patients aged 18 to 60 years. 4. Previously treated cases but off treatment from topical/ systemic antifungal since last 4 weeks. Exclusion criteria 1. Pregnant or lactating patient. 2. Patients with a history of diabetes or immunosuppression. 3. Patients taking drugs that interfere with itraconazole metabolism. 4. History of hepatic and renal impairment. 5. Known cases of congestive heart failure.

Sign and symptoms for ≥ 6 months were used to identify chronic dermatophytosis. Adult patients who used antifungal in the last month, pregnant or lactating mother were excluded from the study.

Patients dispensed 200mg of itraconazole daily for 16 weeks. Assessment of dermatophytosis was performed at the start and finish of the trial. The severity of mycoses was assessed using clinical symptom measures. The severity of dermatophytosis, pruritus, erythema, and active border are among the factors that determine the ratings. A four-point rating system is used for each clinic's symptoms: "0" denotes no symptoms, "1" mild symptoms, "2" moderate symptoms, and "3" severe symptoms. To ascertain the degree of the lesion, hand units were used, with one hand unit equal to 1% BSA. The total (BSA) times the sum of the values for erythema, pruritus, and actively elevated borders yields the final clinical symptom score. Clinical outcomes were classified as "partial cured" if less than 50% of the baseline score improved, "cured" if all lesions cleared completely, and "failure" if there was no response or even an increase following the commencement of antifungal medications.

Statistical analysis

Different descriptive statistical methods (percentages, mean and standard deviation) were used to summarize the demographic and clinical symptom scores at baseline and at the end of the current investigation. The efficacy of treatment responses was assessed by calculating percentage of changes in the clinical symptom score. A two-proportion Z-test was calculated to assess significant difference in each clinical symptom score before and after treatment. The significance of mean reduction of summed total clinical score at the end of trial was assessed by paired t-test. The Cohen *d* effect was used to estimate effect size of treatment course. A p-value <0.05 was considered significant. All the data was processed and analyzed by statistical package SPSS.

RESULTS

At the completion of the study, eleven patients drop out from the trial. The mean age of the patients is 31.02 ± 5.24 years, with a range of 24 to 43 years. There were 46 (54.11%) males and 39 (45.88%) females in the 1.18:1 male-to-female ratio of the sample under study. With a range of 6 to 15 months, the mean duration of dematophytosis \pm standard deviation was 8.05 ± 1.75 months.

The percentage of body surface area involved ranges from 2% to 7% with average and standard deviation of $2.25 \pm 0.67\%$. The clinical symptom score ranges from 14 to 35, with a mean of 24.80 ± 6.27 . Table 1 reveals the changes in clinical symptom scores after sixteen weeks of using itraconazole in dose of 200 mg daily.

The changes in the clinical symptom scores before and after treatment were demonstrated at table 1 and as follows: Five patient (0.07%) complain from mild itch at the end of the study and 1 (0.01%) suffered from moderate itch while the remaining were symptom free; The erythema was vanish completely in 76 (90.54%), mild in 5 (0.07%) and moderate in 2 (0.03%); only one patient show active border; lastly, the extent of lesions dropped significantly from 2.25 \pm 0.67%. to 0.01 \pm 0.003%. The overall clinical score dramatically decreases from 24.80 \pm 6.27 to 0.04 \pm 0.20. All the changes were statistically highly significant (p <0.0001). At the end of the study, clinical outcome score was classified as cure in 68 (91.89%), partial cure in 6 (0.08%), and none was considered failure (see fig 1-2).

 Table 1: Comparison of changes in clinical characteristics between after monotherapy of 200mg Itraconazole daily for 16 weeks.

Characteristics		Baseline N=85	End of trial N=74	P-value
Extent of lesion (BSA)		$2.25 \pm 0.67\%$.	$0.01 \pm 0.003\%$.	0.0001
Itching, No. (%)				0.0001
	None	-	68 (91.89%)	
	Mild	28 (32.94%)	5 (0.07%)	
	Moderate	48 (56.47%)	1 (0.01%)	
	Severe	13 (15.29%)	-	
Erythema, No. (%)				0.0001
	None	-	67 (90.54%)	

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	Mild	27 (31.76%)	5 (0.07%)	
	Moderate	36 (42.35%)	2 (0.03%)	
	Severe	22 (25.88%)	-	
Active border, No.	(%)			0.0001
	None		73 (98.64%)	
	Mild	15 (17.64%)	1 (0.01%)	
	Moderate	43 (50.58%)	-	
	Severe	27 (31.76%)	-	
Clinical symptom score		24.80±6.27	0.04 ± 0.20	0.0001



Fig. 1: Different patients of tinea corporis before (a) and after treatment (b) with itraconazole 200mg daily for 16 weeks.

DISCUSSION

The slight male preponderance in the current study (male: female ratio = 1.18:1) is close to that reported by Lachure etal (1.3:1), but slightly lower than reported by

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Verma, 2021 (male-to-female ratio of less than 2). The higher prevalence of tinea in males could be explained by factors like increased indulgence in outdoor activities. This exposes them to environmental conditions favorable

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for the growth of fungus. [Singh, 2020] The average age of patients was in their early thirties. This is consistent with the data provided by Janardan et al. This finding may be because the patients in this age group are members of the working class and are more likely to be exposed to humidity and close contact at work.

The early relapse and chronic course of current dermatomycoses make antifungals in standard doses and duration no more effective in providing complete cure (Singh, 2020). The high cure rate of itraconazole compared to higher failure rate of other systemic antifungal drugs make it drug of choice (Singh, 2020) However, regimen needs to be revised again. Contrary to earlier recommendations of using small dose in a brief course, now a day, is enough to treat superficial dermatophytosis, nowadays, failure to treat early relapse become more common scenario. An inappropriate dose or duration of itraconazole may increase the chance of developing drug resistance. Increasing number of dermatologist now a day start to select a dose of 200 mg itraconazole empirically to face the current increase number of dermatophytosis (Rengasamy). A recently published study by Khurana etal, 2022 of using itraconazole for treating naïve dermatophytosis in three different doses found cure rate as follows: The cure rates were (82%) in the 100 mg group, (93.2%) in the 200 mg group and (100%) in the 400 mg group. Although 400mg gives a slightly higher cure rate compared to 200mg, this was on expense of cost and side effects (Khurana). The current study show a consistent cure rate (91.89%).

Khurana study also show that duration of treatment is positively correlated to drug efficacy. The duration to achieve a cure vary from 2 to 20 weeks. Early secession of treatment may end up in 47.4% relapse rate. The relapse was attributed partially to failure to clear fungi from difficult to treat site like the buttock or due organism virulence factor. This enforce dermatologist enforce to prolong duration to minimize this risk.

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