GAJKIEWICZ, Magdalena, ZAUCHA, Radosław, FELIŃSKA, Zuzanna, FURA, Tomasz, SILLDORFF, Julia, DUDEK, Marcin, ZAJĄC, Małgorzata, ISZCZUK, Oliwia and ANCZYK, Stanisław. Spironolactone as an alternative way of treating acne in women - review. Quality in Sport. 2024;21:53881. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.21.53881
https://apcz.umk.pl/QS/article/view/53881

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 28.07.2024. Revised: 17.08.2024. Accepted: 20.08.2024. Published: 23.08.2024.

Spironolactone as an alternative way of treating acne in women – review

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Abstract

Introduction and objective:

This paper provides an in-depth exploration of the pharmacology of spironolactone, elucidating its mechanisms of action and clinical implications beyond its conventional indications. Additionally, it examines the pathogenesis, clinical presentation, and current treatment strategies for acne vulgaris, contextualizing spironolactone's role in acne management.

Review methods:

Electronic searches were conducted between 15 and 26 April 2024 and included databases: Pubmed and Google Scholar. The following trials registers were searched using the

search terms “spironolactone” AND “acne”. This review focuses on 3 trials that are limited to years 2020-2024.

Brief description of state of knowledge:

Acne vulgaris is a prevalent chronic inflammatory skin condition characterized by sebaceous gland hyperactivity, follicular hyperkeratinization, microbial colonization, and inflammation. Despite the availability of numerous treatment modalities, therapeutic success can be challenging, particularly in cases of hormonal or treatment-resistant acne. Spironolactone, initially developed as an aldosterone antagonist, has emerged as an off-label option for acne management, especially in individuals with hormonal influences on their condition.

Summary:

Considering conflicting recommendations regarding spironolactone's use in acne management, this review aims to provide a comprehensive synthesis of current evidence, guiding its judicious use in clinical practice. By bridging pharmacological insights with clinical data, this paper contributes to a deeper understanding of spironolactone's influence in the treatment landscape of acne vulgaris.

Keywords: spironolactone, acne vulgaris, women

1. Introduction and objective

This paper explores the pharmacology of spironolactone, elucidating its mechanisms of action and clinical implications beyond its conventional indications. Additionally, it delves into the pathogenesis, clinical presentation, and current treatment strategies for acne vulgaris, providing context for spironolactone's role in acne management.

The comparison of spironolactone's pharmacological profile with acne pathogenesis sets the stage for examining recent clinical trials evaluating its efficacy and safety in acne treatment. These trials shed light on spironolactone's potential as a viable alternative to traditional therapies, offering insights into its comparative effectiveness and tolerability.

Considering conflicting recommendations from regulatory bodies regarding spironolactone's use in acne management, this review aims to provide a comprehensive synthesis of current evidence, elucidating its role and guiding its judicious use in clinical practice. By bridging pharmacological insights with clinical data, this paper contributes to a deeper understanding of spironolactone's influence in the treatment landscape of acne vulgaris.

2. State of knowledge

2.1 Pharmacology of Spironolactone: Mechanisms and Clinical Implications

Spironolactone, a synthetic steroidal compound, primarily acts as a competitive antagonist of aldosterone receptors in the collecting tubule of nephron. This mechanism inhibits aldosterone-induced sodium reabsorption and potassium excretion, leading to natriuresis. Additionally, spironolactone exhibits anti-androgenic effects by blocking the androgen receptor - the biological target of androgens like testosterone and dihydrotestosterone (DHT) and inhibiting the synthesis of androgens being an inhibitor of 5α-reductase. Its efficacy in treating conditions like hypertension, heart failure, and hyperaldosteronism is well-documented. Spironolactone is advised for individuals experiencing persistent symptoms of heart failure (NYHA class II -- IV) and a left ventricular ejection fraction of 35% or less, despite receiving treatment with an ACE inhibitor (or an ARB) and a beta-blocker. This recommendation aims to decrease the likelihood of hospitalization due to heart failure and the risk of premature mortality. Additionally, spironolactone demonstrates efficacy in enhancing diastolic function in essential hypertension and in preventing or reversing myocardial remodeling, including hypertrophy and fibrosis, in patients with congestive heart failure or post-myocardial infarction.

Spironolactone is also prescribed for individuals with cirrhosis and ascites, particularly when secondary hyperaldosteronism occurs, and where the adverse effects of hypokalemia are problematic. However, its use is associated with potential adverse effects such as hyperkalemia, gynecomastia, and menstrual irregularities [1].

It must be mentioned that spironolactone is contraindicated in pregnant or lactating women due to the potential risk of feminization of the fetus. Therefore, it is recommended that oral contraception be co-prescribed to minimize this risk [2].

2.2 Acne Vulgaris: Pathogenesis, Clinical Presentation and Treatment Strategies

Acne vulgaris is a common chronic inflammatory condition of the pilosebaceous follicles. It's one of the most frequently encountered skin conditions seen and managed by healthcare professionals. The incidence of acne vulgaris has notably risen among women over the past decade, with prevalence rates ranging from 15% to 50% across various studies [3-5]. It manifests as a disorder affecting the pilosebaceous units, clinically recognizable by symptoms such as seborrhea, comedones, papules, pustules, nodules and, in some cases, scarring.

Acne development primarily revolves around the interaction of four key elements: I. excessive growth of sebaceous glands leading to seborrhea, II. changes in follicle development and maturation, III. the presence of Propionibacterium acnes in the pilosebaceous unit, and IV. the occurrence of inflammation. Androgens play a significant role in acne formation as they promote the thickening of follicular cells (keratosis) and affect the production of sebum [6]. Genetic predisposition, hormonal fluctuations, lifestyle (diet, smoking, quality of sleep) and environmental factors (humidity, air pollution, sun exposure) also play significant roles in its development [7].

Treatment strategies aim to target different aspects of acne pathogenesis, including topical agents like retinoids, benzoyl peroxide, and antibiotics, as well as systemic therapies such as oral antibiotics, hormonal therapy, and isotretinoin.

Recent advancements in acne management include the development of novel topical formulations, combination therapies, and the exploration of alternative treatment modalities like photodynamic therapy and laser therapy. However, treatment selection should be tailored to individual patient characteristics, considering factors such as age, gender, acne severity, and potential adverse effects [8].

Despite the availability of various treatment options, achieving optimal outcomes in acne management remains challenging, necessitating a comprehensive approach involving patient education, lifestyle modifications, and long-term follow-up. Additionally, addressing

psychosocial aspects and providing psychological support are integral components of acne care, aiming to improve patient satisfaction and quality of life [9].

2.3 Spironolactone as an Alternative Therapy for Acne Vulgaris: Mechanisms and Clinical Implications

Spironolactone, originally developed as a potassium-sparing diuretic and aldosterone antagonist, has gained attention for its off-label use in the management of acne vulgaris [10]. Acne is fundamentally characterized by the overproduction of sebum, leading to obstruction of pilosebaceous follicles, which creates an environment rich in lipids favorable for the proliferation of Propionibacterium acnes. This, in turn, triggers immune responses, prompting the recruitment of leukocytes to the obstructed follicles and contributing to the erythematous reaction observed in acne lesions. Dihydrotestosterone binds to androgen receptors within these follicles, stimulating sebum secretion. Therefore, inhibiting the binding of these androgens to their receptors within sebocytes using spironolactone could reduce sebum production and alleviate inflammation in the pilosebaceous glands [11].

Successful long-term management of acne presents a considerable therapeutic challenge. As an anti-androgen and potential inhibitor of sebogenesis, spironolactone represents a possible alternative to oral isotretinoin and combined oral contraceptives (COCs), licensed anti-acne medications that significantly reduce sebum secretion, but which may be associated with serious adverse effects in some patients. Antibiotics are often over-prescribed in acne, drive antimicrobial resistance in targeted and non-targeted bacteria, and have no effect on sebum synthesis [12].

Although there is growing evidence endorsing spironolactone as a safe and efficacious substitute for oral antibiotics, it appears that its utilization is still limited. In a study from 2020 using data from 2007-2016 tetracyclines were substantially more often prescribed rather than spironolactone in visits with female patients (24.5% vs. 6.6%) [13].

In accordance with guidelines from the American Academy of Dermatology Assosiation, spironolactone is recognized as a therapeutic option for the treatment of acne, particularly in cases of stubborn hormonal acne in adult women. This medication may be an option when other

treatments fail to clear acne [14]. According to the U.S. Food and Drug Administration (FDA) there is no specific approval or indication for the use of spironolactone in acne treatment [15].

This review is to deepen understanding of how spironolactone acts on acne vulgaris and why it's used as an off-label therapy based on the latest clinical trials.

3. Review methods

Electronic searches were conducted between 15 and 26 April 2024 and included databases: Pubmed and Google Scholar. The following trials registers were searched using the search terms "spironolactone" AND "acne". This review focuses on 3 trials that are limited to years 2020-2024.

Over the past decade (2014-2024), a comprehensive search conducted on the PubMed database revealed a limited number of studies focusing specifically on the efficacy of spironolactone in managing acne. Among the available literature, only three studies were identified that directly investigated the effectiveness of spironolactone in acne treatment. The remaining body of research within this timeframe predominantly explores diverse topics such as the topical application of spironolactone gel for acne vulgaris [16], its utilization in addressing polycystic ovary syndrome (PCOS) [17], as well as cost-effectiveness analyses concerning the use of spironolactone in acne management [18].

4. A Review of Recent Clinical Trials Investigating the Utilization of Spironolactone in the Treatment of Acne Vulgaris

4.1 "Effectiveness of spironolactone for women with acne vulgaris (SAFA) in England and Wales: pragmatic, multicentre, phase 3, double blind, randomised controlled trial"

SAFA constitutes a pragmatic, multicenter, double-blind, randomized trial featuring two parallel treatment arms (1:1 ratio): spironolactone versus placebo.

The primary endpoint assessed in the study was the Acne-Specific Quality of Life (Acne-QoL) symptom subscale score at week 12, ranging from 0 to 30, with higher scores indicating better quality of life. Secondary endpoints included Acne-QoL scores at week 24,

participant-reported improvement, Investigator's Global Assessment (IGA) for treatment success, and adverse reactions.

Participants were randomly assigned (1:1) to either 50 mg/day spironolactone or matched placebo until week six, increasing to 100 mg/day spironolactone or placebo until week 24.

The primary analysis included 342 participants (176 in the intervention group and 166 in the control group). Baseline mean Acne-QoL symptom scores were 13.2, which increased to 19.2 for the spironolactone group and 17.8 for the placebo group at week 12. At week 24, the scores were 21.2 for spironolactone and 17.4 for placebo. More participants reported acne improvement with spironolactone than with placebo, with significant differences observed at week 24. Treatment success, as classified by the Investigator Global Assessment (IGA), was achieved by 19% of participants in the spironolactone group compared to 6% in the placebo group at week 12. Adverse reactions, particularly headaches, were slightly more prevalent in the spironolactone group (20% vs. 12%), although no serious adverse reactions were reported.

Spironolactone demonstrated superior efficacy compared to placebo, with more pronounced improvements observed at week 24 compared to week 12. These findings suggest that spironolactone represents a valuable alternative to oral antibiotics for the treatment of acne in women [19].

4.2 "Efficacy of Spironolactone Compared with Doxycycline in Moderate Acne in Adult Females: Results of the Multicentre, Controlled, Randomized, Double-blind Prospective and Parallel Female Acne Spironolactone vs doxyCycline Efficacy (FASCE) Study"

Multicentre, controlled, randomized, double-blind prospective and parallel study was conducted on a total of 133 women with moderate acne. Participants were randomized to receive treatment with: (I) doxycycline 100 mg/day and benzoyl peroxide 5% for 3 months followed by a 3-month treatment with its placebo and benzoyl peroxide 5%, or (II) spironolactone 150 mg/day and benzoyl peroxide for 6 months.

Patients who achieved successful treatment outcomes continued using either benzoyl peroxide or spironolactone as monotherapy for an additional 6 months. The primary endpoints included treatment success evaluated at month 4 and month 6 using the Adult Female Acne

Scoring Tool (AFAST). At each visit, assessments were conducted for the ECLA score, lesion counts, local and systemic safety, and quality of life.

Over the course of the study, both groups exhibited a gradual decrease in the overall AFAST score; however, this decrease was more pronounced in the spironolactone group compared to the doxycycline group.

The average ECLA score for the trunk, along with both inflammatory and non-inflammatory lesion counts, exhibited a consistent decline in both treatment groups from month 2 to month 12, with a more notable reduction observed in the spironolactone cohort.

At month 4 and month 6, treatment with spironolactone demonstrated 1.37 times and 2.87 times greater success rates, respectively, compared to treatment with doxycycline.

Furthermore, this study highlights the differential onset of efficacy between doxycycline and spironolactone, with doxycycline showing faster improvement in acne lesions within the initial 2 months of treatment. Conversely, spironolactone therapy resulted in clinical benefits after just 2–4 months of treatment initiation. Importantly, the efficacy of spironolactone continued to improve beyond the initial 4 months of treatment, a trend not observed with doxycycline.

The incidence of systemic adverse events was higher among participants in the spironolactone group compared to those in the doxycycline group following 6 months of treatment. This discrepancy could be attributed to the fact that treatment with doxycycline was discontinued after 3 months, whereas patients receiving spironolactone continued their treatment regimen for an additional 3-month period. The majority of adverse events associated with spironolactone, such as irregular menstruation, were mild to moderate in severity and did not necessitate discontinuation of treatment by patients. There were no reports of treatment-related serious adverse events [20].

4.3 “Efficacy and tolerability of low-dose spironolactone and topical benzoyl peroxide in adult female acne: A randomized, double-blind, placebo-controlled trial”

This single-center study lasted for 12 weeks. It was a randomized, double blind, placebo-controlled, three-arm study conducted from December 2017 to December 2018. Its objective was to assess the efficacy and tolerability of low-dose spironolactone in Thai women with moderate acne vulgaris.

Sixty-three female participants were evenly randomized into three groups: placebo, spironolactone 25 mg and spironolactone 50 mg. Throughout the study period, all participants were provided with topical benzoyl peroxide 2.5% gel, hydrophilic cream, and sunscreen for daily application. Usage of other acne medications, including dermocosmetics, was prohibited during the study duration.

Evaluations were conducted every 4 weeks over the 12-week treatment period, with a final assessment carried out 4 weeks after treatment cessation. By week 12, the success and improvement rates in the spironolactone 50 mg group were significantly higher compared to the placebo group (75% vs. 30% for both rates). However, no statistically significant difference was observed between the spironolactone 25 mg and 50 mg groups in this regard.

Notably, the spironolactone 50 mg group reported a significantly higher incidence of menstrual irregularities and dizziness compared to both the placebo and spironolactone 25 mg groups. However, all adverse events were mild and transient, with none necessitating treatment interruption. Furthermore, potassium and creatinine levels remained unchanged across all three groups.

This randomized controlled trial reaffirmed the efficacy of spironolactone, when combined with topical therapy, in reducing objective acne counts and improving subjective clinical grading. Additionally, it demonstrated that low-dose spironolactone (25–50 mg/day) was associated with a high success rate and minimal side effects in treating adult female acne. Spironolactone's onset of action was noted to be slower compared to other systemic acne treatments, typically requiring approximately 12 weeks for noticeable effects. Moreover, its effects persisted for at least 1-month post-discontinuation, while continuing topical medication maintenance.

It's important to acknowledge that the concurrent use of topical benzoyl peroxide may have influenced the observed effect of spironolactone.

In conclusion, the combination of low-dose oral spironolactone and topical benzoyl peroxide 2.5% gel represents an effective and well-tolerated treatment option for adult female acne [21].

5. Summary

The pharmacology of spironolactone encompasses its dual action as an aldosterone antagonist and an anti-androgen, contributing to its efficacy in managing various conditions such as hypertension, heart failure, and hyperaldosteronism. However, its off-label use in acne treatment has garnered attention, particularly in cases of persistent or hormonal acne in adult women. Recent clinical trials have explored the effectiveness and safety of spironolactone in acne management, shedding light on its potential as an alternative to traditional therapies.

In a pragmatic, multicenter trial (SAFA), spironolactone demonstrated superior efficacy compared to placebo, with notable improvements observed at week 24. Similarly, the FASCE study revealed that spironolactone was more effective than doxycycline in achieving treatment success, albeit with a slower onset of action. However, adverse events, including menstrual irregularities and dizziness, were more prevalent with spironolactone treatment, although mostly mild and transient.

Furthermore, a single-center trial highlighted the efficacy of low-dose spironolactone in combination with topical benzoyl peroxide for treating moderate acne vulgaris in Thai women. The study underscored the favorable efficacy and tolerability profile of spironolactone, albeit with a higher incidence of menstrual irregularities and dizziness in the higher dose group.

There is also one ongoing trial of spironolactone in acne which chose a higher starting dose of spironolactone (150 mg/day) and the data for tolerability, adherence, and adverse effects will be interesting in this trial. The results of these studies may also present avenues for meta-analysis, enhancing statistical power to investigate outcomes within specific subgroups [22].

Despite the promising results, spironolactone's use in acne management remains controversial, with conflicting recommendations from different regulatory bodies. While the American Academy of Dermatology Association recognizes spironolactone as a therapeutic option for acne, the U.S. Food and Drug Administration has not granted specific approval for its use in this indication. Nonetheless, spironolactone presents a viable alternative to traditional therapies, particularly in cases refractory to standard treatments or where adverse effects limit their use.

In conclusion, spironolactone holds promise as a safe and effective option for managing acne, especially in adult women with hormonal or persistent acne. However, further research and regulatory guidance are warranted to delineate its optimal role and ensure its judicious use in clinical practice.

Disclosure

Author's contribution

Conceptualization: Radosław Zaucha and Magdalena Gajkiewicz; Methodology: Julia Silldorff; Software: Tomasz Fura; Check: Stanisław Anczyk and Marcin Dudek; Formal analysis: Zuzanna Felińska and Oliwia Iszczuk; Investigation: Tomasz Fura and Julia Silldorff; Resources: Małgorzata Zając; Data curation: Oliwia Iszczuk; Writing - rough preparation: Radosław Zaucha and Marcin Dudek; Writing - review and editing: Radosław Zaucha and Magdalena Gajkiewicz; Supervision: Stanisław Anczyk; Project administration: Małgorzata Zając and Zuzanna Felińska; Receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

Financing statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The authors deny any conflict of interest.

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