

A Prospective Randomized Trial Comparing Quality of Life in Adult Female Acne Treated with Azelaic Acid 15% Gel versus Oral Spironolactone

Diogo Pazzini Bomfim¹, Marco Alexandre Dias da Rocha², Adriana Sanudo³, Edileia Bagatin²

¹Translational Medicine, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil; ²Department of Dermatology, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil; ³Department of Preventive medicine, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

Correspondence: Diogo Pazzini Bomfim, Email pazzini.bomfim@unifesp.br

Introduction: In several countries, recent research has shown an increase in the prevalence of adult female acne (AFA), defined as the acne that appears in women aged over 25. This disease brings some particularities and challenges, such as a greater impact on quality of life (QoL) and chronicity. A negative impact on QoL has been observed, as well as anxiety, depression, anger, low self-esteem, and feelings of embarrassment and frustration.

Purpose: To quantify AFA's impact on QoL and the influence of two dermatological treatments.

Material and Methods: A prospective study including 40 women, aging from 25 to 44 years old, with mild-to-moderate acne was conducted. Participants underwent clinical, laboratory, and photographic evaluations. They were randomized into two treatment groups: group 1 – azelaic acid (AZA) 15% gel twice daily; group 2 – spironolactone (SPIRO) 100 mg/day and treated for 6 months. At baseline and at the end of treatments, a specific QoL questionnaire for acne, already translated and validated for Brazilian Portuguese (Acne-QoL-BR), was applied. It contains 19 questions allotted in four domains. Each item within a domain is scored from 0 to 6. The total score ranges from 0 to 114 and domains are distributed as follows: 0–30 (self-perception), 0–30 (role-emotional), 0–24 (role-social), 0–30 (acne-symptoms). Higher scores reflect better QoL.

Results: The mean age was 32.7 (SD: 5.42); 85% presented persistent acne. After treatment regardless of group, there was a significant improvement in total score and all domains' scores of acne QoL-BR ($p < 0.001$), with no difference between groups, despite one treatment being topical and the other systemic ($p=0.918$).

Conclusion: Acne-QoL-BR is a useful tool for quantifying the impact of acne and should be used as an efficacy parameter in clinical trials.

Keywords: adult female acne, quality of life, azelaic acid, spironolactone

Introduction

Acne is extremely common and affects around 9.4% of the global population, making it the eighth most prevalent disease worldwide in different degrees of severity, according to epidemiological data.¹ In several countries recent research has shown an increase in the incidence of adult female acne (AFA) cases,^{2–4} defined as the acne that appears in women aged over 25. This disease brings some particularities and challenges, such as a greater impact on quality of life (QoL).⁵ A negative impact on QoL has been observed, characterized by triggering anxiety, depression, anger, low self-esteem, feelings of embarrassment and frustration, regardless of disease severity.^{6,7}

Studies suggest that psychometric tools can possibly help dermatologists detect patients who are psychologically affected, even when the clinical picture is mild.⁸ Literature has demonstrated that the impact on QoL is not always correlated to the severity of acne. In specific cases, individuals present mild disease with a high impact on their QoL.^{8–11} Furthermore, there are studies proving that the psychological impact caused by the presence of acne seems to affect more female than male patients.¹²

Regarding the clinical characteristics of AFA, most cases acne is persistent, meaning that lesions start in adolescence and persist in adult life. Goulden et al, upon the assessment of 200 adult women with acne, reported that only 18.4% presented a clinical picture of late-onset, that is, beginning after 25 years. In the same study, a familial history of AFA was detected in 50% of patients.¹³

Ozdemir et al analyzed the presence of endocrinological diseases in patients with isolated acne and concluded that over 50% did not present clinical or biochemical evidence of hyperandrogenism.^{14,15} In another study aiming to determine the presence of hormonal alterations in acne patients, evidence of biochemical hyperandrogenism was found in only 37%.¹³

Concerning the treatment for AFA, multiple options are available, like those used to treat adolescents. No topical medication in monotherapy can treat all the etiopathogenic factors related to acne; frequently, topicals added to systemic drugs are required.¹⁶ Among the topical treatments, azelaic acid (AZA) is an important option for adult women as there is no risk of teratogenicity. AZA acts as an antimicrobial, anti-inflammatory, depigmenting, and mild comedolytic; it is also useful for post-inflammatory hyperpigmentation. AZA offers an efficacious and well-tolerated treatment for mild-to-moderate AFA, therefore aligning to all current guidance recommending non-antibiotic agents as a means of reducing antimicrobial resistance.¹⁷ In a case series, the positive outcomes demonstrated that AZA was efficacious, resulted in excellent patient satisfaction in mild to moderate AFA, and could also be effective as a maintenance therapy.¹⁸

Regarding systemic treatments for AFA, spironolactone is not approved by the Food and Drug Administration (FDA) for the treatment of acne, but it has been used off-label for decades.¹⁹ Spironolactone is an aldosterone antagonist with anti-androgenic activity, blocking the androgen receptor and inhibiting androgen effects; it is a safe and efficacious drug for acne, with tolerable side effects.^{20–23} In a cohort study, Roberts et al found that about two-thirds of patients with AFA had a complete response. The average time to onset of response was three months, and the average time to maximum response was five months. They observed efficacy in all subtypes of acne severity, including papule-pustular and nodulocystic. Spironolactone was effective as monotherapy, in prolonged treatment, with an average duration of thirteen months with few adverse events.²⁴

Due to the increased prevalence of AFA and its relevant repercussions, it is very important to know more about the disease, the tools to assess its impact on QoL, as well as the effectiveness and safety of dermatological treatments in this specific group.

Materials and Methods

A prospective study including 40 women, aged 25 to 44 years, with mild to moderate acne, was conducted after approval by the Institutional Research Ethics Committee - CEP/UNIFESP n: 0921/2020 and the signature of the consent form and authorization for images. All participants signed the consent form after understanding study's proposal and agreeing. This study complies with the Declaration of Helsinki. The trial was registered at ensaiosclinicos.gov.br with identifier: 4.679.887. Patients were included from May 2021 to August 2022 at the Dermatology Outpatient Department of the Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil. The use of topical or systemic acne treatment in the last six months was an exclusion criterion.

The study aimed to investigate the clinical and laboratorial characteristics of acne in adult women and to determine the impact of the disease on QoL before and after two different treatments.

After inclusion, they were randomized, using an internet tool (www.randon.org), into two treatment groups: group 1 – azelaic acid (AZA) 15% gel (Azelan[®], LEO Pharma, Brazil) twice daily; group 2 – spironolactone (SPIRO) 100 mg/day (generic drug); and both treated for 6 months. Patients were followed once a month, for 6 months.

Clinical Assessment

Clinical assessment consisted of a complete anamnesis and physical examination. Photographs were taken on the day of inclusion and after 6 months of treatment by Visia[®] (Medsystems[®]), a software camera with a rotating capture module that simplifies the image creation process, providing greater comfort for the patient and diagnostic security. Laboratory tests for control were collected at baseline and after 6 months, including fasting glucose, blood count, serum levels of insulin, homeostasis model assessment – insulin resistance (HOMA-IR), total cholesterol, low-density lipoprotein (LDL), high-

density lipoprotein (HDL), triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transferase (GGT), creatinine, urea, sodium, and potassium, pregnancy test, and hormonal tests: luteinizing hormone (LH), follicle stimulating hormone (FSH), total and free testosterone, and dehydroepiandrosterone sulfate (DHEA-S). Hormonal tests were collected in the follicular phase of the menstrual cycle in the morning.

Investigator's Global Assessment (IGA) of acne severity was performed before and after 6 months of treatment. Acne was graded (grade 0–4) using the simple US Food and Drug Administration (US-FDA) 5-category global system of acne classification according to the predominant lesions (Table 1).²⁵

Assessment of QoL

The term QoL can be characterized subjectively as the patient's perception of the disease and treatment, while the technical concept comprises a series of components related to mental health, physical and functional ability, and the social dimension.²⁶

At baseline and at the end of treatments specific QoL questionnaire for acne was applied (Acne-QoL-BR), already translated and validated for Brazilian Portuguese.²⁶ It contains 19 questions allotted in 4 domains. Each item within a domain is scored from 0 to 6. Total score ranges from 0 to 114 and domains are distributed as follows: 0–30 (self-perception), 0–30 (role-emotional), 0–24 (role-social), 0–30 (acne-symptoms).^{27–29} Patients continued answering the questionnaire as long as necessary, without supervision to maintain the privacy for their answers. Higher scores of Acne-QoL-BR reflect better QoL.

For statistical analysis, the chi-square and Fisher's exact test were used for clinical categorical variables, and a Student's *t*-test was used for quantitative variables. To compare the questionnaire domains, the analysis of variance model with repeated measures adjusted by the Proc-mixed module of SAS software 9.3 was used. Results were considered significant when the *p*-value was less than 5% ($p < 0.05$).

Results

Forty women between 25 and 44 years old with mild-to-moderate acne were included in the study. The mean age was 32.5 (SD: 5.42). Persistent acne was detected in 85% of the population; 12.5% of women smoked and 52.5% drank alcoholic beverages; and 90% had a family history of metabolic syndrome (MS) (Table 2). In this sample, 27.5% reported they had never consulted a dermatologist; the majority 72.5%) were treated for short periods, with a loss of follow-up. Mild acne was diagnosed in 62.5% and moderate acne in 37.5%. A family history of acne was verified in 72.5%.

Regarding laboratory tests, mean cholesterol was 186 (SD 30.3), with 47.5% >190. HOMA-IR levels suggested insulin resistance in 32.5%. Overweight or obese women presented higher HOMA-IR levels compared with normal-weight women ($p=0.008$). Hyperandrogenemia was observed in just one patient (5%). In the SPIRO group, no hyperkalemia was observed after 6 months. Kidney and liver function tests and electrolytes were not altered in the systemic treatment group.

Throughout the six months, there were 15% of dropouts in the AZA group and 25% in the SPIRO group (no difference; $p=0.695$), not related to side effects but for personal reasons, despite clinical improvement. The pre-treatment analysis of the data from the QoL questionnaires demonstrated low scores in all domains of acne-QoL. After treatment,

Table 1 Investigator's Global Assessment (IGA) of Acne Severity

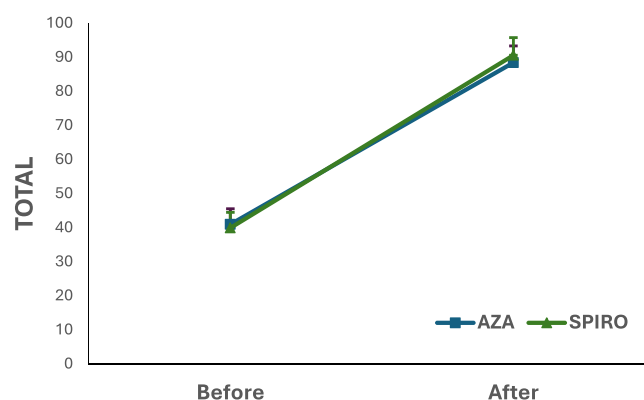
Classification	Description
0. Clear	Indicating no inflammatory or non-inflammatory lesions.
1. Almost clear	Rare non-inflammatory lesions with no more than 1 papule/pustule.
2. Mild	Some non-inflammatory lesions, no more than a few papules/pustules but no nodules.
3. Moderate	Up to many non-inflammatory lesions, may have some inflammatory lesions, but no more than 1 small nodule.
4. Severe	Up to many non-inflammatory and inflammatory lesions, but no more than a few nodules.

Table 2 Clinical Characteristics of the sample

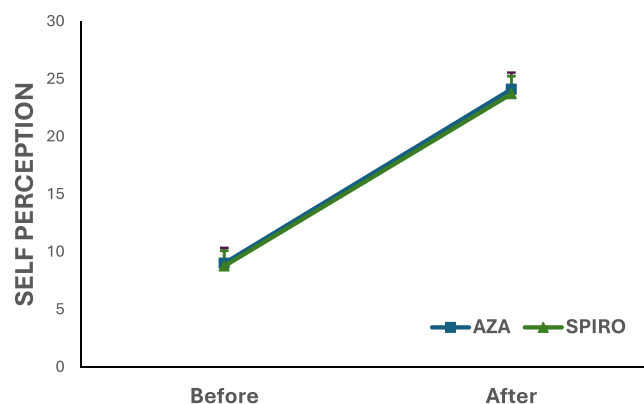
	Level	Count	Proportion	p
Onset of acne	Adolescence	34	0.850	<.001
	Adult	6	0.150	
Smoking	NO	35	0.875	<.001
	YES	5	0.125	
Alcoholism	NO	19	0.475	0.875
	YES	21	0.525	
Family history of MS	NO	4	0.100	<.001
	YES	36	0.900	
BMI	NORMAL	13	0.325	0.038
	Obesity	15	0.375	0.154
	Overweight	12	0.300	0.017

Abbreviations: BMI, Body Mass Index; MS, Metabolic Syndrome.

regardless of group, there was a significant improvement ($p<0.001$) in total score (Figure 1) and all domains: self-perception ($p<0.001$) (Figure 2), role-emotional ($p<0.001$) (Figure 3), role-social ($p<0.001$) (Figure 4), acne-symptoms ($p<0.001$) (Figure 5), with no difference between groups ($p=0.918$).

**Figure 1** Total score of Acne-QoL-BR before and after 6 months of treatment.

Abbreviations: AZA, azelaic acid; SPIRO, spironolactone.

**Figure 2** Self perception score of Acne-QoL-BR before and after 6 months of treatment.

Abbreviations: AZA, azelaic acid; SPIRO, spironolactone.

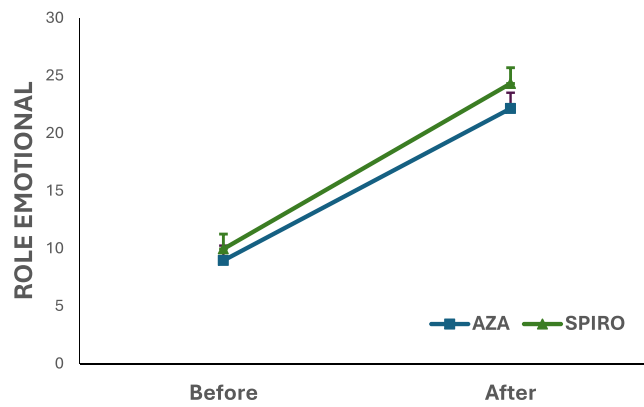


Figure 3 Role emotional score of Acne-QoL-BR before and after 6 months of treatment.

Abbreviations: AZA, azelaic acid; SPIRO, spironolactone.

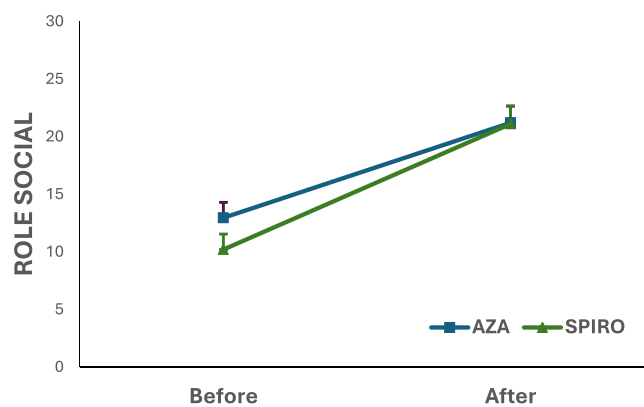


Figure 4 Role social score of Acne-QoL-BR before and after 6 months of treatment.

Abbreviations: AZA, azelaic acid; SPIRO, spironolactone.

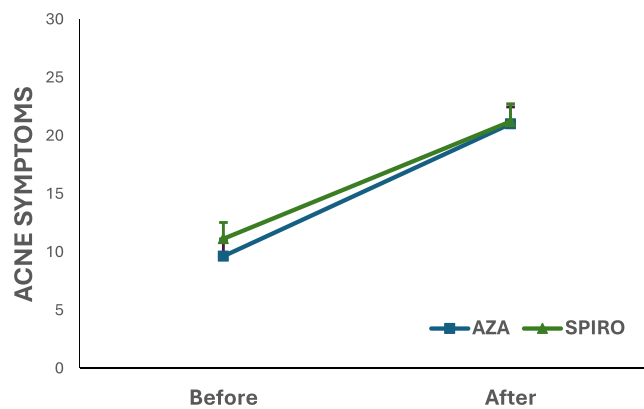


Figure 5 Acne symptoms score of Acne-QoL-BR before and after 6 months of treatment.

Abbreviations: AZA, azelaic acid; SPIRO, spironolactone.

After 6 months, clinical improvement was considered very satisfactory by the investigator and the patient with both treatments. The IGA score was performed by the investigator before and after treatment, according to clinical and photographic evaluation. Both treatments resulted in significant clinical improvement, with no difference, as shown in Figure 6.

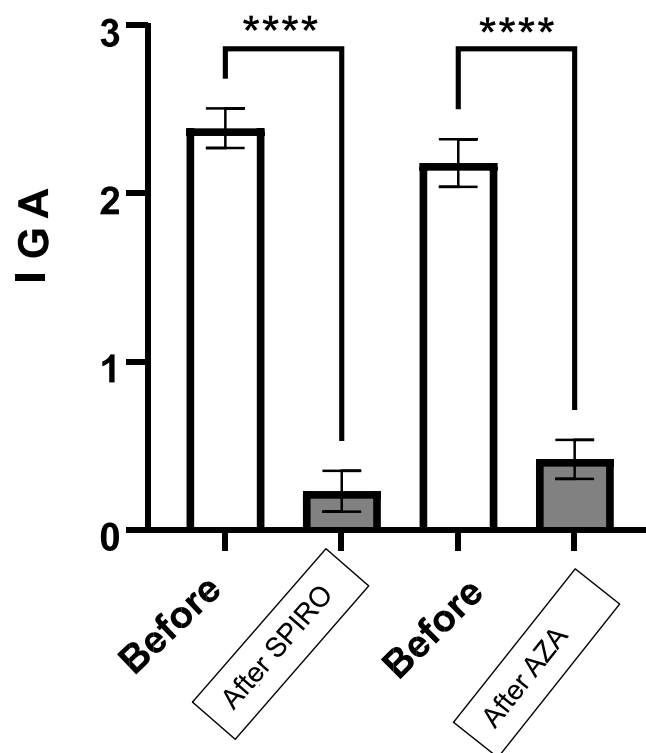


Figure 6 Investigator's Global Assessment (IGA) of acne severity before and after 6 months of treatment. ****: $p < 0.0001$ (ANOVA-Bonferroni).
Abbreviations: AZA, azelaic acid; SPIRO, spironolactone.

Figures 7 and 8 represent one patient from the AZA group with inflammatory papulopustular lesions on the face, more concentrated on the lower third of the face and neck ("U" type acne) associated with acne-induced macular erythema, progress from IGA 2 to IGA 0, and improvement in the macular erythema.

Figures 9 and 10 represents one patient from SPIRO group, with inflammatory papulopustular lesions on the face, more concentrated on the lower third of the face and neck ("U" type acne) associated with atrophic scars and acne-induced hyperpigmentation, progressed from IGA 2 to 0 in 6 months.



Figure 7 Improvement on left-hand side of face, at baseline and 6 months with azelaic acid 15% gel twice a day.



Figure 8 Improvement on right-hand side of face, at baseline and 6 months with azelaic acid 15% gel twice a day.



Figure 9 Improvement on the left-hand side of the face at baseline and 6 months with spironolactone 100 mg/day.



Figure 10 Improvement on the right-hand side of the face at baseline and 6 months with spironolactone 100 mg/day.

Discussion

No previous studies in literature compared these two treatments. In this study, there were no laboratory changes with systemic treatment. The potassium levels in healthy young women taking spironolactone for acne, for 6 months was

equivalent to the baseline level of the study population. Routine potassium monitoring is unnecessary for healthy women taking spironolactone up to 100 mg daily for acne.³⁰ We observed the onset of acne in adolescence, persisting to adult life, low access to treatment and normal hormonal tests, as already reported for most women with acne in the literature.

The results related to Acne-QoL corroborate the literature and demonstrate the high psychosocial impact of acne lesions in adult life, working as a useful tool to measure it. After treatment, regardless of the type (oral or topical), there was a statistically significant improvement in all domains. As the literature has been shown, that impact does not always correlate with the severity of acne.^{8–11} In this study there was no severe acne; patients presented mild or moderate acne, but their initial scores were worsened in all domains. Studying acne in different age groups, Tan et al have shown that total QoL scores worsen as the disease persists.¹⁰ A study by Rocha et al confirmed that AFA has a high negative impact on the patients' QoL, even when they have mild or moderate acne. In the same study, the patients showed an improvement in QoL scores after monotherapy with a combined oral contraceptive or even with topical medication containing azelaic acid. A statistical superiority was observed for the contraceptive group in only two Acne-QoL domains (self-perception and acne symptoms).¹¹

Acne negatively influences all dimensions of a woman's life, and Acne-QoL-BR represents a specific and highly useful tool for quantifying the impact of the disease and should always be used as an efficacy parameter in clinical trials. All patients showed improvement in inflammatory lesions, and additionally, AZA reduced acne-induced hyperpigmentation.

Conclusion

AFA is common in dermatological practice. Unfortunately, clinical studies specifically evaluating the prevalence, clinical presentation, and treatment of this population are sparse in the literature. Our results clearly showed that all treated patients presented significant improvement in the IGA score and in the scores from the four domains that constitute the Acne-QoL, regardless of treatment option. In our opinion, the satisfactory results may also be related to the attention given to these patients when participating in clinical research in a university hospital, with personalized, prolonged consultations, and always by the same doctor. In other words, a good doctor–patient relationship may have contributed a lot.

This study corroborates the usefulness of Acne-QoL-BR for quantifying the psychological impact of AFA as a relevant efficacy parameter in clinical trials.

Abbreviations

AZA, azelaic acid; SPIRO, spironolactone.

Data Sharing Statement

There is no other data to share. All results have been presented on the proof.

Disclosure

The authors report financial support from LEO Pharma in donating the medicines in this work. The authors report no other conflicts of interest in this work.

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