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ORIGINAL ARTICLE

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Use of spironolactone to treat acne in adolescent females

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Abstract

Background/objectives: Studies assessing the utility of spironolactone for treating acne in adolescent females are lacking. Thus, we sought to examine spironolactone's role in treating this patient population.

Methods: A retrospective review was performed to determine the efficacy of spironolactone treatment in adolescent females seen at Mayo Clinic in Rochester, Minnesota, from 2007 to 2017.

Results: In a cohort of 80 pediatric patients with a median age of 19 years (range, 14-20 years), 64 patients (80%) experienced improvement of acne on treatment with spironolactone (median dose, 100 mg daily) with a favorable side effect profile. Approximately a quarter of patients (22.5%) had a complete response; more than half (58.8%) had a complete response or a partial response greater than 50%. Initial and maximal responses were observed at a median of 3 months and 5 months, respectively. Patients received treatment with spironolactone for a median duration of 7 months (range, 3-45 months) with limited side effects.

Conclusions: Spironolactone demonstrated efficacy in treating acne in adolescent females and is a safe long-term alternative to systemic antibiotics in these patients.

KEYWORDS

acne, adolescent, female, polycystic ovary syndrome, spironolactone

1 | INTRODUCTION

Spironolactone is commonly used in dermatology for acne vulgaris treatment in women due to its anti-androgen effects. Recent studies of spironolactone have shown promising results for its use for acne in adult women.[1-6] However, studies examining the efficacy of spironolactone for pediatric patients are lacking. In this retrospective review, we studied the effectiveness and safety of spironolactone for acne treatment in female adolescents.

2 | METHODS

The criteria and methods for the current study are similar to our recent report on the use of spironolactone in adult females.[6] Upon receiving approval from Mayo Clinic's Institutional Review Board, an electronic search of institutional medical records (January 1, 2007, through December 31, 2017) was performed to identify patients younger than 21 years of age treated at Mayo Clinic. Inclusion criteria included the following: females with a diagnosis of acne made

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or confirmed by a dermatologist; received spironolactone treatment for at least 3 months; and followed up in our dermatology clinic at least 3 months after spironolactone initiation. The health records were reviewed manually to extract patient characteristics, clinical presentation, treatment, and response to treatment. Each patient's therapy response was retrospectively graded based on the treating dermatologist's impressions on follow-up as: complete response (CR), greater than or equal to 90% improvement; partial response (PR), either greater than 50% improvement or less than or equal to 50% improvement; and no response (NR), no improvement. Response time was determined by both the treating clinician's evaluation and the patient's subjective assessment of their acne.

We used the 4-grade European classification system to assess severity which included the following: grade 1 (comedonal acne), grade 2 (mild-to-moderate papulopustular acne), grade 3 (severe papulopustular/moderate nodular acne), and grade 4 (severe nodular/conglobate acne).[7] Concurrent therapies included topical medications, oral antibiotics, oral contraceptive pills (OCPs), or a combination of these treatments. Based on previous research, for a patient's treatment to be considered dual therapy with spironolactone and an OCP, the OCP therapy must be combination of estrogen/progesterone and initiated within 6 months prior to spironolactone initiation.[8] If the OCP was taken for greater than 6 months before spironolactone initiation, the patient's treatment was considered spironolactone monotherapy. Using topical therapies in addition to spironolactone was permitted and classified as spironolactone monotherapy. Per the previous methodology in our cohort of adult women, potassium levels or blood pressure was not routinely monitored in these patients unless the patient experienced symptoms or there were reasons for concern.[6]

3 | RESULTS

Eighty patients with a median age of 19 years (range, 14-20 years) met study inclusion criteria. Tables 1 and 2 list the study results. Patients received treatment with spironolactone for a median duration of 7 months (range, 3-45 months), and the mean follow-up time was 16 months. The median dose of spironolactone was 100 mg daily (range, 25-200 mg).

A large majority, 75 patients (93.8%), did not respond to other systemic therapies, which included oral antibiotics, oral contraceptive pills, and/or oral isotretinoin prior to spironolactone. Concurrent therapies while on spironolactone included topical medications (71.9% in responders vs 56.3% in non-responders), oral antibiotics (14.1% in responders vs 6.3% in non-responders), oral contraceptive pills (OCPs) (14.1% in responders vs 31.3% in non-responders), or a combination of these treatments (0% in responders vs 6.3% in non-responders).

While on spironolactone, 64 patients (80%) experienced improvement of acne (Table 2). Approximately a quarter of patients (22.5%) had a complete response, and more than half (58.8%) of patients had a complete response or a partial response greater than 50%. Seventeen patients (21.3%) had a partial response less than 50%. Sixteen patients (20%) had no response and were switched to oral isotretinoin therapy. Patients who responded to spironolactone therapy were more likely to have a cyclic component to their acne (75% in responders vs 56.3% in non-responders) and to have acne in the distribution of their jawline (70.3% in responders vs 56.3% in non-responders) (Table 3). Initial and maximal responses were observed at a median of 3 months and 5 months, respectively.

Thirty-two of the 80 patients in our cohort (40%) were not on an OCP while on spironolactone. Of these patients, 22 patients (out of 64 patients who were classified as responders, 34.4%) responded to spironolactone and 10 patients (out of 16 patients who were classified as non-responders, 62.5%) did not respond. Of the 38 patients (out of 80 patients, 47.5%) who started an OCP >6 months before spironolactone initiation, 33 patients (out of 64 patients who were classified as responders, 51.6%) had a response to spironolactone and 5 (out of 16 patients who were classified as non-responders, 31.3%) did not respond to spironolactone. Of the 10 patients (out of 80 patients, 12.5%) that started an OCP <6 months before

TABLE 1 Characteristics of 80 adolescent patients with ≥3 mo of spironolactone treatment

Characteristics	Value[a]
Age, median (range), y	19 (14-20)
History of PCOS	3 (3.8)
Acne located on jawline	54 (67.5)
Cyclic flares	57 (71.3)
Initial acne European severity classification,[b] mean, grade	3
Acne unresponsive to other oral treatments before spironolactone[c]	75 (93.8)
Background of OCP use	
No OCP	32 (40.0)
OCP	48 (60.0)
OCP started >6 mo before spironolactone initiation	38 (47.5)
OCP started ≤6 mo before spironolactone initiation	10 (12.5)
OCP started after spironolactone initiation	5 (6.3)
Therapy	
Spironolactone monotherapy	55 (68.8)
Oral antibiotics and spironolactone	10 (12.5)
OCP and spironolactone[d]	14 (17.5)
Antibiotics, OCP, and spironolactone	1 (1.3)

Note: Portions of this table are adapted from our retrospective review which was published in the *J Eur Acad Dermatol Venereol*. Permission to reuse was obtained.[6]

Abbreviations: OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome.

[a]Values are presented as number (percentage) of patients unless specified otherwise.

[b]Grade, 1 through 4.

[c]Includes oral antibiotics, oral contraceptive pills (OCPs), and/or oral isotretinoin.

[d]Includes all patients who were on a concomitant OCP during spironolactone treatment regardless of when the OCP was started in relation to spironolactone initiation.

TABLE 2 Treatment outcome of 80 adolescent patients with ≥3 mo of spironolactone treatment

Treatment	Value
Spironolactone dose, median (range), mg	100 (25-200)
Time receiving spironolactone, mo	
Mean (SD)	11.2 (10.0)
Median (range)	7 (3-45)
Follow-up time, mo	
Mean (SD)	16.0 (16.8)
Median (range)	11 (3-110)
Response rate[a]	
Improvement with therapy	64 (80.0)
CR (≥90%)	18 (22.5)
PR (>50%)	29 (36.3)
PR (≤50%)	17 (21.3)
NR	16 (20.0)
NR and subsequently treated with isotretinoin	16 (20.0)
Time to initial response, mo[b]	
Mean (SD)	4.0 (3.0)
Median (range)	3 (1-15)
Time to maximal response, mo[b]	
Mean (SD)	5.4 (3.2)
Median (range)	5 (2-15)
Had adverse effects[c]	3 (3.8)
Discontinued treatment because of adverse effects[c]	3 (3.8)

Note: Portions of this table are adapted from our retrospective review which was published in the *J Eur Acad Dermatol Venereol*. Permission to reuse was obtained.[6]

Abbreviations: CR, complete response; NR, no response; PR, partial response.

[a]Values are presented as number and percentage of patients.

[b]Values are presented for n = 64 patients.

[c]Rash; breast tenderness and diarrhea; headache.

TABLE 3 Classification of patients by response to spironolactone therapy (n = 80)

Characteristics	Responders (n = 64)[a]	Non-responders (n = 16)[a]
Age, median (range), y	19 (14-20)	19 (16-20)
History of PCOS	3 (4.7)	0 (0.0)
Acne located on jawline	45 (70.3)	9 (56.3)
Cyclic flares	48 (75.0)	9 (56.3)
Initial acne European severity classification,[b] mean, grade	3	3
Acne unresponsive to other oral treatments before spironolactone[c]	60 (93.8)	15 (93.8)
Background of OCP use		
No OCP	22 (34.4)	10 (62.5)
OCP	42 (65.6)	6 (37.5)
OCP started > 6 mo before spironolactone initiation	33 (51.6)	5 (31.3)
OCP started ≤ 6 mo before (or concurrently with) spironolactone initiation	9 (14.1)	1 (6.3)
OCP started any time after spironolactone initiation	2 (3.1)	3 (18.8)
Therapy		
Spironolactone monotherapy	46 (71.9)	9 (56.3)
Oral antibiotics and spironolactone	9 (14.1)	1 (6.3)
OCP and spironolactone[d]	9 (14.1)	5 (31.3)
Antibiotics, OCP, and spironolactone	0 (0.0)	1 (6.3)

Abbreviations: OCP, oral contraceptive pill; PCOS, polycystic ovary syndrome.

[a]Values are presented as number (percentage) of patients unless specified otherwise. The percentages are derived based upon the denominator of responders (n = 64) and non-responders (n = 16) in the respective columns.

[b]Grade, 1 through 4.

[c]Includes oral antibiotics, oral contraceptive pills (OCPs), and/or oral isotretinoin.

[d]Includes all patients who were on a concomitant OCP during spironolactone treatment regardless of when the OCP was started in relation to spironolactone initiation.

spironolactone initiation, 9 patients (out of 64 patients who were classified as responders, 14.1%) had a response to spironolactone and 1 patient (out of 16 patients who were classified as non-responders, 6.3%) did not respond to spironolactone. Of note, 5 patients (out of 80 patients, 6.3%) started an OCP after spironolactone initiation.

Although no patient with grade 1 acne was prescribed spironolactone, patients with acne grades 2-4 responded to spironolactone with a mean acne grade of 3 (Figure 1). Three patients (3.8%) had side effects that included rash, breast tenderness, diarrhea, and headache and subsequently discontinued therapy.

4 | DISCUSSION

We have previously reported on the safety and efficacy of spironolactone in the treatment of acne for adult women.[6] Similar to this current study, median spironolactone dose was 100 mg. Interestingly, approximately two-thirds of adult patients (66.1%) experienced a complete response compared to 22.5% of adolescents. This discrepancy might be due to medication adherence and duration of treatment. Of note, median duration of treatment was 13 months in adult women, while it was 7 months in adolescent females. This

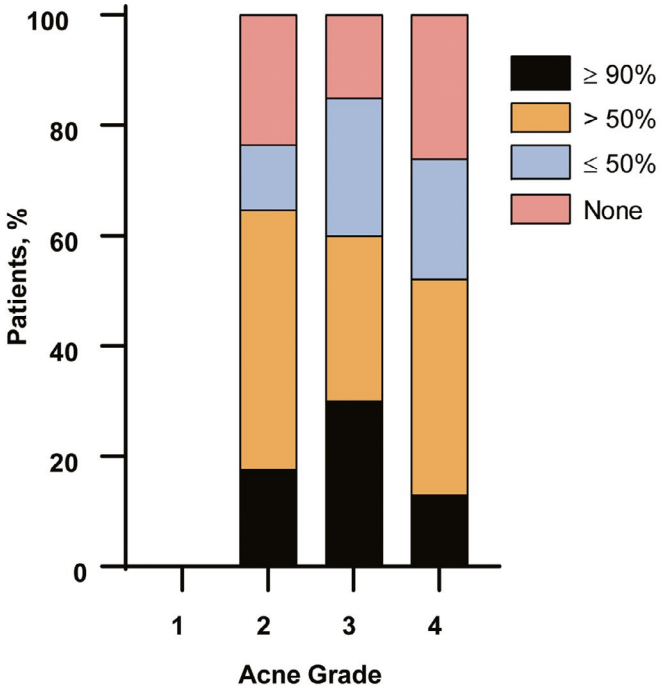

FIGURE 1 Response to spironolactone treatment in 80 adolescent patients, stratified according to acne grade

Response	Grade 1	Grade 2	Grade 3	Grade 4
≥90%	-	17.6% (n=3)	30.0% (n=12)	13.0% (n=3)
>50%	-	47.1% (n=8)	30.0% (n=12)	39.1% (n=9)
≤50%	-	11.8% (n=2)	25.0% (n=10)	21.7% (n=5)
None	-	23.5% (n=4)	15.0% (n=6)	26.1% (n=6)

may be due to multiple reasons including patients discontinuing the medication before allowing the recommended time to visualize a response and lack of medication adherence in younger patients. Some patients were likely lost to follow-up, and continuation was not captured. Initial and maximal responses were observed at a median of 3 months and 5 months in both age groups suggesting several months of therapy are needed to see benefit. Improvement was seen in acne grades 2 through 4 in the adolescent population and in all acne grades for the adult population. Approximately 15%-25% of pediatric patients with grade 3 to 4 acne had no response to spironolactone. The reason for this is unclear. Further studies are warranted to assess whether certain subtypes of acne are more responsive to spironolactone therapy or whether individual factors such as microbiome and epigenetics play a role. Interestingly, only 3.8% of pediatric patients had any side effects from spironolactone which included rash, breast tenderness, diarrhea, and headache (compared to 10.4% of adult patients) and discontinued therapy as a result.

The median age of patients in this study was 19 years, which is relatively high for adolescents. This may be due to hesitancy on the part of the parent and/or physician to start an oral medication in younger patients.

Of note, none of the patients in our study had grade 1 acne. This is likely due to these patients being treated with topicals and other agents. In addition, a higher-grade acne is more likely to be bothersome to adolescents compared to lower grade acne and they are more likely to seek care from a dermatologist for these lesions. It is plausible that grade 1 acne is less likely to respond to spironolactone. However, due to lack of patients with this type of acne in this study, this conclusion cannot be currently inferred.

Since there is frequently a hormonal component to acne, OCPs are frequently used in female patients as a treatment approach. Interestingly, 40% of the patients in our study cohort were OCP naïve. Hesitancy in OCP initiation, often on the part of parents, is greater in the pediatric population. Thus, our results suggest that spironolactone can be beneficial in these patients for acne treatment. Moreover, irregular menses can affect the quality of life of adolescents and young adults. In our cohort of patients, only one patient experienced irregular menses while on spironolactone therapy (without OCP) and as a result discontinued treatment soon after treatment initiation. This suggests that, at least in our cohort, irregular menses is an infrequent side effect.

Hyperkalemia is an uncommon side effect of spironolactone therapy. However, none of the patients in this study had symptoms suggestive of this adverse effect, further suggesting that routine blood monitoring is not required in these individuals. Per our previous report in adult women, a standard departmental laboratory monitoring protocol for spironolactone did not exist during the time frame of our study, but generally potassium levels were routinely checked in patients before 2015, whereas since 2015, potassium levels are no longer checked in young healthy women.[6,9]

As noted in our adult study, blood pressure variations have been previously reported with spironolactone therapy; however, this value was not routinely measured in our practice unless patients noted symptoms of lightheadedness, dizziness, or had concerns regarding low blood pressure. Such symptoms were infrequent in our patient cohort.[6]

Spironolactone is well-tolerated in both pediatric and adult patients, with adolescents having a higher tolerance rate than adults. Thus, spironolactone may be a viable second-line therapy for adolescent females with acne refractory to topical therapy. This may be preferable to oral antibiotics in light of public health antibiotic stewardship and concerns of antimicrobial resistance.[10-12] Spironolactone could be trialed, and if efficacy is not achieved within 6 months, isotretinoin could then be pursued.

Limitations of this study include cohort size, retrospective design, and observer bias. Currently, there is lack of standardization of measuring improvement in acne which further limits the study. Infrequently, the use of spironolactone may be limited by adverse effects. Potential side effects should be discussed with the patient, and spironolactone should be given an appropriate amount of time to exert its effects. Further studies utilizing a prospective design, ideally using spironolactone as true monotherapy without concomitant topical therapy, are needed regarding use of spironolactone in adolescent females with acne.

This retrospective study fills a current practice gap in the pediatric dermatology literature. Spironolactone should be considered second-line treatment for adolescent females with acne. Its use, either as monotherapy or in rational combination with other agents, can lead to significant improvement of acne.

ETHICAL APPROVAL

Mayo Clinic Institutional Review Board has reviewed and approved this study.

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REFERENCES

1. Park JH, Bienenfeld A, Orlow SJ, Nagler AR. The use of hormonal antiandrogen therapy in female patients with acne: a 10-year retrospective study. *Am J Clin Dermatol*. 2018;19(3):449-455.
2. Barbieri JS, Choi JK, Mitra N, Margolis DJ. Frequency of treatment switching for spironolactone compared to oral tetracycline-class antibiotics for women with acne: a retrospective cohort study 2010–2016. *J Drugs Dermatol*. 2018;17(6):632-638.
3. Isvy-Joubert A, Nguyen JM, Gaultier A, et al. Adult female acne treated with spironolactone: a retrospective data review of 70 cases. *Eur J Dermatol*. 2017;27(4):393-398.
4. Grandhi R, Alikhan A. Spironolactone for the treatment of acne: a 4-year retrospective study. *Dermatology*. 2017;233(2–3):141-144.
5. 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(2):111-115.
6. 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(9):2106-2110.
7. 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(8):1261-1268.
8. Guerra-Tapia A, Sancho PB. Ethinylestradiol/Chlormadinone acetate: dermatological benefits. *Am J Clin Dermatol*. 2011;1(1):3-11.
9. Plovanich M, Weng QY, Mostaghimi A. Low usefulness of potassium monitoring among healthy young women taking spironolactone for acne. *JAMA dermatology*. 2015;151(9):941-944.
10. Delost GR, Delost ME, Armile J, Lloyd J. Staphylococcus aureus carriage rates and antibiotic resistance patterns in patients with acne vulgaris. *J Am Acad Dermatol*. 2016;74(4):673-678.
11. Levy RM, Huang EY, Roling D, Leyden JJ, Margolis DJ. Effect of antibiotics on the oropharyngeal flora in patients with acne. *Arch Dermatol*. 2003;139(4):467-471.
12. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945-973.e933.

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