

Efficacy of oral isotretinoin in the treatment of acne vulgaris

Amer Bin Al-Zou (1)
Asia Hassan Abdulla Saleh (1)
Mohamed Saeed Bafadhl (2)
Fathi Elkasah (3)

(1) Associate Professor of Dermatology, Faculty of Medicine, University of Aden, Yemen

(2) Associate Professor, Department of Dermatology, College of Medicine, Hadhramout University, Yemen

(3) Associate Professor, Department of Dermatology, Faculty of Medicine, Sirte University, Libya

Corresponding author:

Dr. Amer Bin Al-Zou

Associate Professor of Dermatology; Faculty of Medicine,
University of Aden, Yemen

Email: amer_zou2009@yahoo.com

Received: July 2022 Accepted: August 2022; Published: September 1, 2022.

Citation: Amer Bin Al-Zou et al. Efficacy of oral isotretinoin in the treatment of acne vulgaris. World Family Medicine. 2022; 20(9): 41-50. DOI: 10.5742/MEWFM.2022.9525134

Abstract

Background: Acne vulgaris is a chronic inflammatory disease of pilosebaceous units.

Objective: To assess the presentation of acne vulgaris and to evaluate the efficacy of oral isotretinoin therapy,

Materials and method: This was a retrospective chart review of patients presenting to the dermatology private clinic in Almansoor, Aden, over a 2-year period, who complained of acne vulgaris and were treated with oral isotretinoin.

The collected data were analyzed by SPSS version 17. P-value < 0.05 was considered as statistically significant.

Results: The total study patients were 86 (68.6% females and 31.4% males).

The mean age of patients was 25.6 ± 7.9 years. The difference between means related to sex shows statistically significant ($p = 0.006$).

The patients of the age group ≥ 20 years were predominant with (70.9%).

The most common side effects were cheilitis (54.7%) followed by dry-skin (12.8%), acne flaring (9.3%), hair loss (7.0%) and the lowest side effect was increased liver enzyme in (1.2%) patients. Papulonodular of acne vulgaris is the most common severity type (36.1%) followed by comedones, papules, pustules (32.5%).

Comedones, papules, pustules are more common in the age group < 20 years of age (24.4%) while papulonodular are more common in the age group ≥ 20 years with (33.7%). The difference between values of severity types of acne vulgaris related to age groups is statistically highly significant ($p = 0.000$). Complete clearance occurred in (80.2%) patients followed by partial clearance. Partial clearance was found in (16.3%) patients, most of them treated within 16 weeks (12.8%). The difference between values of therapy response of patients in relation to therapy duration is statistically highly significant ($p = 0.000$).

Conclusion: The results of our study show that isotretinoin is a safe and effective therapy for acne vulgaris with few side effects.

Key words: Efficacy, isotretinoin, treatment, acne vulgaris, Aden

Introduction

Acne vulgaris is a chronic inflammatory disease of pilosebaceous units, characterized by comedones, papules, pustules, nodules, cysts, abscesses and later on sometimes as widespread scarring [1]. Acne is distributed mainly over the face, upper back, chest and upper arms. This disease occurs worldwide and usually starts in adolescence and resolves by the mid-twenties [2]. According to the severity of acne, there are various treatment modalities. They include both topical and systemic therapy. In systemic therapy, the commonly used drugs are oral antibiotics and oral isotretinoin. Isotretinoin (13-cis retinoic acid) represents the single most important advance in acne therapeutics [3].

Isotretinoin has been shown to be useful in controlling acne that does not respond to usual treatments with oral antibiotics and that can produce significant physical or emotional scarring. Dosage of isotretinoin varies; in general 0.5-1.0 mg/kg/day is recommended for acne vulgaris [4]. However, in cases where side effects are not tolerated at the recommended dose, or when used in mild acne with significant psychological distress, low dose and/or intermittent treatment has been advocated in medical literature [2,5,6].

Charakida et al [7] reported that oral isotretinoin has been used to treat moderate-severe acne vulgaris where standard treatment was not effective. Compared to other treatments, isotretinoin has been shown to be more responsive in decreasing the size and secretion of sebaceous glands.

Many researchers have evaluated which isotretinoin dose would have the most efficacy and less adverse events. Recent studies indicated the safety of the oral isotretinoin therapy where the low dose of isotretinoin (< 0.5 mg/kg/day) had no significant effects in metabolic disorders [6,8]. Effective treatment and less severe side effects were found in a study among 638 patients, both male and female, with moderate acne who were treated with isotretinoin at 20 mg/d (approximately 0.3-0.4 mg/kg per day) for 6 months [6]. Another study among 150 Malaysian patients treated with isotretinoin at 10mg on a daily basis until a cumulative dose of 90-110 mg/kg showed that after 24 weeks of treatment, all patients were cleared of acne lesions with a low rate of elevated liver enzymes and serum lipids at 3.3% and 2.7% respectively. There was no case of discontinuation in treatment [9].

Objective

To assess the presentation of acne vulgaris and to evaluate the efficacy of oral isotretinoin in the therapy of acne vulgaris patients in Aden, Yemen.

Materials and Method

We performed a retrospective chart review of all patients presenting to the dermatology private clinic in Almansoor district, Aden, over a 2-year period from January 2020 to December 2021.

Eighty-six patients were diagnosed with acne vulgaris and treated with isotretinoin capsules 0.5-1 mg / kg body weight once or twice daily. All information was obtained from the patients' charts in our private clinics.

The collected data were sex, age, severity of acne vulgaris, duration of therapy, laboratory result, side effects and therapy response.

The collected data were tabulated and statistical analysis was done by estimating rates, means and standard deviations, Fisher test was used and p-value < 0.05 was considered as statistically significant. The statistical software package SPSS version 17 was used.

Results

We enrolled 86 patients in our study who suffered of acne vulgaris and who were treated with isotretinoin. The study patients included 59 (68.6%) females and 27 (31.4%) males with a ratio female to male of 2.2:1.

The mean age of patients was 25.6 ± 7.9 years (range, 15 to 45 years). The mean age of female patients was 26.1 ± 8.5 years and the mean age of male patients was 24.7 ± 6.5 years. The difference between means related to sex shows statistically significant ($p = 0.006$). The patients of the age group ≥ 20 years were predominant with 61 (70.9%) then the age group < 20 years old with 25 (29.1%), as shown in Table 1, Figure 1 and Figure 2.

Table 2 reveals the distribution of side effects and severity of acne vulgaris related to sex. The most common side effects were cheilitis 47 (54.7%) followed by dry-skin 11 (12.8%), acne flaring 8 (9.3%), hair loss 6 (7.0%), back pain, epistaxis and irregular menses, each one in 3 (3.5%) patients.

Onycholysis and visual disturbance found each one in 2 (2.3%) patients and the lowest side effect was increased liver enzyme in 1 (1.2%) patient.

The difference between values of side effects related to sex is statistically not significant ($p > 0.05$). Papulonodular acne vulgaris is the most common severity type of acne vulgaris 31 (36.1%) followed by comedones, papular, pustules 28 (32.5%) and nodulocystic scar 27 (31.4%). Papulonodular and comedones, papules, pustules are most common in female patients 27 (31.4%) and 21 (24.4%) respectively while nodulocystic scar was found in male patients 16 (18.6%). The difference between values of severity types of acne vulgaris related to sex is statistically significant ($p < 0.05$) as shown in Table 2.

Table 1: Distribution of variables of the study patients (n=86)

Variables	No	%
Sex:		
Female	59	68.6
Male	27	31.4
Age range (years):	15-45	
Mean age + SD (years):		
Mean age of patients	25.6 ± 7.9	
Mean age of females	26.1 ± 8.5	
Mean age of males	24.7 ± 6.5	
p-value	0.006	
Age groups (years):		
< 20	25	29.1
≥ 20	61	70.9
Severity:		
Comedones, papules, pustules	28	32.6
Papulonodolar	31	36.0
Nodulocystic scar	27	31.4
Duration of therapy (weeks):		
12 weeks	10	11.6
16 weeks	60	69.8
20 weeks	16	18.6

Figure 1: Distribution of study patients related to sex

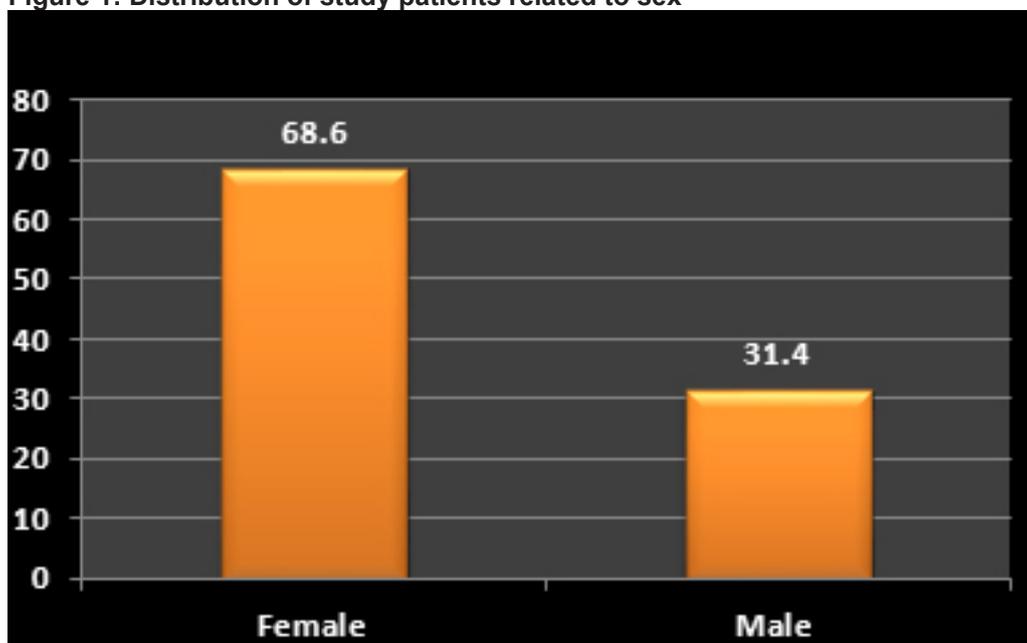


Figure 2: Variables percentage of the study patients

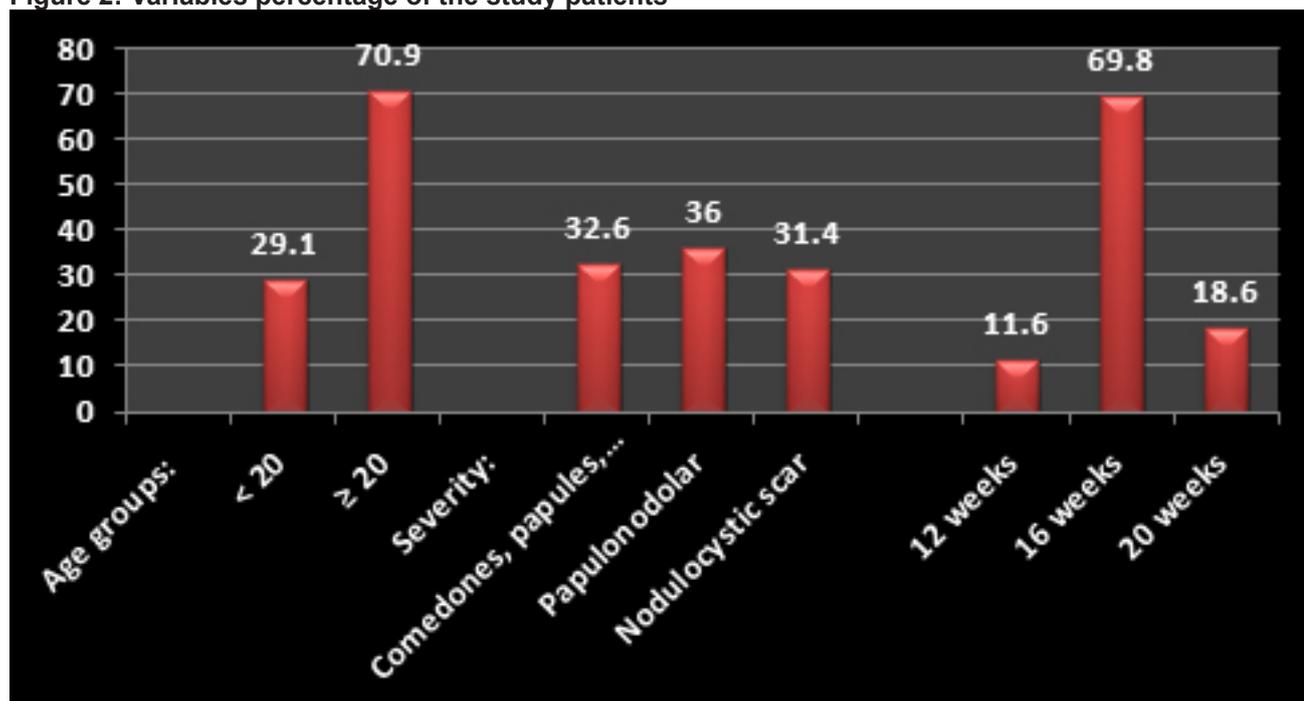


Table 2: Distribution of side effects and severity of acne vulgaris related to sex (n = 86)

Variables	Sex				Total		p-value
	Female		Male		No	(%)	
	No	(%)	No	(%)	No	(%)	
<i>Side effect:</i>							P > 0.05
Cheilitis	33	(38.4)	14	(16.3)	47	(54.7)	
Dry skin	6	(7.0)	5	(5.8)	11	(12.8)	
Acne flaring	5	(5.8)	3	(3.5)	8	(9.3)	
Hair loss	5	(5.8)	1	(1.2)	6	(7.0)	
Back pain	2	(2.3)	1	(1.2)	3	(3.5)	
Epistaxis	1	(1.2)	2	(2.3)	3	(3.5)	
Irregular menses	3	(3.5)	0	(0.0)	3	(3.5)	
Onycholysis	2	(2.3)	0	(0.0)	2	(2.3)	
Visual disturbance	2	(2.3)	0	(0.0)	2	(2.3)	
Increase liver enzyme	0	(0.0)	1	(1.2)	1	(1.2)	
Total	59	(68.6)	27	(31.4)	86	(100)	
<i>Severity:</i>							P = 0.001
Comedones, papules, pustules	21	(24.4)	7	(8.1)	28	(32.5)	
Papulonodular	27	(31.4)	4	(4.7)	31	(36.1)	
Nodulocystic scar	11	(12.8)	16	(18.6)	27	(31.4)	
Total	59	(68.6)	27	(31.4)	86	(100)	

Table 3 reveals the distribution of acne vulgaris severity related to age groups. We determined the patients' ages in two groups, less than 20 years and ≥ 20 years. Comedones, papules, pustules are more common in the age group < 20 years of old 21 (24.4%) while papulonodular was more common in the age group ≥ 20 years with 29 (33.7%) also, nodulocystic scar was more common in the age group ≥ 20 years of old with 25 (29.2%).

The difference between values of severity types of acne vulgaris related to age groups is statistically highly significant ($p = 0.000$) as shown in Table 3.

Table 3: Distribution of severity related to age groups

Variables	Age group (years)				Total		p-value
	< 20		≥ 20		No	(%)	
	No	(%)	No	(%)	No	(%)	
<i>Severity:</i>							
Comedones, papules, pustules	21	(24.4)	7	(8.1)	28	(32.5)	P = 0.000
Papulonodular	2	(2.3)	29	(33.7)	31	(36.0)	
Nodulocystic scar	2	(2.3)	25	(29.2)	27	(31.5)	
Total	25	(29.1)	61	(70.9)	86	(100)	

Table 4 and Figure 3 show the distribution of therapy response of acne vulgaris. Complete clearance was in 69 (80.2%) patients followed by partial clearance in 14 (16.3%) and no clearance in 3 (3.5%) patients.

Table 4: Distribution of therapy response

Variables	No	%
<i>Therapy response:</i>		
Complete clearance	69	80.2
Partial clearance	14	16.3
No clearance	3	3.5
Total	86	100

Figure 3: Therapy response percentage to oral isotretinoin

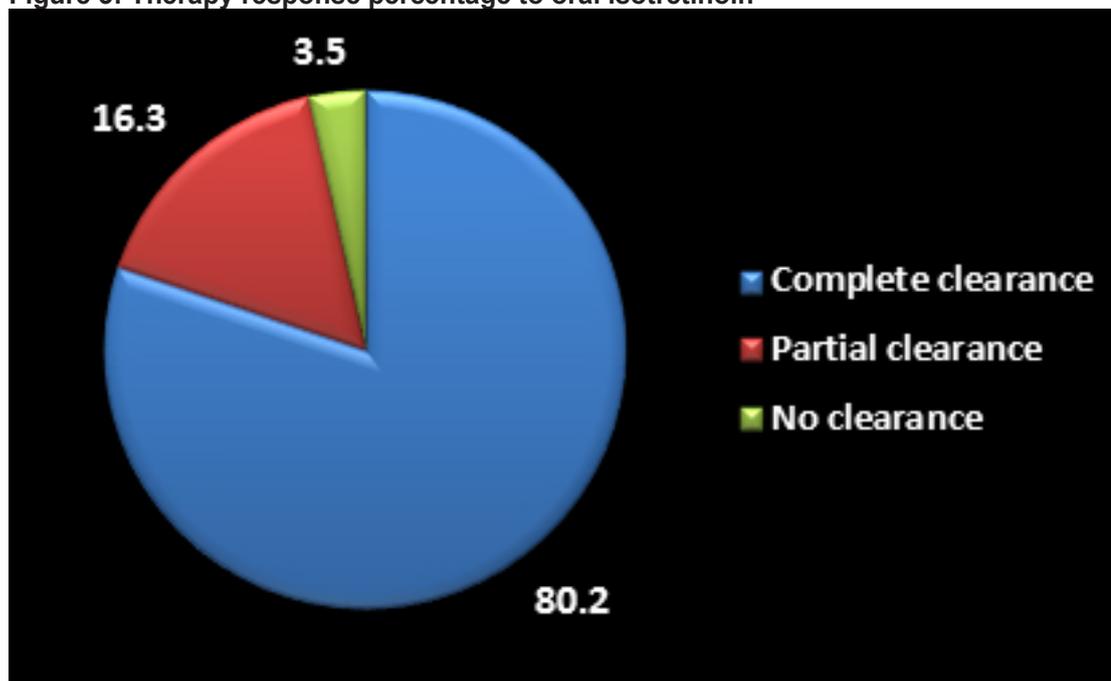


Table 5 illustrates the distribution of therapy-duration related to therapy response. Complete clearance was found in 69 (80.2%) patients, distributed among therapy duration 16 weeks in 49 (57.0%) patients, followed by 20 weeks in 16 (18.6%) patients and 12 weeks in 4 (4.6%) patients. Partial clearance was found in 14 (16.3%) patients, most of them treated within 16 weeks 11 (12.8%). In addition no clearance found in 3 (3.5%) patients treated through 12 weeks. The difference between values of therapy response of patients in relation to therapy duration is statistically highly significant ($p = 0.000$) as shown in Table 5.

Table 5: Distribution of therapy duration related to therapy response

Variables	Therapy response			Total No (%)	p-value		
	No	CC (%)	No			PC (%)	No
<i>Therapy duration:</i>							
12 weeks	4	(4.6)	3	(3.5)	3	(3.5)	P = 0.000
16 weeks	49	(57.0)	11	(12.8)	0	(0.0)	
20 weeks	16	(18.6)	0	(0.0)	0	(0.0)	
Total	69	(80.2)	14	(16.3)	3	(3.5)	

CC = Complete clearance; PC = Partial clearance; NC = No clearance.



Before and after 16 weeks of oral isotretinoin



Before and after 20 weeks of oral isotretinoin



Before and after 4 weeks of oral isotretinoin



Before and after 16 weeks of oral isotretinoin



Acne flaring three weeks after taking oral isotretinoin



Cheilitis side effect of oral isotretinoin

Discussion

Acne vulgaris is one of the most common skin diseases in Europe [10], and the most common in the USA [11], affecting more than 80% of adolescents and young adults [10], and persisting for decades in many cases [12]. It is a chronic inflammatory disease of the pilosebaceous unit, presenting with symptoms of inflammation – erythema, swelling, discomfort – with scarring reported in 43% of patients [13]. As often occurs with dermatological conditions [14], such symptoms have inevitable psychological and social repercussions [15].

Our present study found 86 patients with acne vulgaris treated with oral isotretinoin during the 2 years of the study period and they were 59 (68.6%) females and 27 (31.4%) males with a ratio female to male 2.2:1.

Thai-Van et al [16] reported in their study in Vietnam that the majority of patients were females (80.8%) while male patients were (19.2%) with a ratio female to male 4.2:1.

Previous reviews have reported that the prevalence of acne is higher in females than males [17,18]. Similarly, the Global Burden of Disease Study conducted in 2010 estimated that the prevalence of acne was 8.96% in males, lower than the estimated prevalence of 9.81% in females [19]. Lynn et al [18] also noted higher acne prevalence in females at younger ages, possibly due to the earlier onset of puberty in females relative to males.

In our present study, the mean age of patients was 25.6 ± 7.9 years (range, 15 to 45 years). The mean age of female patients was 26.1 ± 8.5 years and the mean age of male patients was 24.7 ± 6.5 years. The difference between means related to sex shows statistically significant ($p = 0.006$). The patients of the age group ≥ 20 years were predominant with 61 (70.9%) then the age group < 20 years old with 25 (29.1%).

A previous study in Saudi Arabia by Alshammari et al [20] reported similar findings to our results. They mentioned that the mean age of patients using isotretinoin was $25.1(\pm 5.2)$ years; the majority of study patients were females (83.3%).

Algoblan et al [21] reported similar findings to our results. They reported that most of the patients who received isotretinoin were young women.

In the present study we found the predominant side effects were cheilitis (54.7%) followed by dry-skin (12.8%), acne flaring (9.3%), hair loss (7.0%), back pain, epistaxis and irregular menses each one in (3.5%) patients.

Onycholysis and visual disturbance was found each one in (2.3%) patients and the lowest side effect was increased liver enzymes in (1.2%) patient. The difference between values of side effects related to sex is statistically not significant ($p > 0.05$).

A study published by Harfouch et al [22] from Syria reported to some extent similar results as our study results. They mentioned that the most frequent side effect was chapped and dry lips 96.3% and secondly dermatoxerasia 81.6% with no significant relationship with gender. In addition 34.7% of all participants suffered from ophthalmoxerosis.

Also, our results correspond with a previous Indian study where cheilitis was the most common observed adverse effect as a percentage of (98%) of all participants [23].

In a previous Saudi study [24], dryness of the lips and face was on the top of isotretinoin side effects list (64.1%), and in another Saudi study [25], lips dryness percentage was approximately 68%.

Papulonodular acne vulgaris is the most common severity type of acne vulgaris (36.1%) followed by comedones, papules, pustules 28 (32.5%) and nodulocystic scar 27 (31.4%). Papulonodular and comedones, papules, pustules are most common in female patients 27 (31.4%) and 21 (24.4%) respectively while nodulocystic scar was found in male patients 16 (18.6%). The difference between values of severity types of acne vulgaris related to sex is statistically significant ($p < 0.05$).

Williams et al [26] reported that acne patients typically present with comedones, papules and pustules. Comedones can be subdivided into two types – open comedones (blackheads), which are clogged follicles with openings exposing its contents to the air, and closed comedones (white heads), which are clogged follicles without an opening [27]. Papules are raised lesions on the skin that are smaller than 1cm in diameter while pustules are similar to papules but inflamed and filled with pus [27]. In patients with severe acne, nodules and cysts – inflamed, swollen lesions that are at least 5mm large – may be present [26-27]. In addition, other symptoms such as the scars, erythema and hyperpigmentation may be observed in acne patients [27]. Lynn et al [18] found that severe acne is more common in males compared to females.

We found in our study comedones, papules, and pustules are more common in the age group < 20 years of old (24.4%) while papulonodular more common in the age group ≥ 20 years with (33.7%) also, nodulocystic scar was more common in the age group ≥ 20 years of age with 25 (29.2%). The difference between values of severity types of acne vulgaris related to age groups is statistically highly significant ($p = 0.000$).

Acne vulgaris, a chronic, immune-mediated, multifactorial inflammatory disease that affects the pilosebaceous unit is among the three most prevalent dermatoses worldwide [28]. It affects 80% to 90% of the world population at some stage in life, with a peak prevalence between 16–20 years [29,30,31].

In the present study, complete clearance was found in (80.2%) patients, distributed among therapy durations 16 weeks in (57.0%) patients, followed by 20 weeks in (18.6%) patients and 12 weeks in (4.6%). Partial clearance was

found in 14 (16.3%) patients, most of them treated within 16 weeks, 11 (12.8%). The difference between values of therapy response of patients in relation to therapy duration is statistically highly significant ($p = 0.000$).

Picosse et al [32] reported that the efficacy of oral isotretinoin in the treatment of acne vulgaris has been demonstrated in numerous publications since the 80s, with more than 90% of reduction of inflammatory lesions.

Most patients who receive oral isotretinoin will be free of acne by the end of 16 – 24 weeks of treatment depending on the dose administered [33]. Recent clinical experience suggests that the long-term cure rate may be lower than was initially thought [34].

Similar to our finding was that reported by Layton [33] that 85% of patients who receive a dose of 0.5–1.0 mg/kg/day are virtually clear of their acne by 16 weeks.

Conclusion

The results of our study show that isotretinoin is a safe and effective therapy in the treatment of comedones, papules, pustules, papulonodular and nodulocystic scar acne vulgaris with few side effects. In our study, complete clearance was found in (80.2%) patients and partial clearance found in (16.3%) patients. Our results are in agreement with the findings from the most recent published studies.

References

- Dreno B, Poli F. Epidemiology of acne. *Dermatology* 2003;43: 1042-8
- Kaymak Y, Ilter N. The effectiveness of intermittent isotretinoin treatment in mild or moderate acne. *J Eur Acad Dermatol Venereol.* 2006; 20:1256-60
- Harper JC, Thiboutot DM. Pathogenesis of acne: Recent research advances. *Adv Dermatol* 2003; 19:1-10
- Layton A M, Dreno B, Gollnick HPM, Zouboulis CC. A review of the European Directive for prescribing systemic isotretinoin for acne vulgaris *JEADV* 2006; 20: 773 –776.
- Mandekou-Lefaki I, Delli F, Teknetzis A. Low-dose schema of isotretinoin in acne vulgaris. *Int J Clin Pharmacol Res* 2003; 23:41–46.
- Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. *J Am Acad Dermatol* 2006; 54: 644–646.
- Charakida A, Mouser PE, Chu AC. Safety and side effects of the acne drug, oral isotretinoin. *Expert opinion on drug safety.* 2004;3(2): 119–29.
- Sardana K, Garg VK, Sehgal VN, Mahajan S, Bhushan P. Efficacy of fixed low-dose isotretinoin (20 mg, alternate days) with topical clindamycin gel in moderately severe acne vulgaris. *J Euro Acad of Dermatol. and Venereol.* 2009; 23(5):556–60.
- Yap FB. Safety and efficacy of fixed-dose 10 mg daily isotretinoin treatment for acne vulgaris in Malaysia. *J of Cosm dermatol.* 2017; 16(3): 348–52.
- Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol.* 2013;168(3):474–485.
- American Academy of Dermatology [Website]. Available from: <https://www.aad.org/public/diseases/acne-and-rosacea/acne#overview>. Accessed July31, 2019.
- Dréno B, Layton A, Zouboulis CC, et al. Adult female acne: a new paradigm. *JEADV.* 2013;27:1063–1070.
- Tan J, Kang S, Leyden J. Prevalence and Risk factors of acne scarring among patients consulting dermatologists in the USA. *J Drugs Dermatol.* 2017;16(2):97–102.
- Dalgard F, Gieler U, Tomas-Aragones L, et al. The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. *J Invest Dermatol.* 2015;135(4):984–991.
- Guerra-Tapia A, Asensio Martínez Á, García Campayo J. The emotional impact of skin diseases. *Actas Dermosifiliogr.* 2015;106(9):699–702.
- Thai-Van TL, Minh PN, Thuy PTT, Gandolfi M, Satolli F, et al. Efficacy of Oral Low-Dose Isotretinoin in the Treatment of Acne Vulgaris in Vietnam. *Open Access Maced J Med Sci.* 2019; 7(2): 279-282
- Janani, S. & Sureshkumar, R. A Comprehensive Review on Acne, its Pathogenesis, Treatment, In-Vitro and In-Vivo Models for Induction and Evaluation Methods. *Int J Pharm Sci.* 2019; 10(7): 3155–3177.
- Lynn, D. D., Umari, T., Dunnick, C. A. & Dellavalle, R. P. The epidemiology of acne vulgaris in late adolescence. *Adolesc Health Med Ther.* 2016; 7: 13–25.
- Vos T, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet.* 2012; 380(9859), 2163–96,
- Alshammari SA, Alamri Y, Alanazi AM, Almuhan SA, Pinjabi L, Alsnaidi NA. Prevalence and associated risk factors of acne relapse among Saudi acne vulgaris patients using isotretinoin. *Saudi Pharmaceutical Journal.* 2020; 28(3): 374-379
- Algloban S, Bakhsh S, Alharith R. Women's experiences regarding isotretinoin risk reduction counseling in Riyadh. *J Dermatol Surgery.* 2019; 23(1): 1-3
- Harfouch RM, Bitar J, Badawi R, Salloum A, Spih A, Marashli N, Boubou M, Chouman F. A Survey on the most common side effects of Isotretinoin among A Group of Syrian Patients. *Research J. Pharm. and Tech* 2019; 12(1): 40-42.
- Parinitha Rao K, Ramesh Bhat M, Nandakishore B, Dandakeri S, Martis J, et al. Safety and efficacy of low-dose isotretinoin in the treatment of moderate to severe Acne vulgaris. *Indian Journal Dermatology.* (2014). 59: 316
- Al-Harbi M. Concerns and Awareness of Acne Patients About Isotretinoin in Qassim Region of Saudi Arabia. *Int J Health Sci (Qassim).* 2010 Jan; 4(1): 47–51.
- Al-Suhaibani S. The Impact of Oral Isotretinoin Dryness And Depression on Saudi Women in Qassim Region: A Survey. *J Depress Anxiety,* (2016). 5: 245.
- Williams, H. C., Dellavalle, R. P. & Garner, S. Acne vulgaris. *The Lancet.* 2012; 379(9813), 361–372.
- Mahto A. Acne vulgaris. *Medicine.* 45(6), 386–9, <https://doi.org/10.1016/j.mpmed.2017.03.003> (2017).
- Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol.* 2014; 134: 1527–1534.

29. Tan HH, Tan AW, Barkham T, Yan XY, Zhu M. Community-based study of acne vulgaris in adolescents in Singapore. *Br J Dermatol*. 2007;57: 547–551.
30. Bagatin E, Timpano DL, Guadanhim LRS, Nogueira VMA, Terzian LR, Steiner D. Acne vulgaris: prevalence and clinical forms in adolescents from São Paulo, Brasil. *An Bras Dermatol*. 2014; 89:250–258.
31. Augustin MI, Herberger K, Hintzen S, Heigel H, Franzke N, Schafer I. Prevalence of skin lesions and need for treatment in a cohort of 90,880 workers. *Br J Dermatol*. 2011; 165:865–873.
32. Picosse FR, Bonatto DC, Hassun KM, Talarico Filho S, Azulay DR, Bagatin E. Treatment of moderate to severe acne vulgaris with an oral isotretinoin similar to the reference product. *Surg Cosmet Dermatol*. 2016; 8(2):121-7.
33. Layton A. The use of isotretinoin in acne. *Dermatoendocrinol*. 2009; 1(3): 152-169
34. Azoulay L, Oraichi D, Berard A. Isotretinoin therapy and the incidence of acne relapse: a nested case-control study. *Br J Dermatol*. 2007; 157:1240–1248.