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Issue Highlights

- Alterations of the Gut Microbiota in Moderate to Severe Psoriasis Patients
- sICAM-1: A novel Potential Biomarker in Severe Acne Vulgaris
- Association between Paediatric Lichen Planus and Dyslipidemia
- Association of Moderate–Severe Atopic Dermatitis with Dental Anomalies
- Eponyms in Trichoscopy
- Congenital Varicella Syndrome with Isolated Limb Hypoplasia and Scarring
- Patterns and Trends of Tribal Leprosy
- Assessment of Oxidative/Nitrosative Stress and Raftlin in Vitiligo
- Efficacy and Safety of 30% Supramolecular Salicylic Acid Peeling for Papulopustular Rosacea
- Oral lesions in COVID-19
- Effective Treatment of Prurigo Nodularis with Dupilumab

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ORIGINAL ARTICLE

Efficacy and Safety of Adding Low-Dose Isotretinoin to Itraconazole in the Treatment of Chronic Recurrent Dermatophytosis among Sample of Iraqi Patients: An Open-Labelled Therapeutic Clinical Comparative Study

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Abstract

Background: An increasing number of dermatophytosis is seen now in daily clinical practice, with unusual presentations, running a chronic recurrent course and seems to be more resistant to systemic and topical conventional treatments, which necessitate the use of other treatment options that help to cure these challenging clinical conditions such as isotretinoin along with itraconazole. **Objectives and Aim:** This is a prospective randomised open-label therapeutic comparative clinical trial to assess the efficacy and safety of low-dose isotretinoin along with itraconazole to treat and reduce the recurrence of this distressing chronic recurrent dermatophytosis. **Methods:** Eighty-one patients with chronic recurrent dermatophytosis with positive mycological examination were recruited, all of them received itraconazole for 7 days per month for 2 consecutive months duration; half of them were randomly chosen to receive low-dose isotretinoin every other day for 2 months in addition to itraconazole. All patients were followed up at monthly intervals for 6 months. **Results:** The patients who received isotretinoin along with itraconazole showed earlier and complete clearance in 97.5% with a significantly low recurrence rate (12.8%) in comparison with those who received itraconazole alone where the cure rate was relatively slower reported in 53.7% of the patients with a relapse rate of 68.1% with no significant side effects. **Conclusion:** Low-dose isotretinoin with itraconazole seems to be safe, effective and promising choice in the treatment of chronic recurrent dermatophytosis as it induced earlier complete cure with a significant reduction of recurrence rate.

Key Words: *Chronic, dermatophytosis, isotretinoin, itraconazole*

Introduction

Dermatophytosis is superficial fungal infection caused by three genera of fungi that have the unique ability to invade and multiply within keratinised tissues (hair, skin and nails).[1] Dermatophytosis is one of the most common skin diseases affecting millions of people worldwide. In daily clinical 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. In the absence of a susceptibility test, it is difficult to comment if these cases are resistant to antifungal treatment or it is recurrent cases.[2] Dermatophytosis is usually diagnosed clinically, but sometimes we need to confirm the diagnosis, because it may simulate other dermatological diseases. KOH preparation is simple, cheap and accurate test to confirm the diagnosis.[2] The abovementioned causes necessitate adding an adjuvant treatment for these challenging cases.

In the present study, isotretinoin was used due to its keratolytic effect on the skin and immune-modulatory functions as an adjuvant treatment with promising results.[3]

Patients and Methods

Study design

This is a prospective randomised open-label therapeutic comparative clinical study, which was conducted in

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Al Basra teaching hospital (dermatology outpatient consultancy) and private clinic, after Approval Letter No. 272 of the ethical committee of Basra medical college, during a period from January 2020 to January 2021, where a total of 81 patients who were diagnosed clinically and microscopically to have dermatophytosis were recruited in this study, their age ranged from 19 to 65 years.

A detailed history was taken regarding occupation, comorbidities, duration, sites affected, disease progression, treatment that had been used previously (like griseofulvin, fluconazole, ketoconazole and itraconazole alone), time and duration of last treatment used by the patients. All enrolled participants were fully examined and the percentage of body surface area being affected by tinea was calculated. As isotretinoin and itraconazole may alter liver function test and cause hyperlipidemia, hyperglycaemia,[4,5] and is teratogenic, all patients were investigated for liver function test (LFT), renal function test (RFT), lipid profile, fasting blood sugar (FBS), pregnancy test and complete blood count (CBC) at baseline and 3 months later. The safety of treatments was evaluated in each visit by history, clinical examinations and the abovementioned investigations

Inclusion criteria

Chronic dermatophytosis: any type of dermatophytosis that persists for more than 6 months to 1 year.[6]

Recurrent dermatophytosis: dermatophytosis that recurs within a few weeks after completion of the treatment course.[6]

Clinical cure: the condition is considered clinically cured when all clinical features were disappeared (Author criteria).

Mycological cure: When KOH preparation of scrubbed scales is negative, the condition is considered mycologically cured (Author criteria).

Clinical relapse: the condition when any clinical features of dermatophytosis recur after treatment and complete cure. (Author criteria).

Mycological relapse: the condition when the KOH preparation of the scrubbed scales becomes positive after conversion to negative by treatment. (Author criteria).

As all included patients had their disease for more than 6 months and recurred within a few weeks after completion of the treatment course, they were considered chronic and recurrent dermatophytosis,[6] accordingly all patients with chronic, recurrent dermatophytosis involving more than 20% of body surface area and they had no treatment for the past 4 weeks were included in this study.

Exclusion criteria

The following patients were excluded from the study:

1- Patients with chronic liver and renal diseases.
2- Patients with ischaemic heart diseases.
3- Patients with hyperlipidemia.
4- Those on chronic immunosuppressive therapy.
5- Pregnant and lactating women and females of reproductive age who cannot or refused to take contraceptive pills.
6- Elderly patients.
7- Patients with tinea for less than 6 months or limited tinea involving less than 20% of body surface area.

Patient's assessment

The area of maximum severity was regarded as the target area. Severity of clinical lesions was assessed depending on three parameters, which are pruritus, erythema and scales. As the following score: 0 = no, 1 = mild, 2 = moderate and 3 = severe. The summation of these three scores of the target lesion was regarded as a clinical assessment score (CAS).[2] Overall clinical improvement (global assessment index) was graded as follows in each visit:

More than 80% improvement = excellent response.

79%–60% improvement = good response.

59%–40% improvement = moderate response.

Less than 40% improvement = poor response.

Data collection

All of them received itraconazole 200 mg daily for 1 week per month for 2 consecutive month's duration. Half of them had been randomly chosen on computer-based data, received isotretinoin 10 mg every other day for 2 months duration in addition to itraconazole. No topical antifungal drugs had been used for any patients in both groups.

Sample size was calculated according to the following equation:

$$Sample\ size = \frac{Z^2 * P(1-P)}{E^2}$$

Accordingly, the supposed sample size is 184 participants. The study at first included 142 patients, but only 81 participants completed the treatment and follow-up period. The others were considered defaulters.

Patient's satisfaction scoring system

Scoring subjective system was used to assess patient satisfaction as follows:

0 As not satisfied.
1 As partially satisfied
2 As fully satisfied

Follow-up

The patients were followed up monthly for 6 months duration. During the follow-up period, the parameters, which were depended on assessing the cure rate, included the following:

1. Clinical improvement or complete resolution of skin lesions (CAS) and (GAI).
2. Negative microscopical examination for dermatophytes using KOH 10% preparation.
3. Patient satisfaction scoring system.
4. Subsequent photos at pre and during the treatment and follow-up period.
5. Asking and examining for any possible skin or systemic side effects during the period of treatment and follow-up.

Any patient whose disease recur clinically and microscopically within a few weeks after completion of the treatment course was considered to relapse and the relapse rate was calculated in both groups.

Statistical analysis

Was performed using the Statistical Package for the Social Sciences (SPSS) software version 26. Chi-square test was used and *P* value < 0.05 was considered statistically significant

Results

Among the 142 patients who were recruited in this study, only 81 completed the treatment and follow-up period of the two studied groups.

Table 1 shows the demographical features of all participants, the mean age was 39.647 ± 1.988 years for patients who received isotretinoin along with itraconazole and 38.969 ± 1.956 years for patients with itraconazole only. Most of the patients were males; there are no statistically significant differences between the two groups. Fifty-two patients (64.2%) gave a history of contact with domestic cats and dogs.

Among patients who received isotretinoin, 39 (97.5%), showed clinical cures as in [Figures 1 and 2] while 95% were mycologically cured. In addition, the study revealed that those patients had been cured earlier (within the first 2–4 weeks). Relapse rate was 12.8% [Table 2], which occurred three months after the treatment course.

While patients without isotretinoin showed a cure rate of 53.7% (within 5–8 weeks) and 18 patients only had mycological cure with relapse rate of 68.1% [Table 2] occurring within 2–3 weeks after cessation of treatments. Patients who did not show clinical and mycological cure were also followed up for 6 months.

At the end of the study, the patient's satisfaction was as follows:

Among the group with isotretinoin 35 patients (89.7%) were fully satisfied versus three patients (13.6%) from the second group without isotretinoin. On the other hand, four patients (10.2%) were partially satisfied in the first group in comparison with five patients (22.7%) from the second group. In addition, no patient from

Table 1: Demographical features of cases and controls

Variables	Patients without isotretinoin		Patients with isotretinoin		*P*
	No.	%	No.	%	
Gender					
Female	18	43.2	17	42.5	1.000
Male	23	57.5	23	56.1	
Age					
Mean (year) ± SD	38.969±1.956		39.647±1.988		0.864
19-25 years	8	19.5	7	17.5	
26-45 years	25	61	23	57.5	
46-65 years	8	19.5	10	25	
Duration of disease					
2-6 months	17	41.5	18	45	0.668
6 months-1 year	18	43.9	14	35	
More than 1 year	6	14.6	8	20	

Table 2: Percentage of cure and relapse

	Patients without isotretinoin		Patients with isotretinoin		*P*
	No.	%	No.	%	
Mycological cure	18	43.9	38	95	0.00001
Clinical cure	22	53.7	39	97.5	0.00001
Relapse	15	68.1	5	12.8	0.012

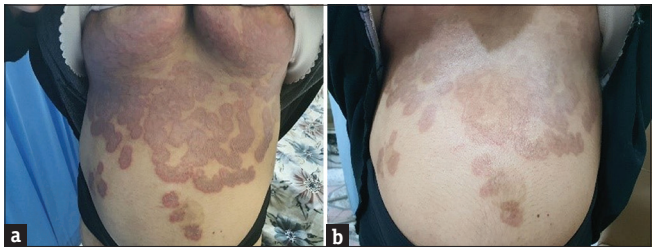

Figure 1: a. Before treatment (Author's own photo) 1. b. 3 months later (Author's own photo).

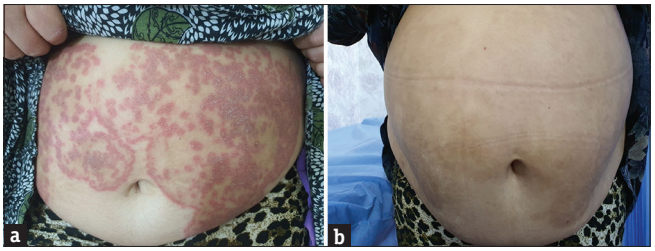

Figure 2: a. Before treatment (Author's own photo). 2. b. After 3 months (Author's own photo).

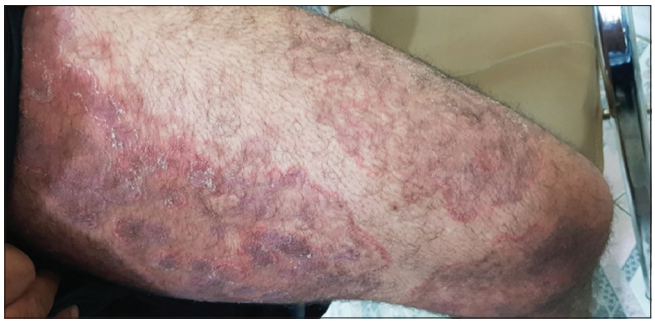

Figure 3: Patient with relapse (author's photo)

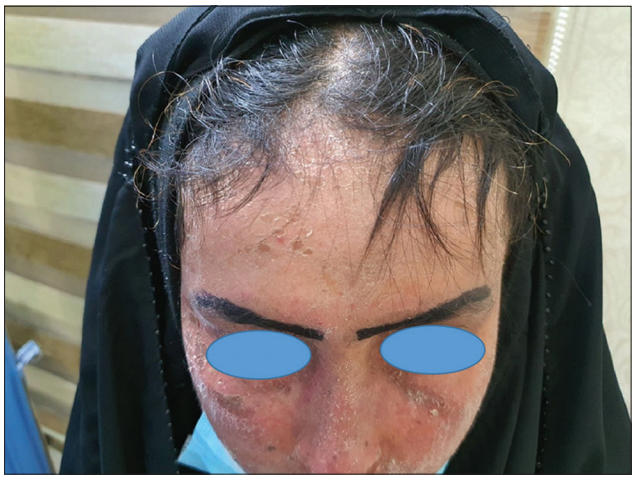

Figure 4: Patient with relapse (author's photo)

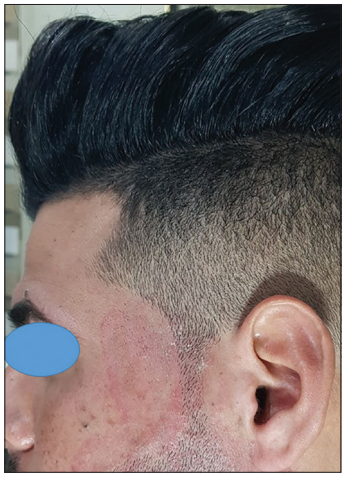

Figure 5: Patient with relapse (author's photo)

the group who received the combination treatment was not satisfied while 14 patients (63.6%) among the other group were not satisfied with the result of pure antifungal drugs.

Finally, the study also showed that no significant side effects had been reported neither clinically nor by laboratory investigations pre and post-treatment and follow-up period [Figures 3-5].

Discussion

In the present study, there is an increase in the incidence of chronic dermatophytosis which may be attributed to our hot, humid and long summer. Most of the included patients were young males, which may be related to the type of their work for long period per day with tight occluded underwears and trousers, which provide optimal media for persistence and recurrence of dermatophytosis where the conditions mostly started as tinea cruris. In addition, it is worthy to mention that the present increase in the prevalence of dermatophytosis with its atypical and inflammatory presentations is possibly attributed to the new trend of having domestic imported cats and dogs in patients' homes, which is the case in a high percentage of patient's history. Although dermatophytosis is a common problem in our country where the prevalence rate is 14.5%,[7] the relatively low sample size is attributed to a high number of defaulters. In addition, this study was conducted during the coronavirus disease 2019 (COVID-19) pandemic with subsequent block downs where the follow-up seems to be difficult for included patients. In an attempt to overcome this, distressing problem, isotretinoin was added as an adjuvant therapy with systemic itraconazole, but although it is recommended in literature to use pulse itraconazole regimen as 200 mg per day for a week each month for three successive months,[1] we adopted shorter regimen for 2 months used in combination with isotretinoin that is supposed to augment its effects, meanwhile, this shorter regimen is thought to reduce the side effects of both drugs. We hoped that this new short regimen gave it superiority over the already known one as it induced the same results with a reduction of side effects. The patients who received low-dose isotretinoin along with itraconazole showed a statistically significant high rate of complete clearance and reduction of recurrence with earlier response in comparison to the other group. Muhammad used 20 mg of isotretinoin daily for 3 months duration with systemic antifungal drugs and found that the combination of itraconazole and isotretinoin is an effective treatment of recalcitrant and recurrent dermatophytosis with no biological and haematological side effects.[2] Furthermore, Fathia Khattab *et al*. treated 30 patients with chronic recurrent dermatophytosis by using a combination therapy of oral itraconazole 200 mg per day plus 20 mg isotretinoin daily for 6 weeks reporting 83.3% mycological cure and 70% of complete mycological and clinical cure with mild and tolerated side effects.[8] In addition, Rahman (2019) used a combination therapy for 3 months that induced 90% of complete cure.[9] Finally, Ardeshna *et al*.[10] used oral isotretinoin 20 mg per day and itraconazole 200 mg daily for 1 month for one patient who showed complete response with no recurrence along 6-months follow-up period. In this study, using low dose of isotretinoin

10 mg every other day for 2 months duration induced relatively same or higher cure rate than the previous studies with nearly free dose-dependent side effects. Despite that, the isotretinoin mechanism of action is not fully understood, but we can give clues for its possible action on the skin and pathogenesis of tinea.

Regarding the pathogenesis of dermatophytosis. Following the adherence and production of keratinases, which allow invasion of the fungi into the stratum corneum. Successful penetration of dermatophytes requires rapid germination of arthroconidia within the stratum corneum.[11] Mannans in the cell walls of dermatophytes have immunoinhibitory effects and may decrease epidermal proliferation, thereby reducing the chance of this proliferating fungus being sloughed off and lost prior to invasion.[12] Mannans are also inhibiting the critical steps in antigen processing and presentation.[13] They found that the free radicals and nitric oxide released in patients with chronic dermatophytosis were 20%–30% lower than that seen in controls, which indicates a defective killing mechanism.[14]

On the other hand, retinoids are structural and functional analogues of vitamin A that exert multiple effects on cellular differentiation, proliferation and on the immune system.

It acts as a modulator of epidermal proliferation and differentiation. To our knowledge retinoid act in favour of normalisation in hyperproliferative epithelia such as in psoriasis while in normal epidermis, they enhance cell proliferation[15] so by increasing epidermal cell turnover, which may hamper the spread of ongoing infection by getting rid of the proliferating dermatophytes from the skin, it will accelerate the clearance of the tinea and reduce the recurrence rate.

Retinoids are also known to change terminal differentiation towards a non-keratinising, metaplastic and mucosa-like epithelium.[3] The optimal media for dermatophyte proteolytic enzymes is acidic pH,[16] retinoid therapy raises the skin pH, so it will possibly inhibit dermatophyte growth.[17]

Retinoid are also thought to be an immunomodulator (stimulate humoral and cellular immunity)[3] they also stimulate T helper cells, enhancing antibody production. Cell surface antigens of T cells and natural killer cells have been reported to be increased after retinoid exposure *in vitro*.[18] It is important to note that in the normal population, macrophages and neutrophils migrate towards the skin in response to dermatophytic invasion and they phagocytised and get rid of the fungi. While in patients with chronic dermatophytosis, it has been observed that there is a defect in phagocytosis.[2]

Conclusion

Combination of low-dose isotretinoin with itraconazole seems to be safe and effective treatment for chronic, recurrent dermatophytosis as it induced relatively earlier and complete cure with less recurrence rate and relatively less side effects and a higher patient satisfaction rate in comparison with conventional antifungal therapy alone.

Limitations

The limitations of this study are:

1. The study was conducted during COVID-19 pandemic with a frequent block down, which results in lowering sample size.
2. Like any other study with a follow-up period, the number of defaulters is expected to be high.

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Conflicts of interest

There are no conflicts of interest.

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