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# EFFICACY OF ITRACONAZOLE VS ITRACONAZOLE PLUS ISOTRETINOIN IN TREATMENT OF CHRONIC RECURRENT TINEA

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## ABSTRACT

**Background:** Dermatophytes are the most common skin infections and are increasingly seen in daily clinical practice, with unusual presentations, running a chronic recurrent course and seems to be more resistant to systemic and topical conventional treatment, necessitating an effective adjuvant drug that reduces the possibility of recurrence and resistance in combination with systemic antifungals. **Aim:** This study aimed to assess and compare efficacy and safety of itraconazole vs itraconazole plus isotretinoin in treatment of chronic recurrent tinea. **Materials and methods:** This was a randomized controlled comparative study was conducted, included 40 patients with chronic recurrent tinea corporis or tinea cruris, were randomly divided into two treatment groups: 20 patients treated with itraconazole plus isotretinoin and 20 patients treated with itraconazole alone, for 4 weeks, with monthly follow- up for 6 months after treatment to assess recurrence. Side effects of both treatments were also assessed. **Results:** After 4 weeks of treatment, complete cure was recorded in 90% of patients in the first group and 70% of patients in the second group with a statistically significant difference (p: 0.01). During the follow- up after treatment, recurrence was recorded in 11,1% of patients in the first group and 42,9% of patients in the second group with a statistically significant difference (p:0.01). Side effects were more in the second group and the most common was skin and mucosal dryness. **Conclusion:** Combination therapy with oral itraconazole and isotretinoin is efficient and safe for the treatment of chronic recurrent tinea, as it induces earlier complete cure with a significant reduction of recurrence rate.

**KEYWORDS:** Dermatophytosis, itraconazole, isotretinoin.

## INTRODUCTION

Dermatophytosis is a superficial fungal infection caused by three genera of fungi that have the ability to invade and multiply within keratinized tissues (hair, skin and nails).[27] Dermatophytosis is one of the most common skin diseases affecting millions of people worldwide,[27] and are more in areas with hot and humid climatic conditions.[26] Itraconazole is an antifungal medication that works by blocking the cytochrome p450- dependent enzyme, thereby affecting the demethylation of lanosterol to ergosterol.[26] In daily practice, an increasing number of dermatophytosis are seen with an unusual presentation (widespread, affecting more than one family member, severely itchy and being resistant to conventional therapy), chronic, recurrent course that recurs within a few weeks after completion of treatment course with topical and systemic antifungal agents, which necessitate adding an adjuvant treatment for these challenging cases.[27] Retinoids are thought to cause enhanced desquamation of the epidermis, resulting in fast keratinocyte sloughing and elimination of fungal spores, lowering the fungal burden. This study was therefore conducted to compare the effectiveness of oral itraconazole and oral itraconazole combined with oral isotretinoin for the treatment of resistant and recurrent tinea.[26]

## MATERIALS AND METHODS

This prospective, randomized comparative study was conducted on 40 patients aged 13 to 58 years who attended the Dermatology Clinic of Latakia University Hospital during the period from July 2023 to July 2024 The patients were categorized into two groups.

1. The first group: included 20 patients treated with oral itraconazol (200 mg daily dose) combined with oral isotretinoin (20 mg daily dose) for four weeks.
2. The second group: included 20 patients treated with oral itraconazole (200mg daily dose) for four weeks.

Patients were accepted after providing a detailed explanation of the treatment's protocol and obtaining informed consent from them. Upon admission, patients underwent a clinical evaluation included taking a detailed medical history, documenting personal data,

conducting a precise clinical examination and evaluating the following clinical signs: erythema, itching and scaling. Lesions were photographed and then direct microscopic examination was performed as follows: The tissue was scraped off with a scraper, the edge of a glass slide or a brush, then the tissue was placed in the center of the glass slide and covered with a coverslip, then potassium hydroxide at a concentration of 10% was placed on the edge of the coverslip and entered under it using capillary action. The sample was gently heated, the excess KOH was blotted off with a tissue, and then viewed under microscope at 10 and 40 magnifications.

**Inclusion criteria:** Patients who have tinea corporis and tinea cruris that haven't been treated for two weeks and meet all of the following criteria.
Resistant tinea: that lasts 6 months or more
Recurring tinea : recurrence within several weeks after the end of the full course of treatment.

**Exclusion Criteria**
Pregnant and lactating women, patients with diabetes, patients with chronic liver and renal diseases, patients with ischaemic heart diseases, patients with a history of drug allergy, patients with immune disorders or on chronic immunosuppressive therapy, patients with hyperlipidemia, elderly people (60 years or more).

All patients were investigated for liver function test (LFT), renal function test (RFT), lipid profile, fasting blood sugar (FBS) and complete blood count (CBC) at baseline and two weeks later.

Patients were followed and assessed at baseline, after two weeks and after four weeks. Severity of clinical lesions was assessed depending on three parameters: erythema, pruritus and scales. As the following score: 0= no, 1 = mild, 2 = moderate, 3 = severe. The response was assessed accordingly as: A - healing, B - noticeable improvement, C - remaining lesions (more than 50%), D - no change, E - got worse. KOH test was performed at baseline and at the end of treatment. Patients were considered cured in the absence of erythema, pruritus and scales with KOH negative. Side effects were assessed. Patients were followed - up for 6 months after the end of treatment to assess recurrence.

**Statistical Analysis**
The chi-square or Fisher exact test was used to study the relationships between categorical variables. The Independent T student test was employed to compare the mean differences between the two groups. All variables were tested using univariate regression, and the statistically significant variables were then entered into a multivariate analysis equation. Results were considered significant if the p-value was less than 5%. IBM SPSS Statistics software was used to compute the statistical parameters and analyze the results.

**RESULTS**
A total of 40 participants were included in the study. Among them, 17 (42.5%) were males and 23 (57.7%) were females. The mean age of study participants was $13.4 \pm 32.82$ years with minimum age of 13 and maximum age of 58 years. 50% of participants were less than 30 years old. Tinea corporis and cruris was present in majority of participants (75%) followed by tinea corporis (17.5%) and tinea cruris (7.5%). The mean duration of the disease was $15.9 \pm 16.12$ months with minimum duration of 6 and maximum duration of of 84 months. Both groups were comparable in demographic characteristics (table 1). There was a gradual reduction in erythema in both groups as shown in (table2). However, there was greater reduction in the first group (97.07%) than the second group (85.71%)and the difference was statistically significant (p:0.0001). There was gradual reduction in pruritus in both groups as shown in (table 3), but the reduction was more in the first group (96.61%) than the second group (91.07%) and the difference was statistically significant (p:0.0001). Similarly, there was gradual reduction in scales in both groups as shown in (table 4), the reduction was slightly more in the first group (96.96%) than the second group (93.33%) and the difference was statistically significant (p:0.0001). Complete cure response was recorded in 18 patients (90%) in the first group, while in the second group, complete cure response was recorded in 14 (70%) patients , a statistically significant treatment response was observed between both the groups (p:0.01), On subsequent follow - up visits for six months, 2/18 (11.1%) patients in the first group and 6/14 (42.5%) patients in the second group had relapses (p:0.01) (table5).

Side effects were more in the first group, Mucous membranes dryness and low mood were recorded only in the first group, while gastrointestinal discomfort was recorded in 5 (25%) patients in the first group and 3 (15%) patients in the second group (table 6). No patient in either group needed treatment discontinuation due to hematologic or biochemical abnormalities.

**Table 1: Comparison of demographic characteristics.**

| characteristics | First group | Second group | p-value |
|---|---|---|---|
| Gender<br>Male<br>Female | <br>8(40%)<br>12(60%) | <br>9(45%)<br>11(55%) | 0.7 |
| Age(years) | $37.25 \pm 13.3$ | $33.65 \pm 11.3$ | 0.3 |
| Duration in months | 12[6-84] | 10.5[624] | 0.06 |

| Table 2: Comparison of erythema. | | |
|---|---|---|
| **Time** | **First group** | **Second group** |
| Baseline | 2.55±0.6 | 2.10±0.5 |
| End of 2nd week | 1.15±0.3 | 1.15±0.3 |
| End of 4th week | 0.10±0.3 | 0.30±0.4 |
| p-value | 0.0001 | 0.0001 |

| Table 3: Comparison of pruritus. | | |
|---|---|---|
| **Time** | **First group** | **Second group** |
| Baseline | 2.95±0.2 | 2.80±0.4 |
| End of 2nd week | 0.65±0.5 | 1.15±0.3 |
| End of 4th week | 0.10±0.3 | 0.25±0.4 |
| p-value | 0.0001 | 0.0001 |

| Table 4: Comparison of scales. | | |
|---|---|---|
| **Time** | **First group** | **Second group** |
| Baseline | 1.65±0.8 | 1.50±0.6 |
| End of 2nd week | 0.45±0.5 | 0.50±0.5 |
| End of 4th week | 0.05±0.2 | 0.10±0.3 |
| p-value | 0.0001 | 0.0001 |

| Table 5: Comparison of cure response and relapse. | | | |
|---|---|---|---|
| **Response of cure** | **First group** | **Second group** | **p-value** |
| A | 18(90%) | 14(70%) | 0.01 |
| B | 2(10%) | 6(30%) | |
| **Relapse** | 2/18(11.1%) | 6/14(42.5%) | 0.01 |

| Table 6: Comparison of side effects. | | | |
|---|---|---|---|
| **Side effects** | **First group** | **Second group** | **p-value** |
| No side effects | 5(25%) | 17(85%) | 0.0001 |
| Mucous membranes dryness | 14(70%) | 0(0%) | 0.0001 |
| Gastrointestinal discomfort | 5(25%) | 3(15%) | 0.4 |
| Low mood | 1(5%) | 0(0%) | 0.3 |

## DISCUSSION

A fungal skin infection increases all over the globe. A warmer and humid environment, unrestricted usage of topical corticosteroid – based combinations, increasing usage broad- spectrum antibiotics and the rise of antifungal drug resistance are all major causes. Previously, normal dosages and durations of topical or oral antifungal medications were sufficient to treat these infections, but they are now becoming more difficult to cure. Relapses after a seemingly complete recovery are also not unusual. A combined treatment with oral isotretinoin and oral itraconazole was shown to be efficacious in the management of chronic recurrent tinea and persistent dermatophytosis.[26]

Most of the included patients were young, which may be due to excessive sweating and wearing tight occluded underwears and trousers for long periods. In our study, complete cure response was recorded in 90% of patients in the first goup and 70% of patients in the second group. Relapse was recorded in 2/18 (11.1%) patients in the first group and 6/14 (42.9%) in the second group.

Isotretinoin modulates epidermal proliferation and differentiation and regulates hyperproliferative epidermis by increasing epidermis cell turnover, this result in clearance and sloughing of growing dermatophytes.[26] Moreover, dermatophytes proliferate in acidic ph, Isotretinoin alter skin ph towards alkalinity thereby inhibiting its growth.[24]

Side effects were more in the first group, most of which were dryness of the mucous membranes and low mood, this is mainly due to the association of these effects with isotretinoin.

Muhammed et al[25] performed a study on 40 patients with itraconazole in combination with isotretinoin and recorded complete cure in 90% of patients. Relapse was recorded in 15% of patients.

Naseemullah et al[26] conducted a study with itraconazole alone and in combination with isotretinoin. In which, complete cure was higher in combination group compared to itraconazole group.

Dooha et al[27] showed that complete cure was higher in combination group (97.5%) than itraconazole group (53.7%). Relapse was lower in combination group (12.8%) compared to itraconazole group (68.1%).

In 2023, Divya et al[24] reported in a randomized clinical trial higher complete cure and lower relapse in combination group with more side effects (mainly lip cheilitis, skin dryness, hepatic abnormalities and dyslipidaemia).

**Limitations**

The study was limited by small sample size and absence of fungal culture.

## CONCLUSIONS

Our study concluded that combination therapy with oral itraconazole and isotretinoin is efficient and safe for the treatment of chronic tinea, it helps in achieving faster cure with fewer relapses. Our study recommends conducting study based on large sample size and assess the effectiveness and safety of combining isotretinoin with other available systemic antifungals.

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