Journal of Clinical & Experimental Dermatology Research

Skroza et al., J Clin Exp Dermatol Res 2015, 6:5
DOI: 10.4172/2155-9554.10000300

Research Article Open Access

Gender Matter in Isotretinoin Therapy for Acne Vulgaris? A Retrospective Study

Nevena Skroza, Riccardo Pampena[#], Ersilia Tolino[*#], Sara Zuber, Giorgio La Viola, Nicoletta Bernardini, Ilaria Proietti, Veronica Balduzzi, Fowzieh Rasras, Concetta Potenza

Dermatology Unit "Daniele Innocenzi", Dept. of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino, Terracina, Italy

[#]These authors contributed equally to this work

[*]**Corresponding author:** Ersilia Tolino, Dermatology Unit "Daniele Innocenzi", "Sapienza" University of Rome, A. Fiorini Hospital, via Firenze, snc 04019, Terracina (LT), Italy, Tel: +39 0773708811; E-mail: ersiliatolino@gmail.com

Received date: Apr 20, 2015; **Accepted date:** August 26, 2015; **Published date:** August 31, 2015

Abstract

Introduction: Gender differences have been recently highlighted for several aspects of acne vulgaris such as epidemiology, pathogenesis, clinical course, quality of life and treatment outcome. In particular a shorter but more severe clinical course has been reported in males than in females; nevertheless, usually men have their quality of life less affected.

Aim: To determine if the response and the adverse events to 1 cycle of oral isotretinoin therapy can be influenced by gender.

Methods: A retrospective study was conducted on consecutive patients affected by acne vulgaris and treated with oral isotretinoin. Global acne grading system (GAGS), acne-related quality of life (AQoL) and isotretinoin-related adverse events were considered as outcome measures and were evaluated before (T0), every month during administration and 4 weeks after the withdrawal (T1) of oral isotretinoin therapy. Mann-Whitney U test and Wilcoxon signed-rank test were used for quantitative parameters and Fisher exact test for qualitative ones.

Results: Forty-nine acneic patients were retrospectively selected (33 males 67.3% and 16 females -32.7%; median age: 19 years). Patients had received a median dosage of isotretinoin of 0.4 mg/kg/die for a median period of 5 months; no differences in outcome measures among genders were reported.

Limitations: The study is retrospective and the sample is small and not homogenously distributed among genders, as males are double in number than females.

Conclusions: In our study population gender didn't influence neither the clinical and the quality of life outcome measures nor the occurrence of adverse events to oral isotretinoin therapy for acne.

Keywords: Acne; Gender; Isotretinoin; Therapy; Adverse events

Abbreviations:

GAGS: Global Acne Grading System; AQoL: Acne-Related Quality of Life; PCOS: Polycystic Ovarian Syndrome; GWAS: Genome Wide Association Study

Introduction

Acne (synonym "acne vulgaris") is one of the most frequent skin diseases. It primary involves adolescents of Western industrialized countries, with a prevalence between 50% and 95%. It shows a male predominance and the frequency of moderate and severe forms is 20-35% [1,2].

The pathogenesis involves both innate and adaptive immunity and 4 main factors interact: seborrhoea, pilar infundibular hyperkeratinization, propionibacterium acnes follicular colonization and release of inflammatory mediators [3].

Acne is a polymorphic disease and several clinical forms have been described; however 3 major subtypes could be recognised: comedonal, papulopustular and nodular/conglobate [4].

The therapeutic armamentarium involves both topical and systemic treatments. Oral isotretinoin is widely considered as the most effective treatment option, as it acts against all major pathogenic factors of acne [5].

In last decades, few studies have suggested that the clinical course and the therapeutic outcome of acne could be influenced by gender, although conflicting results have been reported at these purposes [6]. In particular male patients seem to be prone to develop more severe forms, with a shorter clinical course, than females, [7] while females usually have their quality of life indexes more affected than males [8,9].

An expert panel of Canadian dermatologists [10] has recently recommended that the therapeutic management of acne should be based not only on clinical severity assessment, as suggested by the majority of guidelines, [11] but on multiple demographics and psychosocial aspects, including gender [12]. Furthermore, male gender has

been associated with the occurrence of more severe flares, during oral isotretinoin therapy, than females [13,14].

We retrospectively analyzed a 2-year experience with oral isotretinoin for acne, evaluating clinical and quality of life indexes and side effects occurrence, in order to assess if gender could influence these outcome measures.

Methods

Study population

We retrospectively selected consecutive patients affected by acne vulgaris and treated with oral isotretinoin, who were attending our outpatient clinic from January 2009 to January 2011.

Demographic data and information about clinical history and oral isotretinoin therapy were collected from our records, which included: comorbidities, family history of acne, previous therapies, number of therapeutic cycles, mean dosage and duration of treatment (expressed as the duration in months of the first cycle), GAGS (global acne grading system) and AQoL (acne-related quality of life) values at T0 (baseline) and T1 (4 weeks after the first isotretinoin cycle withdrawal).

Furthermore database was checked for clinical and laboratory isotretinoin-related adverse events; the former included: cheilitis, xerosis, scalp or hand dermatitis, keratitis, myalgia, and epistaxis, while the latter consisted of: altered blood cell count, high lipid levels, liver and/or renal dysfunction. All the patients had been monthly evaluated for such adverse events during the isotretinoin treatment and at least for 1 month after therapy withdrawal.

Outcome measures

We considered GAGS and AQoL scores and occurrence of clinical and/or laboratory adverse events as outcome measures. Regarding adverse events, patients were classified in 2 groups, according to both the occurrence (presence or absence) and the number (1 or >1) of adverse events.

Our primary endpoint consisted in the evaluation of gender influence on outcome measures. For this purpose we compared the improvement of GAGS and AQoL scores (from T0 to T1) and to the occurrence of adverse events among genders. As secondary endpoint we considered the clinical and quality of life improvement (GAGS and AQoL scores) and the occurrence of adverse event in the entire study population.

GAGS score is widely used to express clinical severity of acne vulgaris. It ranges from 0 to 44: for each type of lesion is given a value depending on severity (no lesions=0, comedones=1, papules=2, pustules=3 and nodules=4); a local score for different areas (forehead, right cheek, left cheek, nose, chin, chest and upper back) is calculated using the formula: Local score=Factor × Grade. A factor of 3 is assigned to the chest and upper back, a factor of 2 to the forehead and cheeks and a factor of 1 to the other sides. The global score is the sum of local scores. A score of 1-18 is considered mild; 19-30, moderate; 31-38, severe; and >39, very severe [15].

AQoL is a 19-item patient reported outcome measure evaluating the the acne-related quality of life.

The questionnaire consists of 4 domains: self-perception, role-emotional, acne symptoms and role-social. The first 3 domains are composed of 5 items each with scores ranging from 0 to 30. The role-social domain includes 4 items with scores ranging from 0 to 24. Responses are based on a 7-point adjectival scale; responses of "extremely" to "not at all" are used for 16 of the 19 items and responses of "extensive" to "none" are used for 3 of the 5 symptom-related items. The higher the AQoL score, the better the quality of life [16].

Statistical Analysis

Data are expressed as median values

Mann-Whitney U test and Wilcoxon signed-rank test were used to compare the quantitative parameters, as the normality test of Kolmogorov-Smirnov failed (age, months of the first cycle, dosage, GAGS and AQoL values and GAGS and AQoL % improvement).

Fisher exact test was employed for qualitative variables (family history of acne vulgaris, occurrence and number of clinical and laboratory adverse events).

Statistical analysis was performed with IBM SPSS 21.0 package (Statistical Package for Social Sciences, SPSS Inc., Chicago, Ill.). Statistical significance was fixed at $p<0.05$.

Results

We retrospectively selected 49 patients affected by acne and treated with oral isotretinoin. Thirty-three (67.3%) were males and 16 (32.7%) were females, with a median age of 19 (16-37) years. Table 1 summarizes demographic features of the study population.

The median age was significantly lower in males than females (18 years vs. 23.5 years, respectively; Mann-Whitney U test, $p<0.001$).

Almost all the patients received 1 cycle of oral isotretinoin and were treated for a median period of 5 months with a median dosage of 0.4 mg/kg/die; only 3 (6.1%) female patients received more than 1 cycle (2 received 2 cycles and only 1 received 3 cycles); thus we decided to consider only the duration of the first cycle for these patients.

No differences were highlighted among genders regarding family history of acne, isotretinoin doses, duration of the first cycle of therapy and in GAGS and AQoL scores at T0.

Regarding comorbidities, only 5 females were affected by polycystic ovarian syndrome (PCOS) and had been previously treated with oral estroprogestins; another female patient had received doxycycline 100 mg/bid for 3 months. However no concomitant therapies to oral isotretinoin were reported.

We found a significant improvement of the median values of both GAGS and AQoL scores after 1 cycle of oral isotretinoin in the entire study population (from 27 to 5 for GAGS and from 59 to 92 for AQoL; Wilcoxon signed-rank test $p<0.001$ for both [data not tabulated]), however no differences were highlighted among genders both in median values of GAGS and AQoL at T1 (median GAGS at T1: 5 in males and 2 in females; median AQoL at T1: 93 in males and 92 in females; Mann-Whitney U test $p=0.876$ and $p=0.393$, respectively) and in their median percentage of improvement from T0 to T1 (median GAGS% improvement: 47.7% in males and 51.1% in females; median AQoL% improvement: 30% in males and 33% in females; Mann-Whitney U test $p=0.492$ and $p=0.337$, respectively) (Table 2).

Variables		Males 33 (67.3%)	Females 16 (32.7%)	Total 49	p value#
Median Age (years)		18 (16-33)	23.5 (17-37)	19 (16-37)	<0.001*
Number of cycles		1 (1-1)	1 (1-3)	1 (1-3)	0.011*
Months of the first cycle		5 (1-6)	5 (1-6)	5 (1-6)	0.899*
Dose/kg (mg/kg/die)		0.4 (0.2-0-6)	0.4 (0.3-0.5)	0.4 (0.2-0-6)	0.727*
Familiar history of acne vulgaris	No	11 (33.3%)	3 (18.7%)	14	0.336†
	Yes	22 (66.7%)	13 (81.3%)	35	
Comorbidities	No	33 (100%)	11 (68.7%)	44	0.002†
	Yes	0 (0%)	5 (31.3%)	5	
GAGS T0		25 (20-41)	29 (22-36)	27 (20-41)	0.164*
AQoL T0		61 (8-92)	57 (10-87)	59 (8-92)	0.393*

#p value<0.05; *Mann-Whitney U test for quantitative variables; †Fisher test for qualitative variables; GAGS: Global Acne Grading System; AQoL: Acne Quality of Life.

Table 1: Demographic data and GAGS and AQoL values at T0, expressed per gender.

Variables		Males 33 (67.3%)	Females 16 (32.7%)	Total 49	p value#
Number of clinical adverse events	1	28 (84.8%)	10 (71.4%)	38	0.419*
	>1	5 (15.2%)	4 (28.6%)	9	
Occurrence of clinical adverse events	No	0 (0%)	2 (12.5%)	2	0.102†
	Yes	33 (100%)	14 (87.5%)	47	
Occurrence of laboratory adverse events	No	32 (97.0%)	16 (100%)	48	0.673†
	Yes	1 (3.0%)	0 (0%)	1	
GAGS T1		5 (0-25)	2 (0-25)	5 (0-25)	0.876*
AQoL T1		93 (15-120)	92 (20-120)	92 (15-120)	0.393*
GAGS% improvement		47.7% (15.9%-93.2%)	51.1% (9.1%-81.8%)	50.0% (9.1%-93.2%)	0.429*
AQoL% improvement		30.0% (7.0%-78.0%)	33.0% (3.0%-94.0%)	30.0% (3.0%-94.0%)	0.337*

#p value<0.05; *Mann-Whitney U test for quantitative variables; †Fisher test for qualitative variables; GAGS: Global Acne Grading System; AQoL: Acne Quality of Life.

Table 2: Adverse events and GAGS and AQoL values and percentage of improvement at T1, expressed per gender.

Figures 1 and 2 report the clinical pictures of a male and a female patient, respectively, before and after 1 cycle of oral isotretinoin therapy.

All but 2 female patients experienced at least 1 isotretinoin-related clinical adverse event, however no severe or systemic events were reported. Only 1 male patient experienced a laboratory adverse event, namely a transitory mild thrombocytopenia that resolved in 1 week after isotretinoin withdrawal.

Thirty-seven patients had only 1 clinical adverse event (27 males-73.0% and 10 females-27.0%); the most common were cheilitis (22 patients-59.5%; 16 males-72.7% vs. 6 females-27.3%) and xerosis (12 patients-32.4%; 10 males-80.3% vs. 2 females-19.7%), while epistaxis and scalp dermatitis were reported only in 2 different female patients (5.4% in total) and myalgia only in 1 male (2.7%).

Nine patients experienced 2 clinical adverse events (5-55.6% males and 4 females-44.4%) and 1 male patient (2.1%) reported 3 of them (cheilitis, xerosis and keratitis). The most common association was between cheilitis and xerosis (6 patients-66.7%; 4 males vs. 2 females); moreover 1 male (11.1%) had both cheilitis and keratitis and 2 females (22.2%) had both cheilitis and scalp or hand dermatitis.

No significant differences were reported among genders regarding both the occurrence and the number (1 or >1) of clinical and laboratory adverse events (Table 2).

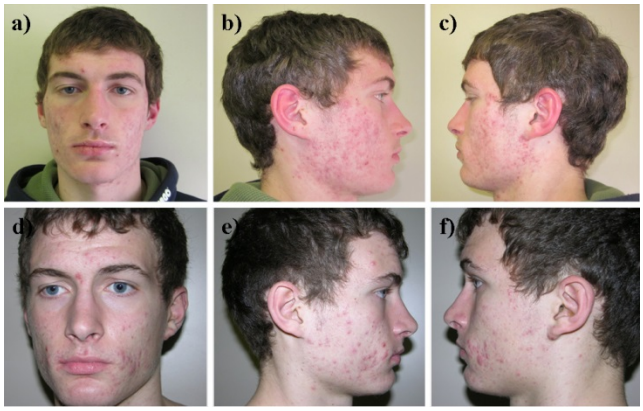

Figure 1: A 19-year-old male patient: a-c) before and d-f) after a 4 months cycle of oral isotretinoin therapy.

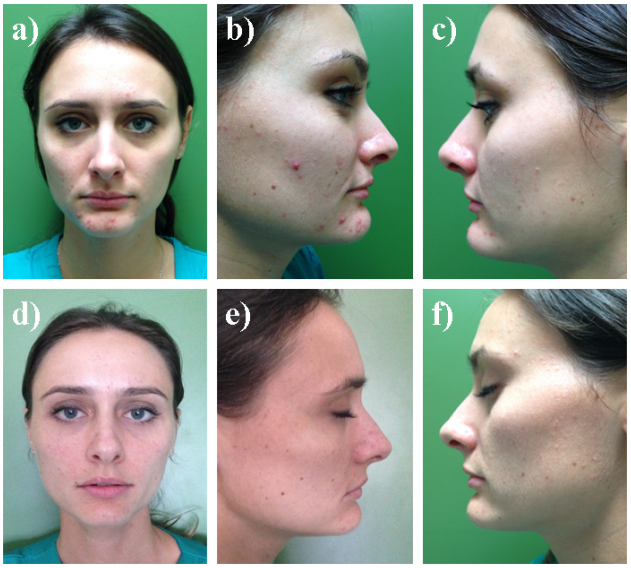

Figure 2: A 26-year-old female patient: a-c) before and d-f) after a 5 months cycle of oral isotretinoin therapy.

Discussion

In this study we didn't find significant differences among genders, neither in clinical and quality of life outcome measures of isotretinoin therapy, nor in isotretinoin-related adverse events.

Acne is a common skin condition with substantial cutaneous and psychological disease burden. [5] Studies suggest that the emotional impact of acne is comparable to that experienced by patients with systemic diseases, like diabetes and epilepsy [17]. Most severe forms of acne vulgaris are usually associated with greater quality of life impairment [18].

Acne is a multi-factorial inflammatory skin disease involving both genetic and environmental factors. The latter primarily regard life style and in particular diet habits [19]. The former have been primarily suggested by the increased risk of acne in case of a positive family history [20]. Recently a genome wide association study (GWAS) identified several chromosomal loci associated with acne vulgaris; [21] probably also gender and ethnical differences in clinical course and therapy outcomes of acne could be related to genetic factors.

Oral isotretinoin is considered as the most effective treatment in severe forms of acne [5,22]. Recently the European evidence-based guidelines for the treatment of acne stated that systemic isotretinoin must be considered the first-choice treatment for severe papulopustular and nodular/conglobate forms of acne because of its clinical effectiveness, prevention of scarring and quick improvement of patients' quality of life. [5] Experience from more than 3 decades has clearly defined efficacy and safety profiles of this drug [23,24].

Previous studies have only partially clarified the differences between females and males regarding isotretinoin use [13,14].

We reported no significant gender differences in family history of acne vulgaris and in doses and duration of isotretinoin therapy parameters, in our study population; however, only female patients had comorbidities (PCOS) and underwent previous therapies. Besides, males resulted significantly younger than females; this is not surprising, as isotretinoin therapy is usually reserved to the most severe forms of acne vulgaris that involve more frequently male patients, younger than females [7].

Furthermore, GAGS and AQoL showed no significant differences among genders both at T0 and at T1. Contradictory results about the influence of gender on clinical course and quality of life of acne vulgaris have been reported in literature. A greater impairment of clinical scores in males and of quality of life in females has been often reported [7-9].

Regarding adverse events, we didn't find statistically significant differences among genders, both regarding their occurrence and number (1 or >1), even if males are more likely to experience cheilitis and more than 1 averse event, while females are more affected by xerosis.

Limitations of this retrospective study are represented by the small study sample and by the fact that males are double in number than females.

In conclusion, our study didn't show significant differences among genders, neither in clinical and quality of life outcomes of oral isotretinoin treatment nor in isotretinoin-related adverse events occurrence. However further prospective studies, with wider patient samples, are needed to confirm our observations.

References

1. Nijsten T, Rombouts S, Lambert J (2007) Acne is prevalent but use of its treatments is infrequent among adolescents from the general population. J Eur Acad Dermatol Venereol 21: 163-168.
2. Smithard A, Glazebrook C, Williams HC (2001) Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community-based study. Br J Dermatol 145: 274-279.
3. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, et al. (2009) New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol 18: 821-832.

4. Williams HC, Dellavalle RP, Garner S (2012) Acne vulgaris. Lancet 379: 361-372.
5. Nast A, Dréno B, Bettoli V, Degitz K, Erdmann R, et al. (2012) European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 26 Suppl 1: 1-29.
6. Berg M, Lindberg M (2011) Possible gender differences in the quality of life and choice of therapy in acne. J Eur Acad Dermatol Venereol 25: 969-972.
7. Holland DB, Gowland G, Cunliffe WJ (1985) Sex-linked differences in acne vulgaris. Acta Derm Venereol 65: 551-553.
8. Yazici K, Baz K, Yazici AE, Köktürk A, Tot S, et al. (2004) Disease-specific quality of life is associated with anxiety and depression in patients with acne. J Eur Acad Dermatol Venereol 18: 435-439.
9. Aktan S, Ozmen E, Sanli B (2000) Anxiety, depression, and nature of acne vulgaris in adolescents. Int J Dermatol 39: 354-357.
10. Lynde C, Tan J, Andriessen A, Barankin B, Dutil M, et al. (2014) A consensus on acne management focused on specific patient features. J Cutan Med Surg 18: 243-255.
11. Skroza N, Tolino E, Proietti I, Bernardini N, La Viola G, et al. (2014) Women and acne: any difference from males? a review of literature. G Ital Dermatol Venereol .
12. Dréno B1 (2015) Treatment of adult female acne: a new challenge. J Eur Acad Dermatol Venereol 29 Suppl 5: 14-19.
13. Demircay Z, Kus S, Sur H (2008) Predictive factors for acne flare during isotretinoin treatment. Eur J Dermatol 18: 452-456.
14. Fleischer AB Jr, Simpson JK, McMichael A, Feldman SR (2003) Are there racial and sex differences in the use of oral isotretinoin for acne management in the United States? J Am Acad Dermatol 49: 662-666.
15. Doshi A, Zaheer A, Stiller MJ (1997) A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol 36: 416-418.
16. Martin AR, Lookingbill DP, Botek A, Light J, Thiboutot D, et al. (2001) Health-related quality of life among patients with facial acne -- assessment of a new acne-specific questionnaire. Clin Exp Dermatol 26: 380-385.
17. Tasoula E, Gregoriou S, Chalikias J, Lazarou D, Danopoulou I, et al. (2012) The impact of acne vulgaris on quality of life and psychic health in young adolescents in Greece. Results of a population survey. An Bras Dermatol 87: 862-869.
18. Barnes LE, Levender MM, Fleischer AB Jr, Feldman SR (2012) Quality of life measures for acne patients. Dermatol Clin 30: 293-300, ix.
19. Skroza N, Tolino E, Semyonov L, Proietti I, Bernardini N, et al. (2012) Mediterranean diet and familial dysmetabolism as factors influencing the development of acne. Scand J Public Health 40: 466-474.
20. Dreno B, Poli F (2003) Epidemiology of acne. Dermatology 206: 7-10.
21. Zhang M, Qureshi AA, Hunter DJ, Han J (2014) A genome-wide association study of severe teenage acne in European Americans. Hum Genet 133: 259-264.
22. Leyden JJ, Del Rosso JQ2, Baum EW3 (2014) The use of isotretinoin in the treatment of acne vulgaris: clinical considerations and future directions. J Clin Aesthet Dermatol 7: S3-3S21.
23. Gollnick HP, Zouboulis CC (2014) Not all acne is acne vulgaris. Dtsch Arztebl Int 111: 301-312.
24. Hogan DJ, Strand LM, Lane PR (1988) Isotretinoin therapy for acne: a population-based study. CMAJ 138: 47-50.