Advanced Medical Journal, Vol.9, No.3, P.125-133,2024 https://doi.org/10.56056/amj.2024.285

Efficacy and safety of systemic spironolactone for acne in female patients in Sulaymaniyah teaching center of dermatology

Soma Khasrow Abdullah* Mohammed Yousef Saeed Jaff**

Abstract

Background and objectives: Acne vulgaris is a common disease in which hormone plays a role in its pathogenesis. Spironolactone, an androgen receptor blocker is used to treat acne. This study aims to evaluate the efficacy and safety of systemic spironolactone for acne in female patients in our local area.

Methods: Open-label therapeutic trial study performed in the Sulaymaniyah teaching center of dermatology between 1/2/2022 - 1/9/2022, on a total of 47 patients aged 12-38 years old. Patients were divided into two groups in regard to age. Hormonal profile was assessed for all the patients. The 4-grade European classification system was used to classify the acne severity. Spironolactone 100 mg once daily at morning was given to them with follow up monthly for 3 months. Clinical response of the drug was assessed through a decrease in the number of the lesions. Signs and symptoms of the side effects were checked monthly.

Results: In a total of 47 patients, 22 patients were ≤ 25 years and 25 patients were >25 years. A significant difference was recorded in the response rate among the patients' ages and hormonal status of them as 83.3%, 61.1% and 50% of the complete response was in those who were >25 years old and had abnormal testosterone and DHEA-s levels respectively. 100% of non-responder patients were below 25 years old with normal hormonal levels. 55.32% of the patients had no side-effect and menstrual irregularity was the most commonly reported side effect.

Conclusion: Spironolactone is statistically considered an effective and safe line for the treatment of acne vulgaris particularly for acne in female over 25 with abnormal hormonal levels.

Key word: Acne, Female, Hormonal acne, Post-adolescent acne, Spironolactone.

* M.B.Ch.B, KHCMS Dermatology trainee, Shahid Jabar Dermatological Teaching Center, Sulaimani Directorate of Health, Sulaimaniyah, Iraq. Email: - soma.kh88@gmail.com. Corresponding author

** M.B.Ch.B. FIBMS (dermatology),ISDS, ESLDC, Assistant Professor of dermatology, Department of Medicine, College of Medicine, University of Sulaimani, Sulaimaniyah, Iraq, Email: - mohammad@derma-care.org

Introduction

Acne vulgaris is a common, chronic, and treatable disorder of the pilosebaceous unit, characterized by comedones, erythematous papules, and pustules formation on the face, neck, upper trunk, and upper arm, primarily in the oily areas of the skin.[1,2] Age, genetics and gender are counted as important factors in the prevalence of acne vulgaris. The mean age of presentation for treatment is 24 years, with 10% of visits occurring when patients are between the ages of (35-44) years.[3,4] In regards to genetics: One study of 200 patients with post-adolescent acne found that 50% of patients had at least one first-degree family relative with acne.[5] According to gender: acne significantly has a higher women-to-men ratio in all age groups.[4] The pathogenesis of acne vulgaris is multifactorial and includes four main pathways: 1) excess sebum production by androgen-mediated stimulation of sebaceous glands, 2) abnormal keratinization of the follicles leading to plugging and comedone formation, 3) cutibacterium acnes colonization, and 4) inflammation of the follicle and surrounding dermis.[6] Androgens (free testosterone, dehydroepiandrosterone sulfate [DHEA-S]) are the most important hormones in the pathogenesis of acne vulgaris.[7] They implicate their action either through increased levels of androgen production or through enhanced sebaceous glands response to what are normal levels of these hormones (increased target organs sensitivity).A combination of the effects of circulatory androgens and the effects of their metabolism at the hair follicle affect sebum production and acne severity.[6,7]Based on those etiological factors discussed above, many treatment modalities are available such as topical treatments (topical antibiotics, topical retinoid, benzoyl peroxide, salicylic acid, azelaic acids, topical dapsone) and systemic treatments in form of antibiotics, isotretinoin, and hormonal treatments (Cyproterone acetate, Flutamide, & spironolactone). Current treatment guidelines generally recommend topical treatments for mild acne or a combination of topical and systemic treatments for moderate-to-severe acne.[8] Spironolactone is a potassium-sparing diuretic and aldosterone antagonist. Beside its various indication in the field of internal medicine, it is also used in treatment of dermatological diseases such as hirsutism, acne and androgenic alopecia through blocking androgen receptor.[9] The anti-androgenic effects are achieved through several mechanisms:1) competition with testosterone and dihydrotestosterone (DHT) for androgen receptors, thereby decreasing androgen-stimulated sebum production; 2) halting the conversion of androstenedione to testosterone; 3) inhibition of 5α-reductase, thus halting the conversion of testosterone to DHT; and 4) increasing the level of serum hormone binding globulin (SHBG).[5,7]Side effects of spironolactone are dose-related, and consist of menstrual irregularities which are most common, breast tenderness/enlargement and decrease libido (infrequent), mild hyperkalemia, headache, dizziness, drowsiness, confusion, nausea, vomiting, anorexia, and diarrhea.[10]We conducted this prospective study to comprehensively describe the outcomes of patients treated with spironolactone in our routine clinical practice, comparing the outcome between different age groups, assessing the outcome with hormonal level, and determining its side effects, also as a support for other researches which is performed in the other countries.

Patients and methods

This is a prospective open-label therapeutic trial study. Fifty female patients aged twelve years and older were collected with mild to moderate and moderate to severe acne in the Sulaymaniyah teaching center of dermatology between 1/2/2022 - 1/9/2022. Forty-seven of the patients met the inclusion criteria of female patient, age above 12 years old, and diagnosis of acne by a dermatologist. Patients were assessed

https://doi.org/10.56056/amj.2024.285 https://amj.khcms.edu.krd

for illegibility for treatment with spironolactone (100mg) for 3 months and liability for dermatological follow-up monthly for 3 months after spironolactone initiation. Exclusion criterias were pregnancy, comedonal acne and severe nodulocystic acne as it need only topical medication and more complex treatments respectively. patients having polycystic ovarian disease as it need more than one line of management and for longer duration, patients with contra-indication to use spironolactone such as a history of renal failure, hyperkalemia, Addison's disease and concomitant use of drugs that have synergistic effects like potassium citrate, eplerenone which is a mineralocorticoid receptor antagonist. Out of fifty patients three of them have been excluded from the study, one of them because of planning to become pregnant and the other two had the feature of polycystic ovarian syndrome (PCOS) by clinical assessment, laboratory investigation and Ultrasonography. The consent achieved from the patients and the research approved by ethical committee of Kurdistan Higher Council of Medical Specialties (KHCMS). Before starting the treatment, the entire patient's medical history was entered into a data collection sheet through well-designed self-prepared questionnaire, data points included age, marital state, duration of acne, location of acne, aggravating factors, associated features in form of (androgenic alopecia, hirsutism, and menstrual irregularity) in order to exclude PCOS cases, drug history including topical and systemic acne treatments and ensuring they stopped any form of them within last two months. Each patient examined by a dermatologist and they were classified according to the number of inflammatory lesions by using the 4-grade European classification system: comedonal acne (grade 1), mild to moderate papulopustular acne (grade 2), severe papulopustular/moderate nodular acne (grade 3), and severe nodular/conglobate acne (grade 4).[11] Patients were divided into two groups age (age ≤ 25 and age >25). Each patient's Serum level of testosterone and DHEA-S were assessed, pelvis ultrasound was sent to exclude PCOS. Photos were taken before starting the treatment and after stopping it. Spironolactone (100 mg) once daily at morning was given for three months. Follow-up of patients was performed monthly for three months in form of assessing the severity of the acne, and asking about side effects of the drug (hyperkalemia) in terms of muscle weakness and fatigue and also the other side effects of the drug such as menstrual irregularities, breast tenderness or enlargement, decreased libido, headache, dizziness, drowsiness, confusion, nausea, vomiting, anorexia, and diarrhea. No serum potassium has been sent because none of the patients reported signs and symptoms of hyperkalemia during the treatment. After three months period of taking the drug, the severity of the acne was qualitatively reassessed by the treating dermatologist through a reduction in the number of lesions. A complete response (CR) was regarded as greater than or equal to 90% improvement; partial response1 (PR1) greater than 50% improvement; partial response2 (PR2) less than or equal to 50% improvement; and no response (NR) regarded as no improvement. The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26. The Chi-Square test was used to determine the relationship between the categorical data. P Value ≤ 0.05 considers a significant difference.

Results

In our study there was a total of 47 female patients, the mean ±SD of age was 26 ±6.44, 22 patients (46.8%) were ≤ 25 years old and 25 (53.2%) were > 25 years of old. Regarding the grade of acne of our patients; 16 patients (34%) were grade two and 31 patients (66%) were grade three of acne. No grade one and grade four were taken.

Table (1): Frequency of age and grade of acne

https://doi.org/10.56056/amj.2024.285 https://amj.khcms.edu.krd

Variable	Frequency	Percent
Age		
≤ 25 years	22	46.8%
> 25 years	25	53.2%
Grade of Acne		
Grade 1	0	0.0%
Grade 2	16	34%
Grade 3	31	66%
Grade 4	0	0.0%

According to response rate of the drug, as shown in Figure (1), only 6.38% (*n*=3) of the patients had no response, the complete response was recorded the highest level 38.3% (*n*=18), followed by partial response-1 (29.79% (*n*=14), While the partial response-2 was 25.53% (*n*=12).

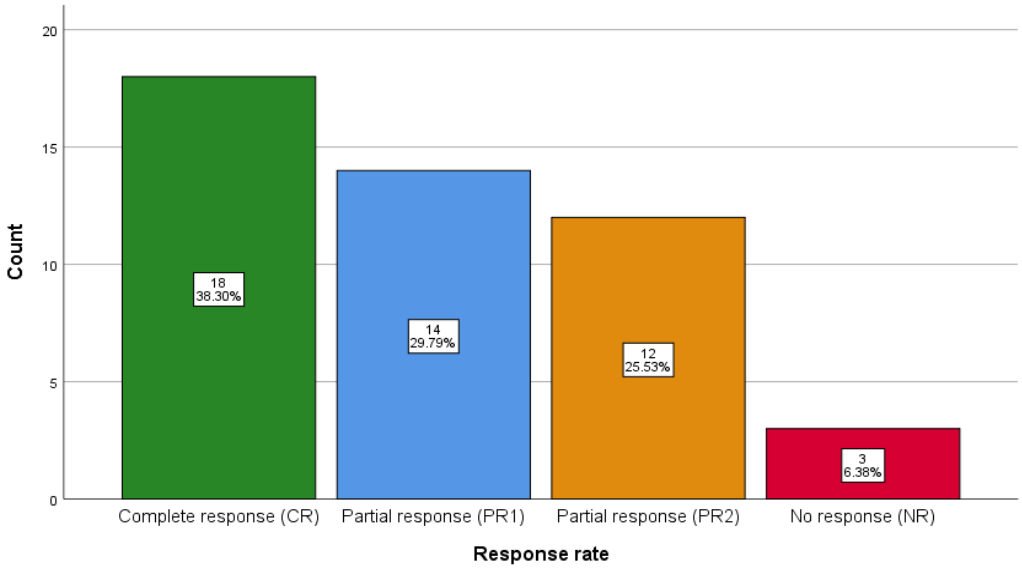

Figure (1): Response rate distribution

In regards to the age of patients as shown in Table (2), significant difference was recorded (P= 0.003) in the response rate among the patients' ages. 83.3% (n=15) of the complete response (n=18) was in those who aged above 25 years. While only 16.7% (n=3) documented in ≤ 25. 100% (n=3) of the no-response patients were in ≤ 25 years.

Table (2): The response rate among ages of the patients

Response rate		Age			p value
		≤ 25 year	> 25 year	Total	
Complete response (CR)	Count	3	15	18	0.003 *

https://doi.org/10.56056/amj.2024.285 https://amj.khcms.edu.krd

	% within response rate	16.7%	83.3%	100.0%	
Partial response (PR1)	Count	7	7	14	
	% within response rate	50.0%	50.0%	100.0%	
Partial response (PR2)	Count	9	3	12	
	% within response rate	75.0%	25.0%	100.0%	
No response (NR)	Count	3	0	3	
	% within response rate	100.0%	0.0%	100.0%	
Total	Count	22	25	47	
	% within response rate	46.8%	53.2%	100.0%	

*significant deference.

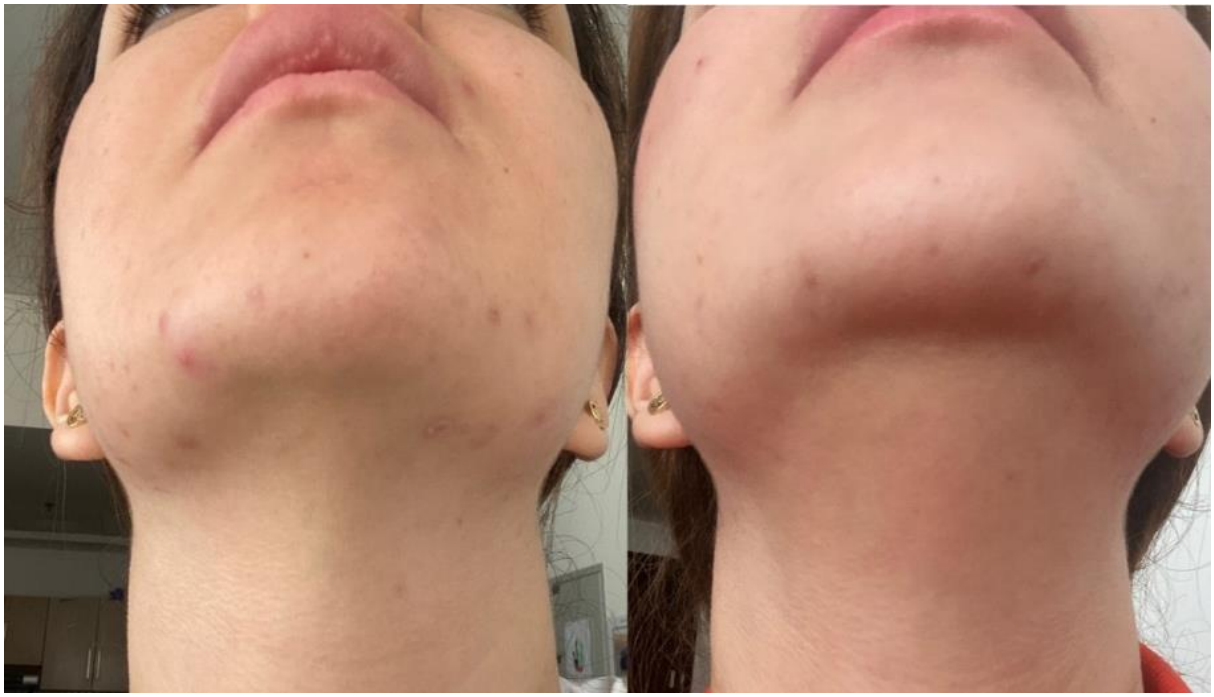

Figure (2): (33) years old patient with grade 2 acne before starting 100 mg spironolactone (right), after 3 month of using the drug the response rate calculated as (PR1) (left)

In the current study, there was a significant difference notified in the response rate between testosterone levels (P= 0.014). 61.1% (n=11) of those patients had a complete response associated with abnormal testosterone level and 100% (n=3) of the no-response patients had normal testosterone concentration. As shown in Table (3).

Table (3): Testosterone levels compared to the response rate

Response rate		Testosterone level			p value
		Normal	Abnormal	Total	
Complete response (CR)	Count	7	11	18	0.014 *
	% within response rate	38.9%	61.1%	100.0%	
Partial response (PR1)	Count	9	5	14	

https://doi.org/10.56056/amj.2024.285 https://amj.khcms.edu.krd

	% within response rate	64.3%	35.7%	100.0%	
Partial response (PR2)	Count	11	1	12	
	% within response rate	91.7%	8.3%	100.0%	
No response (NR)	Count	3	0	3	
	% within response rate	100.0%	0.0%	100.0%	
Total	Count	30	17	47	
	% within response rate	63.8%	36.2%	100.0%	

*significant deference.

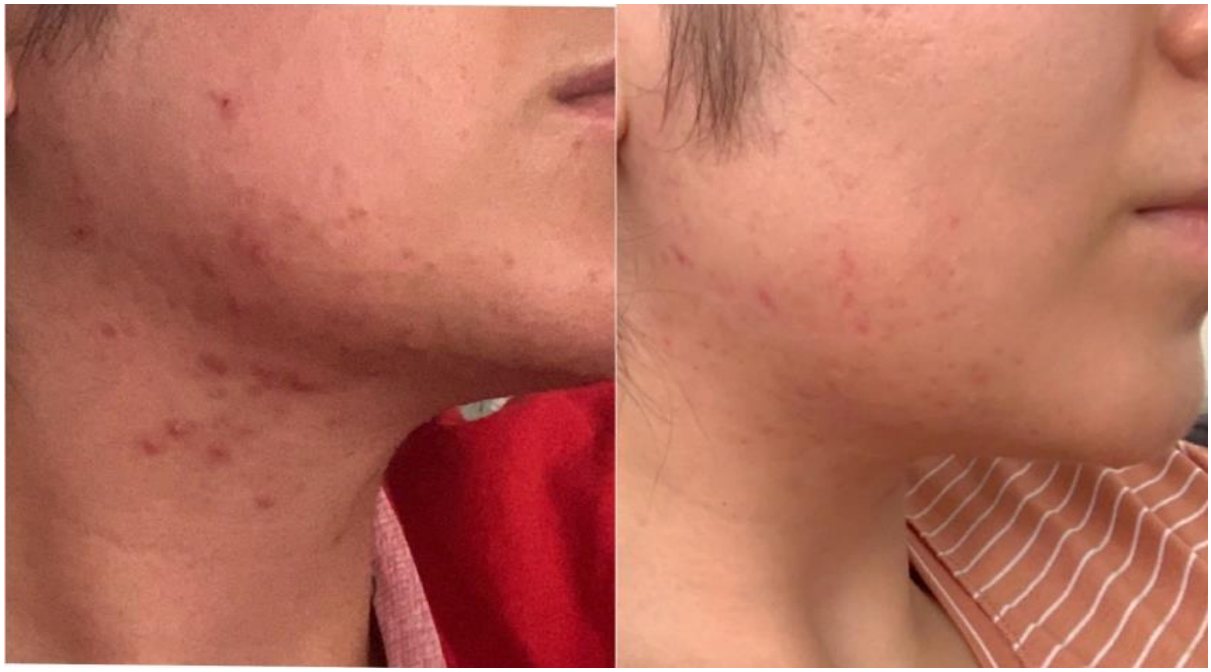

Figure (3): 19 years old female patient with grade 3 acne and abnormal testosterone level before starting spironolactone (right) response rate calculated as (CR) after 3 month of using the drug (left).

Regarding DHEA-s levels, table (4) showed that the complete response was equally distributed among the normal and abnormal levels of DHEA-s level. 71.4% (n=10) of the partial response (PR1) had a normal level of this hormone, 100 % partial response (PR2) and 100% of non-responders (NR) also were having a normal level of DHEA-s. The deference of the response was significant among DHEA-s levels (P=0.017).

Table (4): Response rate compared to the DHEA-s levels

Response rate		DHEA-s level			p value
		Normal	Abnormal	Total	
Complete response (CR)	Count	9	9	18	0.017 *
	% within response rate	50.0%	50.0%	100.0%	
Partial response (PR1)	Count	10	4	14	
	% within response rate	71.4%	28.6%	100.0%	

https://doi.org/10.56056/amj.2024.285 https://amj.khcms.edu.krd

Partial response (PR2)	Count	12	0	12	
	% within response rate	100.0%	0.0%	100.0%	
No response (NR)	Count	3	0	3	
	% within response rate	100.0%	0.0%	100.0%	
Total	Count	34	13	47	
	% within response rate	72.3%	27.7%	100.0%	

*significant deference.

According to side effects of the drug in our study, 55.32% of the patients (n=26) had no side effect, and most frequently recorded side effect was menstrual irregularity (n=14), While weakness was recorded as the least frequent side effect level (n=0).All these finding explained in Table (5).

Table (5): Side effects distribution

Side effects	Frequency	Percent
Non	26	55.32%
Menstrual irregularity	14	29.79%
Dizziness	6	12.77%
Nausea and vomiting	1	2.13%
Weakness	0	0.00%
Total	47	100.00%

Discussion

Acne vulgaris is an enormously common skin disorder among adolescents that can frequently persist into adulthood, result in disfigurement, dyspigmentation and permanent scarring, with a serious negative impact on psychosocial development, such as anxiety, depression, and social isolation.[13]Numerous therapeutic lines are existing to control acne vulgaris which are based on multiple etiological factors such as (anti-microbial, anti-hormonal, and isotretinoin) in form of topical or systemic preparation.[8]Although oral antibiotics are the most commonly prescribed systemic treatment for acne vulgaris, frequent use of antibiotics can result in antibiotic-associated adverse effects and increased incidence of antibiotic resistance.[9,14] While isotretinoin is a potential alternative to oral antibiotics, it has been associated with a lack of tolerance, relapse after discontinuation and teratogenicity.[14] Because hormones play an important role in the development of acne, spironolactone that target this pathogenic factor can be effective for patients with acne. However, compared to oral antibiotics, spironolactone is relatively underused; oral antibiotics are prescribed 3 to 7 times more often than spironolactone.[15]In our study, the finding was similar to previous studies done in which 70% of the patients had improvement in their acne either in form of total clearance or partial improvement of their acne with reporting the highest improvement among patients older than 25 years of age indicating that spironolactone is regarded as an effective line of treatment for post-adolescent acne and adds to the growing body of literature supporting the usefulness and tolerability of spironolactone for women with acne.[16-21] Marked improvement and lack of non-responder among those patients who had abnormal testosterone and DHEA-S level supporting the previous studies those consider spironolactone as first-line treatment in hormonal acne.[16]Regarding the patients who had improvement in their acne while having normal hormonal levels indicating that enhanced peripheral androgen metabolism has been found, either the androgen receptors are high or the target organs were hypersensitive to the circulating androgens, which supports the fact that hormone issues play the main role in the pathogenesis of acne vulgaris in post-adolescent acne.On the subject of the safety of spironolactone no significant side effects were reported during the treatment, most commonly reported side effect was menstrual irregularities, but did not necessitate to discontinue the treatment as

https://doi.org/10.56056/amj.2024.285 https://amj.khcms.edu.krd

published by previous studies.[22] Blood pressure of all patients was normal throughout the treatment duration, none of the patients reported symptoms of hyperkalemia such as muscle weakness, fatigue, and vomiting there for no serum potassium has been checked based on the guideline which is written in the textbooks and previous studies regarding the usefulness of checking serum potassium during prescribing spironolactone for acne in young female patients.[12]The limitation of this study was the short duration of time, small sample size, and lack of comparison groups between spironolactone and other lines of acne vulgaris treatment.The major strength of this study is that it is a prospective study with a wide range of age groups ranging from 12-38 years old and documenting the hormonal status of all the patients and comparing the result to it. In the other studies done before the effectiveness of spironolactone is evaluated retrospectively on either adolescent or post-adolescent age groups.

Conclusion

Spironolactone is statically considered an effective and safe line for the treatment of acne vulgaris in a wide range of group age female patients including adolescent and post-adolescent patients. It is effective on patients with normal hormonal profiles as long as those patients with abnormal hormonal levels. This fact enhances the increasing prescription of spironolactone for women with acne and may represent an opportunity to improve outcomes and reduce our reliance on oral antibiotics and isotretinoin for the treatment of acne vulgaris.

Conflict of interest

The author reports no conflicts of interest.

References

1. Cunliffe WJ And Simpson NB. Disorder of the Sebaceous Glands. In: Rook's Text Book of Dermatology, Burns T, Breathnach S, Cox N, Griffiths C. Vol 2, 7th ed. Blackwell Scientific Publication, 2004; 43: 1927-84.
2. Odom RB, James W, Timetly BG. Acne. In: Andrews Disease of the Skin, Clinical Dermatology, 9th ed. WB Sounder Company Philadelphia 2000; 13: 284-306.
3. James W. Acne. N Engl J Med. 2005; 352(14):1463-72.
4. Collier C, Harper J, Cantrell W, et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008; 58:56-59.
5. Goulden V, Clark S, Cunliffe W. Post-adolescent acne: a review of clinical features. Br J Dermatol. 1997; 136:66-70.
6. Haider A, Shaw JC. Treatment of acne vulgaris. JAMA Dermatol. 2004; 292(6):726-35.
7. Hunter JAA, Savin JA, Dahl MV. Sebaceous and Sweat Gland Disorder. In: Clinical Dermatology, 3rd ed., Blackwell Publishing Company 2002; 21:148-62.
8. Zaenglein AL, Pathy AL, Schlosser BJ. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016; 74:945-73.
9. Karch AM. Lippincott's Nursing Drug Guide. Lippincott William and Wilkins 2003; 522-3.
10. Habif TP. Acne, Rosacea and Related Disorder. In: Clinical Dermatology, A color Guide to Diagnosis and Therapy, 4th ed. Mosby 2004; **7**: 162-94.
11. Nast A, Dreno B, Bettoli V, et al. European evidence based (S3) guideline for the treatment of acne - update 2016 - short version. J Eur Acad Dermatol Venereol. 2016; 30: 1261-8.
12. Plovanich M, Weng QY, Mostaghimi A. Low Usefulness of Potassium Monitoring Among Healthy Young Women Taking Spironolactone for Acne. JAMA Dermatol. 2015; 151(9):941-4.
13. Koo JY, Smith LL. Physiological aspect of acne. Pediatr Dermatol. 1991; 8:185-8.
14. Barbieri JS, Spaccarelli N, Margolis DJ, et al. Approaches to limit systemic

antibiotic use in acne: systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments. J Am Acad Dermatol. 2019; 80(2): 538-49.
15. Guzman AK, Barbieri JS. Comparative analysis of prescribing patterns of tetracycline class antibiotics and spironolactone between advanced practice providers and physicians in the treatment of acne vulgaris. J Am Acad Dermatol.2020; 06:044.
16. Ebede TL, Arch EL, Berson D. Hormonal treatment of acne in women. J Clin Aesthet Dermatol. 2009; 2(12):16-22.
17. Charny JW, Choi JK, James WD. Spironolactone for the treatment of acne in women, a retrospective study of 110 patients. Int J Womens Dermatol. 2017; 3: 111-5.
18. Roberts EE, Nowsheen S, Davis DMR, et al. Use of spironolactone to treat acne in adolescent females. Pediatr Dermatol. 2020; 00:1–5.
19. Roberts EE, Nowsheen S, Davis MDP, et al. Treatment of acne with spironolactone: a retrospective review of 395 adult patients at Mayo Clinic, 2007-2017. J Eur Acad Dermatol Venereol. 2020; 34:2106-10.
20. E. Sharquie Khalifa. Therapeutic Evaluation of Spironolactone and Finasteride in the Treatment of Acne Vulgaris. IPMJ. 2007; 6 (3): 206-10.
21. Grandhi R, Alikhan A. Spironolactone for the treatment of acne: a 4-year retrospective study. Dermatology. 2017; 233:141-4.
22. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenetic alopecia. Br J Dermatol. 1985; 112: 124-5.