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Efficacy and safety of low dose oral isotretinoin in comparison with oral itraconazole in the treatment of seborrheic dermatitis among patients attending Erbil dermatology teaching center in Erbil City

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Abstract

Background and objective: Seborrheic dermatitis is chronic skin disease with exacerbation and remission, many topical and systemic therapies were used, including oral antifungal itraconazole, oral isotretinoin efficacy in the treatment of seborrheic dermatitis less studied. This study aimed to compare the efficacy and safety of low dose oral isotretinoin and oral itraconazole in the treatment of patients with seborrheic dermatitis.

Methods: A total of 68 patients with seborrheic dermatitis were participating in a randomized, parallel-group study. One group (n = 31) took 200-mg/day oral itraconazole for one week of the first month, followed by 200 mg for the first two days of the next two months. The second group (n = 37) took oral isotretinoin 20 mg twice weekly for three months. Seborrheic dermatitis area severity index and intensity of itching and burning sensation were calculated before, during three months and one month after treatment.

Results: Both drugs significantly reduced the severity of seborrheic dermatitis (P <0.05). When the two groups were compared, patients taking oral isotretinoin showed a significantly greater decrease in seborrheic dermatitis area severity index score than itraconazole group particularly in the second and third months of treatment.

Conclusion: Low dose oral isotretinoin is more effective than oral itraconazole in treating seborrhea dermatitis.

Keywords: Seborrheic dermatitis; Itraconazole; Oral Isotretinoin.

Introduction

Seborrheic dermatitis is a common chronic inflammatory skin disorder. It is limited to specific areas of the skin such as the scalp, face, upper trunk, and flexures.[1] Seborrheic dermatitis typically affect humans at two time points during their lifespan: infancy and adulthood.[2] Clinically, seborrheic dermatitis is characterized by scaling and erythematous regions observed at anatomic sites that have a high concentration of sebaceous glands (scalp, face, upper trunk, and flexures).[3] However, variations in this clinical picture are common. Patients may vary markedly concerning erythema, the degree of flaking and 'greasy' appearance of lesions.[4] The prevalence of seborrheic dermatitis in the general population has been reported between 2.35% and 11.3% depending on the country studied.[5] A greater occurrence can be observed in the immunocompromised population and individuals with neurological conditions such as Parkinson's disease.[6] The cause of seborrheic dermatitis is unknown; however, many factors have been cited as possible contributors to the development of this disorder. These include exogenous factors (seborrheic dermatitis is more common in the winter) and various endogenous host factors.[4] Hormone levels, sebum production, lipid composition on the skin surface, *Malassezia* species and patient predisposition to immune or inflammatory reactions have been suggested as important factors in the development of seborrheic dermatitis.[2,7] *Malassezia furfur*, one of the members of the microbiologic flora of the skin, causes

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pityriasis versicolor and has also been implicated in the pathogenesis of other superficial dermatoses, the most important being seborrheic dermatitis. The mechanism by which the yeast causes these dermatoses, however, is not clear.[8] Correlation of severity of the disease with the number of yeast and a decrease in the number of *Malassezia* organisms after treatment seems to support this concept.[9] Despite the lack of a clear correlation between sebum levels and the development of seborrheic dermatitis, there still appears to be some connection between seborrheic dermatitis and sebum levels.[4] The hypothesis would be that the fungus uses lipids from the skin surface to produce unsaturated and saturated fatty acids that, when left in the individual's skin milieu induce an inflammatory response.[6] Moreover, the distribution of lesions on the body reflects the distribution of sebaceous glands.[4] Seborrhea is a skin condition that involves hypersecretion by the sebaceous glands in response to androgenic stimuli. It is associated with acne, seborrheic dermatitis, and dandruff.[10] Topical treatments are the first choice for seborrheic dermatitis. Topical agents (mild or weak corticosteroids, antifungal agents, zinc pyrithione, selenium sulfide, and lithium succinate) are usually effective in the treatment of seborrheic dermatitis.[8] However, in exceptional cases, it is necessary to resort to systemic drugs.[11] In cases where the lesions of seborrheic dermatitis are particularly widespread or are refractory to topical treatment, an oral medication may be preferred by both physician, and patient.[4] Systemic antifungals such as itraconazole, fluconazole, ketoconazole, terbinafine, and pramiconazole have been tried in the treatment of selected seborrheic dermatitis patients.[12] Itraconazole is the most frequently reported oral treatment for seborrheic dermatitis and the most commonly reported dosing regimen for itraconazole is a pulse regimen generally associated with an excellent therapeutic and safety profile in the treatment of moderate to severe seborrheic dermatitis.[12,13] Oral isotretinoin is the drug of choice for the treatment of severe or moderate resistant acne. Conventional treatment regimens suppress secretion by sebaceous glands by reducing their size, decreasing proliferation, and inducing basal sebocyte apoptosis.[10] Orfanos and Zouboulis first reported the use of low-dose oral isotretinoin (0.10.mg/kg) to treat severe seborrhea.[14] Geissler et al.[15] successfully used an alternative regimen for seborrhea associated with acne. The anti-inflammatory properties of oral isotretinoin have been described, including decreased interleukin production by keratinocytes and sebocytes, polymorph nuclear cell migration, and Toll-like receptor 2 activities.[16] Based on these mechanisms, some authors have administered oral isotretinoin combined with topical products or oral corticosteroids for moderate to severe seborrheic dermatitis.[10] This study aimed to verify the efficacy and safety of oral isotretinoin compared with oral itraconazole in the treatment of seborrheic dermatitis among patients attending Erbil dermatology teaching center in Erbil City.

Methods

A comparative study was conducted on patients with seborrheic dermatitis attending outpatient-clinic of Erbil dermatology teaching center in Erbil City during the period from January 2017 to January 2018. Sixty-eight patients with seborrheic dermatitis were enrolled in the study. The diagnosis was made on the clinical basis by assessing the morphology of lesions and involved sites. To reach a clinical diagnosis of detailed history and thorough physical examination done. The inclusion criteria of patient selection were both male and female over 18 years old and had no use of topical steroids, topical antifungals, and other topical agents for at least two weeks before enrollment to the study, and systemic therapy for at least

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three months before conducting the study. Patients were excluded if they had chronic and inflammatory dermatoses on the scalp and face such as psoriasis, history of renal, liver or cardiac disease, pregnant or planning pregnancy and lactating women, previous treatment with oral retinoids, tetracycline and its derivatives, multivitamins including vitamin A, chemotherapy, carbamazepine and phenytoin; and those patients who had alteration in laboratory tests such as lipid profile and liver function test. The seborrheic dermatitis area severity index (SDASI) scoring system by Baysal et al. was applied in the measurement of dermatitis severity. The scalp, face, and chest were examined in the patients, graded for erythema, papule, and scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe). The areas of involvement were measured on a scale of 1 to 5 (1 = less than 10%; 2 = 11–30%; 3 = 31–50%; 4 = 51–70%; 5 = more than 70%)". The severity of seborrheic dermatitis was divided into three groups based on the SDASI scores (mild = 0–7.9, moderate = 8–15.9, and severe >16).[8] Symptoms including itching and burning sensation grading were evaluated by assigning scores of patients, where 0=none, 1=mild, 2=moderate, and 3=severe this according to Comert et al.[9] The first group (37 patients) was treated with isotretinoin capsule 20 mg orally twice weekly for three consecutive months. The second group (31 patients) was treated with itraconazole capsules 200 mg daily during the first week of the first month; then 200mg daily was given in the first two days of every month for next two months. Both groups were with the same clinical severity of moderate to severe seborrheic dermatitis. All patients were instructed to use 1% hydrocortisone ointment once daily and 2% ketoconazole shampoo three times weekly for all involved areas just for the first two weeks of the first month for each patient group. Patients were evaluated clinically at baseline and every month. The SDASI severity score was assessed at baseline and the end of each month of treatment and one month after treatment and scores were noted. Subjective assessment of pruritus and the burning sensation was assessed at baseline and at the end of treatment and one month follows up. Laboratory tests as complete blood count; lipid profile and Liver function test were checked at baseline before treatment and in the second month of treatment. Ethical consideration and informed written consent was obtained from all participants after explaining the aim of the study and the study approved by the ethical committee of the Kurdistan Board of Medical Specialties. Statistical analysis: the statistical package for the social science (version 21) used for data analysis. Paired t-test was used to compare the effect of each treatment strategy on the mean scores of the different intervals. Student t-test was used to compare the mean reduction of scores between the two treatment strategies. Statistical significance was set at P <0.05.

Results

Sixty-eight adult outpatients with the clinical diagnosis of seborrheic dermatitis 47 men, 21 women; age range, 18 – 70 years; mean age ± SD, 31.26 ± 14.15 years, mean duration of disease was 2.45 ± 3.41, entered the study. Ultimately, 31 patients (19 male, 12 female) receiving itraconazole and 37 patients (9 female, 28 male) receiving isotretinoin completed the study and were evaluated as shown in Table 1. Patients in both groups showed a statistically significant decrease in SDASI score from baseline through three months of the treatment course (P <0.001). Meanwhile, both groups also demonstrated a statistically significant decrease in the mean SDASI score between baseline before treatment and one month follow up after treatment (P <0.001) as shown in Figure1.

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Table 1: Demographic characteristics of participants.

Variable	No.	(%)
Sex		
Male	47	69.1
Female	21	30.9
Age		
mean± SD	31.26±14.15	
Range	18-70	
Mean duration of disease/ years	2.45±3.41	

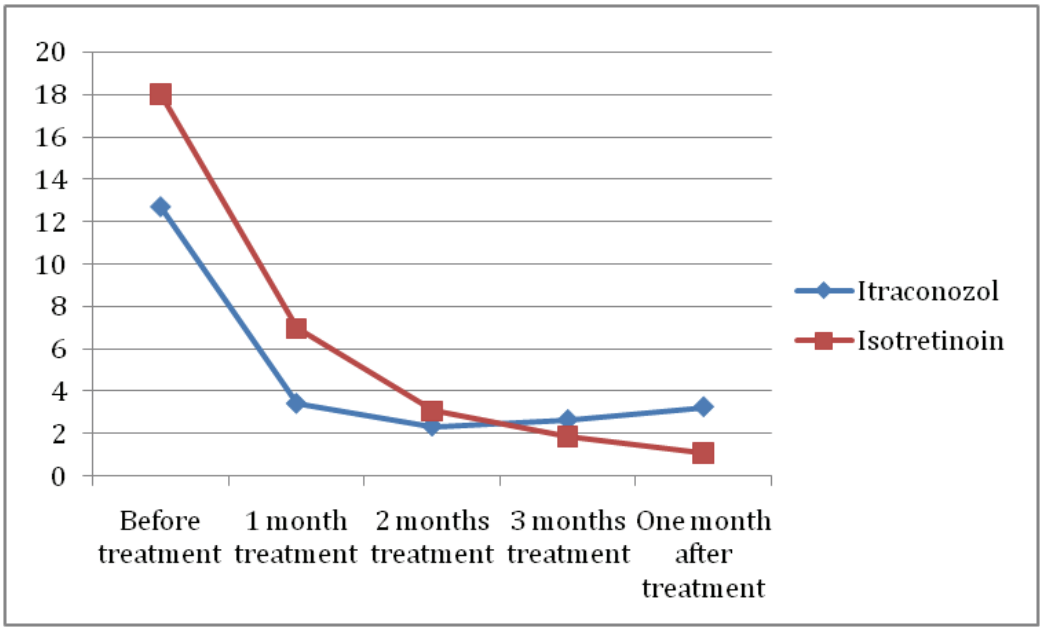

Figure 1: Comparison of mean SDASI score in the different phases of study for each treatment modality

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When the two groups were compared, patients taking isotretinoin showed a significantly greater decrease in SDASI score than patients receiving itraconazole (*P* <0.001). These were for all time group treatment except before and one-month after treatment, which was not significant (*P* = 0.170) as shown in Table 2. Regarding the effect of drugs on both itching and burning sensation there was no significant difference in itching in both groups before treatment, but after treatment, the itching was significantly more in itraconazole group (0.81) than isotretinoin group (0.46), *P* = 0.003. However, regarding burning sensation, there was no significant decrease regarding both drugs as shown in Table 3. Itraconazole was well tolerated with no significant adverse effect was noticed during the study. However, cheilitis and mucocutaneous dryness was the most frequent adverse effect on isotretinoin group. Five patients on isotretinoin complained from epistaxis in addition to mucocutaneous dryness.

Table 2: The effect of itraconazole and isotretinoin on decreasing SDASI.

Mean decrease of SDASI	Itraconazole Mean ± SD	Isotretinoin Mean ± SD	*P* value
Before treatment and at the end of 1st month9.29 ±5.12	9.29 ±5.12	11.05 ± 5.31	0.170
Before treatment and at the end of 2nd month	10.35 ± 6.19	14.95 ± 7.30	0.007
Before treatment and at the end of 3rd month	10.06 ± 6.19	16.14 ± 8.40	0.001
Before treatment and one month after the 3 months of therapy	9.45 ± 6.33	16.95 ± 8.60	<0.001

Table 3: Comparison of itching and burning sensation in the different phase of the study.

	Drugs	Without No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)	Mean ± SD	*P* value*
Itching before Rx	Itraconazole	0 (0)	3 (9.7)	16 (51.6)	12 (38.7)	2.29 ± 0.64	0.077
	Isotretinoin	0 (0)	0 (0)	17 (45.9)	20 (54.1)	2.54 ± 0.51	
Itching after Rx	Itraconazole	6 (19.4)	25 (80.6)	0 (0)	0 (0)	0.81 ± 0.40	0.003
	Isotretinoin	20 (54.1)	17 (45.9)	0 (0)	0 (0)	0.46 ± 0.51	
Burning before Rx	Itraconazole	3 (9.7)	24 (77.4)	4 (12.9)	0 (0)	1.03 ± 0.48	0.136
	Isotretinoin	2 (5.4)	26 (70.3)	7 (18.9)	2 (5.4)	1.24 ± 0.64	
Burning after Rx	Itraconazole	28 (90.3)	3 (9.7)	0 (0)	0 (0)	0.10 ± 0.30	0.509
	Isotretinoin	35 (94.6)	2 (5.4)	0 (0)	0 (0)	0.05 ± 0.23	

* This *P* value is for comparison of the means

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Discussion

The prevalence of seborrheic dermatitis is unclear due to the lack of validated diagnostic criteria.[17] Seborrheic dermatitis is clinically present in two age groups infants and adults. In adult seborrheic dermatitis, the peak prevalence is approximately 30 to 60 years of age.[11,17] In our study the mean age of patients was 31.26 (SD = 14.15) years. This was comparable with previous studies in Turkey, Iran, Spain, and Brazil.[8-12] Seborrheic dermatitis is a well-known chronic inflammatory dermatosis with remissions and exacerbations; its lesions are more common in areas with high concentration of sebaceous gland. The exact cause is still unknown, however many factors have been implicated, including Malassezia spp., sebum production and lipid composition of the skin surface. Many topical treatments such as topical corticosteroids and topical antifungals have been used in the treatment of seborrheic dermatitis but with poor patient compliance and high rate of relapse after stopping the treatment, and as the condition is chronic, the safety of prolonged use of these topical treatments are also debatable. Our study showed that itraconazole are effective in the treatment of seborrheic dermatitis through three months of treatment and one month follow up after treatment this was comparable with other studies have been using systemic antifungal itraconazole in the treatment of seborrheic dermatitis with same dose regimen as ours but in different durations.[8,12,13] Itraconazole is a lipophilic and keratophilic systemic antifungal, its high lipophilicity means that it persists in the skin even after cessation of therapy.[18] Both antifungal, anti-inflammatory action of itraconazole may account for this improvement. Regarding isotretinoin, our results showed a significant decrease in the SDASI score and severity of the disease during the three months of treatment, and one month of follow up, this was in agreement with a comparative study done in Brazil[10] which showed improvement in symptoms and severity of the disease using the same dose regimen and duration. Oral isotretinoin is the most effective drug in decreasing size of sebaceous glands, and also in decreasing sebum production, however isotretinoin also has an anti-inflammatory role, which could be accounted for its role in improving seborrheic dermatitis. In our study, patients taking oral isotretinoin showed a significant decrease in symptoms and SDASI score when compared with those taking itraconazole, particularly in the second and third months of treatment and one month follow up. During the first month, there was no significant change, which could be the effect of topical treatments that we administered with both systemic treatment in the first month and effect of isotretinoin in reducing scale, erythema became more evident after stopping the topical treatment. Because there is no previous study comparing isotretinoin with systemic antifungal in treating seborrheic dermatitis, comparison of our study was not applicable. A significant reduction in itching was noticed in patients taking isotretinoin as compared to itraconazole group. This might bean other helpful parameter in considering isotretinoin as a treatment choice for seborrheic dermatitis, which could be accounted for its role in decreasing sebum production and oiliness on the face and scalp, which increase the itching. Comparing with other studies using systemic antifungal all they showed reduced itching and burning sensation.[8-10,12,13] However, in our study, there was no any decrease in burning sensation regarding both treatments. The adverse effects related to isotretinoin are well documented, however in our study all side effects were related to mucocutaneous dryness, and chelitis were common and no any other serious even noticed. Our study has some limitations. First, the small sample size. Second, the follow-up period, which could be more than one month, as we know seborrheic dermatitis,

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is a chronic, relapsing disease. Finally, we did not perform a fungal culture to correlate the clinical improvement with yeast colonization. However, our study regarded as the first comparative study using oral isotretinoin for treating seborrheic dermatitis.

Conclusion

Oral isotretinoin is more effective and saferthan itraconazole in treating severe and relapsing seborrheic dermatitis.

Competing interests

The authors declare that they have no competing interests.

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