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Original article

Prevalence and associated risk factors of acne relapse among Saudi acne vulgaris patients using isotretinoin

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ABSTRACT

Background: Acne vulgaris is a self-limiting condition that may affect the patients quality of life. The most efficacious treatment of choice for acne is isotretinoin. However, adverse effects and relapse of acne after completing an isotretinoin course pose major hurdles for treatment compliance and adherence.
Method: The authors conducted a cross-sectional study using a self-administered questionnaire. The prevalence and risk factors associated with the relapse of acne following isotretinoin use among Saudi patients were assessed. In addition, the reasons for discontinuing treatment, extent of awareness about isotretinoin use-associated teratogenicity, side effects such as liver enzymes impairments, dry mouth, skin, eyes, and the number of people using isotretinoin without a prescription were determined.
Results: Four hundred and twenty seven acne vulgaris patients (mean age: 25.0 years, female: 83%) were included in this study. Of the 57% subjects who used isotretinoin, 45.12% patients showed relapse. The daily dose of oral isotretinoin of 20 and 40 mg/day was taken by 80% in both group of patients, and the mean duration of isotretinoin use was 7.15(±4.5) months. Those patients who were taking higher doses of oral isotretinoin reported having more relapses.

Although a majority of patients received the medication through prescription, unfortunately, they were not aware of relapse and side effects.
Conclusion: Almost half of the patients showed relapse of acne after using isotretinoin. A lack of understanding regarding relapse and side effects indicates a need to improve public and professional awareness of isotretinoin.

1. Introduction

Inflammatory or non-inflammatory lesions and varying degrees of scarring characterize Acne vulgaris. Worldwide acne is the eighth most prevalent disease affecting a 9.4% of the population (Tan and Bhate, 2015).

This self-limiting condition significantly impairs a patient's quality of life to varying degrees. Higher grade of acne, female gender, obesity, illiteracy and poverty are the proposed risk factors for impaired quality of life in acne cases. (Shams et al., 2018) The prevalence of acne was highest in adolescents/young adults in the European countries. Heredity was the main risk factor for developing acne. (Wolkenstein et al., 2018)

Oral isotretinoin is considered as the gold standard (Bagatin et al., 2019) for the treatment of acne particularly when adequate courses of standard therapy with systemic antibacterial and topical approaches fail (Seth and Mishra, 2015). Furthermore, moderate acne that is either treatment-resistant or that relapses quickly after the discontinuation of oral antibiotic therapy can be treated efficacious by oral isotretinoin. The dose for oral isotretinoin is usually 0.5–1 mg/kg daily, although it is recommended to start with a daily dose of 0.5 mg/kg for the first month followed by a gradual increase (Zaenglein et al., 2016) over the course of 16–20 weeks of therapy. Although the isotretinoin is remarkably effective, serious side effects were reported. These unwanted effects range from dryness of the mucosa and skin to depression and hepatitis (Seth

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and Mishra, 2015). Interestingly, an increase in the number of prescriptions of oral isotretinoin has been observed among patients worldwide along with a rapid increase of up to 250% (Wysowski et al., 2002). Unfortunately, oral isotretinoin is considered to be a highly teratogenic medication and fetal exposure can lead to life-threatening congenital abnormalities (Zouboulis, 2006).

A common factor following discontinuation of oral isotretinoin for acne is relapse. Although the relapse rates vary between studies, a range of 10–60% has been noted based on the regimen and duration of the treatment (Morales-Cardona and Sánchez-Vanegas, 2013) and after stopping treatment (Quereux et al., 2006; Azoulay et al., 2007). Significantly effective treatment and decreasing relapse rates of acne can be achieved with higher doses of isotretinoin and without increasing adverse effects. In the lower-dose (<220 mg/kg) treatment group, the relapse rate was 47.4% in contrast to 26.9% in the high-dose (>220 mg/kg) group (Blasiak et al., 2013). (Bagatin et al., 2019; Blasiak et al., 2013)Many risk factors were found to influence the relapse rates. A relationship between the risk of relapse and sex was reported wherein the risk in men was found to be twice that in women (Morales-Cardona and Sánchez-Vanegas, 2013).

Thus far, no study conducted in Saudi Arabia has addressed isotretinoin-associated risk factors for relapse of acne vulgaris. Therefore, the objective of this study was to determine the prevalence and risk associated with acne vulgaris relapse in addition to the reasons for discontinuing the treatment, extent of awareness about isotretinoin teratogenicity, and number of people who were on isotretinoin without prescription.

2. Materials and methods

The authors conducted this cross-sectional study in Riyadh Region over a period of 10 months from 21 January to 22 November 2018. Saudi male and female acne vulgaris patients aged between 12 years (only after puberty) and 45 years on isotretinoin were enrolled. Patients who started isotretinoin after 25 September 2017 were excluded as the drug was restricted by Saudi FDA. Patients were included for the analysis if they used the medication for 3 months and more.

The respondents were acne vulgaris patients from Riyadh Region who attended clinics in King Khalid University Hospital, King Abdullah University Hospital, and Princess Nourah Bint Abdulrahman University. After a review of previous related studies, a self-administered questionnaire was designed for a pilot study involving 20 patients who visited King Khalid Hospital; minor adjustments were made for the full study. The questionnaire was designed in Arabic and English; it contained 37 questions along with lists of possible answers. Data on sex, age, family history, total dose of isotretinoin, treatment duration, attitudes, behavior during isotretinoin therapy, relapse, prescribed drugs, non-prescribed drugs, side effects such as liver enzymes impairments, dry mouth, skin, eyes, pregnancy, and other complaints were collected. With regards to the basic routine for isotretinoin requested lab at start and during follow up we thought it would simpler to patients to ask them about the most common lab request usually done ie LFT.

The respondents were asked to choose the most relevant response to each question. Relapse was defined as the reappearance of acne according to the patient's opinion and their need for treatment.

The data were collected in collaboration with doctors and nurses who were working in clinics of the above-mentioned health facilities during the time of the study. Ethical approval for this study was obtained from the Ethics Committee in King Saud University and Princess Nourah Bint Abdulrahman University. The returned questionnaires were entered into a database and were analyzed using a statistical program.

2.1. Statistical analysis

SPSS version 22 was used throughout the analysis to generate descriptive and summary tables. Categorical data were compared using Chi-square test while numerical data were compared using the independent sample *t*-test. p-value of < 0.05 were considered to be significant results.

3. Results

Four hundred and twenty seven patients participated in our retrospective review, and completed the self-administered questionnaire. Of these, 181 subjects (42.3%) used medications other than isotretinoin. The mean age of patients using isotretinoin was 25.1 (±5.2) years; a majority were female (83.3%), unmarried (80.4%), and pursuing university education (87.8%). The prevalence of isotretinoin use was 57.61% (n = 246), and of those on isotretinoin, 45.12% (n = 111) patients experienced a relapse. Approximately 83% (n = 204) of the patients completed the treatment regimen, while 42 (17%) subjects discontinued the treatment after at least 3 months of use. Cases of relapse were reported by 96 (46,8%) female and 15 (36,6%) male patients. But these differences were not statistically significant (Table 1).

Risk factors such as smoking, family history, and BMI did not influence relapse rates. There were no statististically significant differences (Table 2). Only 68 patients (27.6%) used a maintenance therapy after completing the isotretinoin course while 42 patients suddenly discontinued the course because of the side effects. Taking isotretinoin with or without a fatty meal did not affect the relapse rate. On the other hand, dosage, the time at which the daily dose of isotretinoin was taken (before or after the meal), and completion of the treatment course significantly influenced the relapse (Table 3). The daily dose of oral isotretinoin of 20 and 40 mg/day was taken by 80% in both group of patients, and the mean duration of isotretinoin use was 7.15(±4.5) months. Those patients who were taking higher doses of oral isotretinoin reported having more relapses.

Patients' practice of isotretinoin use indicated that 173 (70.3%) patients were not informed about potential relapse by health care providers; 46.2% of these subjects relapsed and 53.8% did not. Seventy-five (56.7%) patients discussed the use of contraception methods while using isotretinoin. Approximately 21 (8.5%) patients never took the liver enzyme test, 58 (23.6%) took it only at the beginning of the course, and 97 (39.4%) took it monthly. Before the restriction on isotretinoin use in Saudi Arabia, patients were able to take the medication without a prescription and approximately 6 patients (2.4%) started the course without a prescription (Table 4). In the relapse group (n = 111), approximately 45% (n = 50) of the patients decided to start the isotretinoin course, with 62% (n = 31) and 28% (n = 14) of the subjects taking a second course or two courses after the initial course. Approximately 10% (n = 5) of the patients received multiple courses of treatment.

The side effects reported by the participants were shown in Table 5. About half of the participants did not suffer from any side effects. Ninety (36.6%) participants reported that they experienced some side effects but they did not specified it. Dry mouth and skin were the most common among side effects specified by the participants.

Table 1
Sociodemographic Characteristics versus Relapse Rate.

Characteristics	N = 246	Relapsed N (1 1 1)	Did not Relapse N (1 3 5)	P-value
Age (years)				
<20	46	18 (39.1%)	28 (60.1%)	
21 to 25	112	56 (50%)	56 (50%)	0.553
26 to 30	53	22 (41.5%)	31 (58.4%)	
Above 30	35	15 (42.8%)	20 (57.14%)	
Sex				
Female	205	96 (46.8%)	109 (53.2%)	
Male	41	15 (36.6%)	26 (63.4%)	0.229
Marital Status				
Married	48	16 (33.3%)	32 (66.6%)	0.067
Not Married	198	95 (47.9%)	103 (52.02%)	
Education level				
University	216	98 (45.3%)	118 (54.6%)	0.834
Below University	30	13 (43.3%)	17 (56.6%)	
Location				
In Riyadh	209	97 (46.4%)	112 (53.5%)	0.334
Outside Riyadh	37	14 (37.8%)	23 (62.16%)	

Table 2
Risk Factors for Relapse.

Risk Factors	N = 246	Relapsed N(1 1 1)	Did not Relapse N(1 3 5)	P- value
Smoking				0.544
Yes	23	9 (39.13%)	14 (60.86%)	
No	223	102 (45.73%)	121(54.26%)	
Family History				0.93
Yes	190	86 (45.26%)	104 (54.73%)	
No	56	25(44.64%)	31 (55.35%)	
BMI				
<25 Normal	130	46(35.38%)	84 (64.61%)	
25–29.9 Overweight	71	35(49.29%)	36 (50.70%)	0.09
=>30 obese	26	11(42.30%)	15 (57.69%)	

Table 3
Medication-related variables versus relapse rate.

Medication Variables	N = 246	Relapsed N (1 1 1)	Did not Relapse N (1 3 5)	P-value
Maintenance Therapy				
Yes	68	28 (41.17%)	40 (58.82%)	
No	178	83 (46.62%)	(95) (53.37%)	0.442
Dose				
>40 mg	13	9 (69.23%)	4 (30.77%)	
40 mg	91	46 (50.54%)	45 (49.45%)	0.021
30 mg	34	18 (52.94%)	16 (47.05%)	
20 mg	93	30 (32.25%)	63 (67.74%)	
10 mg	15	8 (53.34%)	7 (46.67%)	
Medication with Fatty Meals				
Yes	88	38 (43.18%)	50 (56.81%)	0.648
No	158	73 (46.20%)	85 (53.8%)	
Medication before or after Meals				
Before	28	18 (64.29%)	10 (35.71%)	0.030
After	218	93 (42.67%)	125 (57.34%)	
Complete Medication Course				
Yes	204	81 (39.70%)	23 (60.29%)	0.0002
No	42	30 (71.42%)	12 (28.57%)	

Table 4
Patient Practice toward Isotretinoin.

Patient Practice	N	Relapsed N (1 1 1)	Did not Relapse N (1 3 5)	P-value
Use with Prescription				
Yes	240	107 (44.5%)	133 (55.4%)	0.283
No	6	4 (66.7%)	2 (33.3%)	
Place of Prescription				
Special/Clinic	180	81 (45%)	99 (55%)	0.949
Governmental	66	30 (45.4%)	36 (54.5%)	
Was the Patient Informed about Potential Relapse?				
Yes	73	31 (42.4%)	42 (57.5%)	0.587
No	173	80 (46.2%)	93 (53.8%)	
Liver Enzyme Test				
Never	21	10 (47.7%)	11 (52.3%)	
Only at the Beginning of Medication Use	58	28 (48.2%)	30 (51.7%)	0.646
Monthly	97	45 (46.3%)	52 (53.6%)	
Every 2 months	51	20 (39.2%)	31 (60.8%)	
3–6 months	19	8 (42.1%)	11 (57.9%)	
Was Contraception Discussed?				
Yes	75	36 (48%)	39 (52%)	0.935
No	55	26 (47.2%)	29 (52.8%)	

Table 5
illustrate the side effects reported by the participants (N = 246).

Side effects	Frequency(%)
Did not experience any side effects	121(49.2)
Side effects not specified by participants	90(36.6)
Dry lips‘	9(3.7)
Dry skin	9(3.7)
skin itching	8(3.3)
Hair loss	6(2.4)
Depressive symptoms	8(3.3)
Joints and muscle pain	6(2.4)
Increased heart rate	1(0.4)
Headache	1(0.4)
Impaired liver enzymes	1(0.4)

NB:Participants may chose more than side effects.

4. Discussion

Due to an increase in the use of isotretinoin in Saudi Arabia, acne relapse became a huge concern; however, not enough local studies were conducted regarding the causes of relapse. During our literature review, we came across only few studies on isotretinoin use prevalence and none related to relapse rate or associated factors.

The prevalence of isotretinoin use in the current study was 57.61%. The participants were young 25.1(+5.2) years and the majority were female. This finding is similar to previous study where most of the patients who received isotretinoin were young women. (Algoblan, 2019)

In the last few years, investigators reported considerable variability in relapse rates of cases using isotretinoin. These differences could be due to the differences in the relapse definitions, daily dose prescriptions and the selection criteria of the patients.

The relapse rate found in the present study was 45.12%, which is consistent with previous findings. The inclusion of many variables in the current study may help to identify the possible causes of relapse. Furthermore, our study had more female participants than male participants, which may affect the results. Out of cases of 46,8%, women and 36,6% of men reported relapse. Nevertheless, these differences were not statistically significant. However, this relapse rate conforms with a previous study where the relapse rate was 44%, which appeared to increase in the higher age group. (Dreno et al., 2019)

Acne vulgaris significantly impairs quality of life (QoL), particularly in patients of a higher grade of acne, female gender, obesity, illiteracy, and poverty. These patients may benefit from counseling and psychological intervention in parallel with medical management. (Shams et al., 2018) Also, acne relapses were significantly associated with impaired quality of life and productivity loss/absenteeism. (Dreno et al., 2019)

The daily dose of oral isotretinoin of 20 and 40 mg/day was taken by 80% in both group of patients, and the mean duration of isotretinoin use was 7.15(±4.5) months.

Surprisingly our participants who were taking higher doses of oral isotretinoin reported having more relapses. It is puzzling to us but was reported by the patients. This may attributed to recall bias, noncompliance or other which need to be investigated in-depth.

However this finding is similar to a study was conducted among medical students at King Saud University, Riyadh, which showed that 55.5% of the students suffered from acne. (Harfouch et al., 2019; Alajlan et al., 2017) Interestingly, subjects who took higher doses of isotretinoin (40 mg or more) had a higher relapse rate of 49.5%. This finding contrast with the previous study, where investigators found that patients receiving significantly higher doses of isotretinoin are adequately treated and had fewer relapse rates. Rash was the only adverse effect that was significantly more common in the high-dose group during treatment. (Blasiak et al., 2013)

Further, the two major factors contributing to acne relapse were dosage, the time at which the daily dose of isotretinoin was taken (before or after the meal) plus completion of the treatment course. Although the Menstrual history, hormonal disturbances and co-morbidity are very important we did not include them in the self administered questionnaire because hormonal disturbances and co-morbidity need confirmatory test which is beyond the scope of the study.

Reviewed evidence from randomized controlled trials stated that isotretinoin is considered effective and generally safe. While these adverse events were generally mild and dryness related, severe adverse events requiring participant withdrawal occurred in 3_2% of patients randomized to isotretinoin. (Vallerand et al., 2018)

The majority of our participants, 83%, claimed that they completed the treatment regimen, and completion of the treatment course significantly influenced the relapse. While (17%) subjects discontinued the treatment after at least three months of use due to the side effects. About half of the participants did not suffer from

any side effects. Ninety (36.6%) participants reported that they experienced some side effects, but they did not specify it. Dry lips and skin were the most common among side effects specified by the participants. The previous study found that the median persistence for isotretinoin treatment was 139 days and was higher for men. (Biset et al., 2018)

A study in another Arab community found that the most common side effect was chapped and dry lips 96.3%, and secondly, dermatoxerasia 81.6%. It was surprising that 55.6% of all participants suffered from mood disorders and depression. (Harfouch et al., 2019) Ozkol et al. study revealed that decreased paraoxonase-1 activity and increased oxidative stress may have a crucial role in the pathogenesis of isotretinoin's side effects (Ozkol et al., 2015).

A literature review showed a significant association of the use of isotretinoin with improved symptoms compared with the baseline before treatment. Furthermore, there was an association with depressive disorders retrospective studies, but in prospective studies. The authors concluded that the review suggested an association of the use of isotretinoin in patients with acne with significantly improved depression symptoms (Li et al., 2019).

In our study, variables such as smoking, sex, BMI, and family history had no significant relationship with relapse rates. In a retrospective analysis of acne patients in Croatia, investigators did not find a statistically significant correlation between sex, age of onset, and positive family history of acne (Šijak et al., 2019). Another study indicate the association between overweight/obesity and acne (Lech and Reich, 2019).

Acne has various psychosocial impacts on the quality of life of patients. The treating physician should tailor his management to the women's needs taking into consideration preferences, pregnancy, and lactation (Tan et al., 2018).

Approximately 21 (8.5%) patients never took the liver enzyme test, 58 (23.6%) made it only at the beginning of the course, and 97 (39.4%) received it monthly. Our finding is better than a previous study where 55% of participants, had not done liver function tests before starting the course (Harfouch et al., 2019). A *meta*-analysis showed that isotretinoin is associated with a change in the white blood cell count, hepatic and lipid panels. However the proportion of patients with laboratory abnormalities was low. The evidence from this study does not support monthly laboratory testing for use of standard doses of oral isotretinoin (Lee et al., 2016).

The proportion of female patients 205(83.3%) of childbearing potential receiving isotretinoin who may become pregnant should be manage carefully and counsel about pregnancy and test (Goodfield et al., 2010).

In our study, a high number of patients, 173 (70.3%), were not informed about potential relapse by health care providers; and about of these subjects had relapsed. Furthermore, fifty-five (26.8) women did receive counseling on the use of contraception methods while using isotretinoin. A previous study found out that doctors discussed teratogenicity risks in 80% of the patients, and about 50% of patients received written information about risks. Health providers discussed contraception methods, with 58% of patients. About 79% did not do pregnancy tests while on isotretinoin (Algoblan, 2019).

Before the restriction on isotretinoin use in Saudi Arabia, patients were able to take the medication without a prescription, and approximately six patients (2.4%) started the course without a prescription. In the relapse group, approximately 45% of the patients decided to initiate the isotretinoin course once or multiple times. In another study among Arab participants, 8.4% had taken oral isotretinoin without a medical prescription (Harfouch et al., 2019).

The study has some limitations owing to the absence of randomization or blinding. Moreover, patients were managed by different doctors. Since the data entirely depend on patients' honesty, the study has limited generalizability. However, this study provided important information on the possible risk factors that influence relapse rate following oral isotretinoin use.

5. Conclusions

The relapse rate in the present study was high. This study has identified a gap in risk reduction counseling in women who are on isotretinoin. Therefore, it is essential to improve public and professional awareness of isotretinoin use. Measures such as providing advice and written materials emphasizing medication adherence, explaining teratogenicity risks, contraception, and pregnancy test are needed. In addition patients should receive education about the physical and psychological adverse effects of this medication use.

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Ethics approval and consent to participate

The institutional review board of the College of Medicine, King Saud University and Princess Nourah Bint Abdulrahman University approved the project proposal prior to the initiation of the study. Also consent were granted from all participants.

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