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Moderate Acne Vulgaris: Efficacy, Tolerance and Compliance of Oral Azithromycin Thrice Weekly for 12 Weeks

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SUMMARY The aim of the study was to investigate the efficacy, safety and compliance of 500 mg azithromycin thrice weekly for 12 weeks in moderate inflammatory acne vulgaris. An open-label, noncomparative study was carried out for 12 weeks at Department of Dermatology and Plastic Surgery, La Sapienza University in Rome. Fifty-seven patients (20 male and 37 female) between 13 and 41 years of age, affected by moderate papulo-pustular and nodular acne vulgaris, were enrolled in the study. Azithromycin 500 mg was administered orally thrice weekly for 12 weeks. Patients were examined at baseline, 4 weeks, 8 weeks and 12 weeks (completion of treatment), evaluating both clinical (Global Acne Grading System, GAGS) and quality of life (Acne Quality of Life Questionnaire, AQoL) improvements. Forty-six patients completed the study and showed significant improvement. Six patients interrupted their treatment, while five patients did not complete the study for unknown reasons. Side effects (diarrhea and abdominal pain) were recorded in eight patients. Azithromycin, 500 mg thrice weekly for 12 weeks, is a safe and effective treatment for moderate acne vulgaris with excellent patient compliance.

KEY WORDS: moderate acne vulgaris, azithromycin

INTRODUCTION

Acne is an inflammatory cutaneous disorder involving the pilosebaceous unit with a multi-factorial pathogenesis. According to epidemiological studies, acne is a common condition affecting 80% of young people between 12 and 18 years of age as well as 5% of females and 1% of males in adulthood. It is also the most common reason for consultation in private dermatology practices (1). The most notable pathophysiological factors that influence the development of acne are sebaceous gland hyperplasia with seborrhea, abnormal desquamation of sebaceous follicle epithelium (comedogenesis), increased bacterial colonization of the follicle (*Propionibacterium acnes*), and inflammatory and immune reactions (1-3).

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Acneic lesions often leave lifelong scars and hyperpigmentations. Both scarring and hyperpigmentation may result in substantial disfigurement that can have an effect on the patients' self-image, impacting considerably on their emotional health and quality of life (4). Comparisons with other chronic illnesses have shown that acne patients have levels of social, psychological and emotional impairments that are similar to those reported by patients with more serious diseases such as asthma, epilepsy, diabetes, back pain or arthritis (5). It is necessary to find an effective treatment to reverse this social and psychological disability. A typical aspect of acne is the lesional pleomorphism with different lesions simultaneously present in the same patient. For this reason, acne may be present in a wide variety of clinical forms depending on the type, number and severity of the predominant lesion. There are many classifications of acne; if we consider the severity of symptoms and the type of predominant lesions, acne may be mild – comedonal and papulopustular with few lesions; moderate – papulopustular with numerous lesions and nodular with small nodules; and severe – nodular-conglobate (some authors would also add a very severe category). The pathophysiological features of acne suggest that combination therapy is the best choice and it should be utilized as early as possible to simultaneously attack two or more pathogenic factors, as recommended by a recent therapeutic algorithm (2,6,7). Topical therapies include comedolytic agents such as topical retinoids, alpha hydroxy-acids, salicylic acid and azelaic acid, or antibacterial agents such as benzoyl peroxide and topical antibiotics. Systemic treatments for acne vulgaris include oral antibiotics, hormonal agents and isotretinoin (2,6,7).

Oral antibiotics continue to play an integral role in the management of acne and should be used in moderate-to-severe inflammatory forms. In addition to their indirect anti-inflammatory action, the interference with the growth and metabolism of *Propionibacterium acnes*, thought to trigger the inflammatory response in acne, oral antibiotics also have a direct anti-inflammatory action, inhibiting neutrophil chemotaxis, cytokine production and macrophage functions. In acne treatment antibiotics are typically administered for a prolonged period of time, from a minimum of 6-8 weeks to a maximum of 12-18 weeks but should not be used as monotherapy (1,6,7). In fact, in order to reduce the risk of bacterial resistance, it is recommended to use topical retinoids in association with benzoyl peroxide during and between antibiotic courses. The preferred agents of choice include tetracyclines and macrolides (1,6,7).

Azithromycin is an orally administered macrolide, structurally related to erythromycin, but with an enhanced spectrum of activity against gram-positive and gram-negative pathogens as well as a longer serum and tissue half-life, allowing for once-daily dosing. In addition to its use in the treatment of lower and upper respiratory tract infections (acute exacerbations of chronic bronchitis and pneumonia) or odontogenic infections, azithromycin is also indicated for skin and soft tissue infections. Good results have also recently been reported in the literature regarding its use in the treatment of inflammatory acne vulgaris.

The pharmacokinetic profile of azithromycin is characterized by a rapid and extensive uptake from the circulation into the intracellular compartments, followed by slow release (8). These factors allow for a single dose regimen and the potential for increased compliance. Azithromycin is rapidly absorbed from the small intestine and peak serum concentration is reached within 2-3 hours after ingestion (9). Patient age has minimal effect on the absorption of azithromycin, while food and antacids decrease the peak serum concentration but do not influence the overall absorption of the drug (9,10).

Upon absorption, azithromycin is redistributed from the circulation and delivered by phagocytes to the foci of infection *via* the activation of chemotaxis (11,12). Accumulation of macrolides, and in particular azithromycin, is inflammation-dependent: phagocytic cells such as macrophages and polymorphonuclear leukocytes (PMNs) actively take up azithromycin, producing intracellular concentrations up to 200 times those found in serum (12). The drug concentrates intracellularly in lysosomes. Although concentration in host cells is a feature of the macrolides as a class, the intracellular concentrations that can be achieved by azithromycin are much higher than the levels attainable by other related compounds (12). The presence of bacteria at the infection site stimulates the release of azithromycin from phagocytes (13). In addition, the subsequent fusion of lysosomes (containing high concentrations of azithromycin) with phagosomes exposes microorganisms to azithromycin (13). Moreover, fibroblasts may act as a tissue reservoir of azithromycin, and the drug may then be either slowly released from these cells at local sites of infection, or transferred to phagocytes, which can then transport it to the infected tissues (14). The most common side effects in adults receiving

a multiple or single-dose regimen of azithromycin are related mainly to the gastrointestinal system, and include diarrhea/loose stools, nausea/vomiting, abdominal pain and dyspepsia.

This study was carried out in order to estimate the efficacy of azithromycin in the treatment of moderate inflammatory acne vulgaris **(**papulopustular and nodular). Moreover, the aim of this study was to assess the patients' perception of the disease, the impact of acne on their emotional health and quality of life and, finally, the possible effects of successful treatment on these aspects of life.

MATERIALS AND METHODS

In order to estimate the efficacy, tolerance and compliance of systemic azithromycin in the treatment of moderate inflammatory acne vulgaris, an open-label, non-comparative study was carried out for 12 weeks at the Department of Dermatology and Plastic Surgery, La Sapienza University in Rome. Fifty-seven Caucasian patients (20 male and 37 female) aged 13-41 and affected by moderate acne, defined as a score of 1 to 30 on the Global Acne Grading System (GAGS) scale (15), were enrolled and examined: 55 patients were affected by moderate papulopustular acne and two by moderate nodular acne. All patients were given azithromycin, 500 mg, orally thrice weekly for 12 weeks. Patients were excluded if they met any of the following criteria: renal disease, hypersensitivity to azithromycin, or a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Also excluded were patients who were unwilling or unable to undertake acne therapy. Together with systemic azithromycin, patients were given 0.1% topical adapalene (gel or cream) to apply to the affected areas of the face and trunk once daily in the evening, and benzoyl peroxide (gel) to apply to inflammatory lesions of the face and trunk once daily in the morning after the skin had been cleansed and dried.

Patients were examined at baseline, 4 weeks, 8 weeks and 12 weeks (completion of treatment), in order to evaluate their clinical improvement and to measure the psychological effects of acne. Clinical improvement was assessed using a clinical evaluation system (GAGS). The GAGS global score is calculated by rating six different locations (forehead, right cheek, left cheek, nose, chin and chest/upper back) as 0 (no lesions), 1 (≥1 comedo), 2 (≥1 papule), 3 (≥1 pustule) or 4 (≥1 nodule), and then multiplying each rating by a factor that is specific to the area. Factors are based on the surface area and distribution/density of pilosebaceous units. Global score is the sum of all six location scores and global grade is defined according to the global score (Table 1). Global score (15) correlated with the severity of acne (15).

Although many clinical measures are acceptable for assessing acne severity, patient perception of the disease may include factors other than the severity and number of lesions. As facial acne is highly visible and carries a certain degree of social negativity, it has been hypothesized that even mild acne can decrease the person's self-confidence, body image, and willingness to be seen in public and social interactions. To assess the

Table 1. Global Acne Grading System (GAGS) (15)

Location (factor)	Clinical presentation (grade)	Local score (factor x grade)
□ Forehead (2)	No lesions (0) ≥one comedo (1) ≥one papule (2) ≥one pustule (3) ≥one nodule (4)	
□ Right cheek (2)	No lesions (0) ≥one comedo (1) ≥one papule (2) ≥one pustule (3) ≥one nodule (4)	
□ Left cheek (2)	No lesions (0) ≥one comedo (1) ≥one papule (2) ≥one pustule (3) ≥one nodule (4)	
□ Nose (1)	No lesions (0) ≥one comedo (1) ≥one papule (2) ≥one pustule (3) ≥one nodule (4)	
□ Chin (1)	No lesions (0) ≥one comedo (1) ≥one papule (2) ≥one pustule (3) ≥one nodule (4)	
□ Chest/upper back (3)	No lesions (0) ≥one comedo (1) ≥one papule (2) ≥one pustule (3) ≥one nodule (4)	
Global score		

Global score	Grade	Severity
0	0	None
1-18	1	Mild
19-30	2	Moderate
31-38	3	Severe
≥39	4	Very severe

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effects of acne on patient quality of life, individual points of view and the impact of treatment on quality of life parameters, each participant was asked to complete an acne-specific questionnaire (Acne Quality of Life Questionnaire AQoL) (16) upon entering the study and during follow up. This questionnaire, self-administered to the patients, contains 19 questions, each referring to the past week, organized into four domains (self-perception, role-social, role-emotional, acne symptoms). AQoL domain scores are calculated by summing all items within a domain. Responses to all items are on a scale from 0 ("extremely"or "extensive") to 6 ("not at all"or "none") with each item within a domain weighed equally. For all domains, higher scores reflect better AQoL (16).

The GAGS and AQoL values were used to detect clinical and psychological improvement during treatment.

Statistical analysis

We calculated means (standard deviations) of quantitative variables (GAGS and AQoL levels). Differences between two periods were estimated using the nonparametric test for paired data (Wilcoxon test). Analysis of variance (ANOVA) with repeat measurements (F test) was used in order to verify differences in GAGS and AQoL levels over time. Spearman correlation coefficient (rho) was used to asses the correlation between GAGS and AQoL levels for each time period. The significance level was set at $p<0.05$.

RESULTS

Forty-six of 57 patients (19 male and 27 female, mean 17.8±2.9 and 20.8±6.7) completed the study and showed significant improvement of acneic lesions. Eight patients complained of gastrointestinal side effects (abdominal pain and diarrhea): six of them interrupted their azithromycin regime before the end of treatment, three during the first month of therapy, and another three during the second month. Another five patients discontinued treatment during the first month for unknown reasons.

Efficacy was defined as percentage reduction of lesions. Patients enrolled and followed-up showed a reduction in lesions from treatment week 4 onwards. This reduction was evaluated through an objective criterion (GAGS). In fact, at the end of treatment the GAGS average score was lower (GAGS: 9.15) than the scores obtained before therapy (GAGSpre: 22.2), at 4 weeks (GAGS:16.28) and at 8 weeks (GAGS:12.58) of therapy.

The ANOVA for repeat measurement revealed a significant difference for GAGS levels over time (F test=5.754; p=0.002). In this case there were no sex (p=0.935) or age (p=0.335) differences. Comparison of GAGS levels before treatment yielded a highly statistically significant difference against each follow up period (Wilcoxon test: $p<0.001$) (Fig. 1).

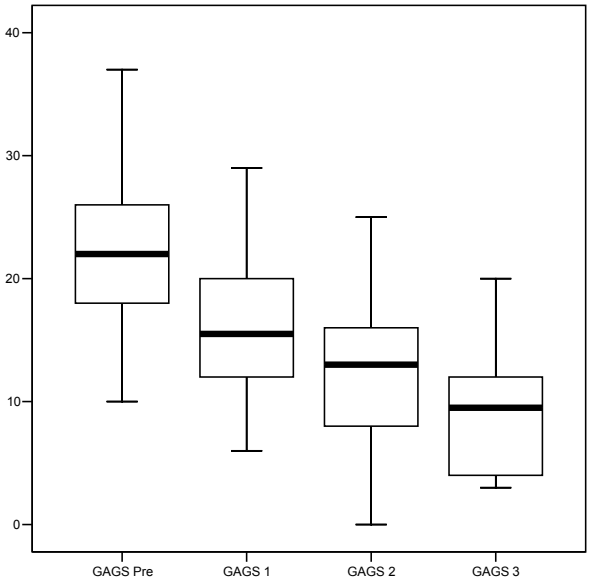

Figure 1. Average Global Acne Grading System (GAGS) in 46 patients

The reduction of acneic lesions, both inflammatory and non-inflammatory, was associated with lower psychological and emotional impairment, as demonstrated by AQoL questionnaire scores obtained before treatment and at 4, 8 and 12 weeks. More specifically, the average score at the end of therapy (AQoL 91.21) was higher than before therapy (AQoL 69.34), at 4 weeks (AQoL 81.78) and at 8 weeks (AQoL 83.52).

ANOVA for repeat measures revealed a significant difference of AQoL levels over time (F test=31.040; $p<0.0001$); once again there were no sex (p=0.267) and age (p=0.076) differences. Comparison of AQoL levels before treatment showed a highly statistically significant difference against each period of follow up (Wilcoxon test: $p<0.001$) (Fig. 2).

Comparison of the average trend for the two independent parameters, GAGS and AQoL, suggested an association between the progressive reduction of GAGS, relating to clinical improvement, and the increase in AQoL values, relating to improvement in the quality of life.

Spearman correlation coefficients between GAGS and AQoL over time are shown in Table 2. It is evident that there is no strong correlation between these two variables before and after treatment, (p>0.10).

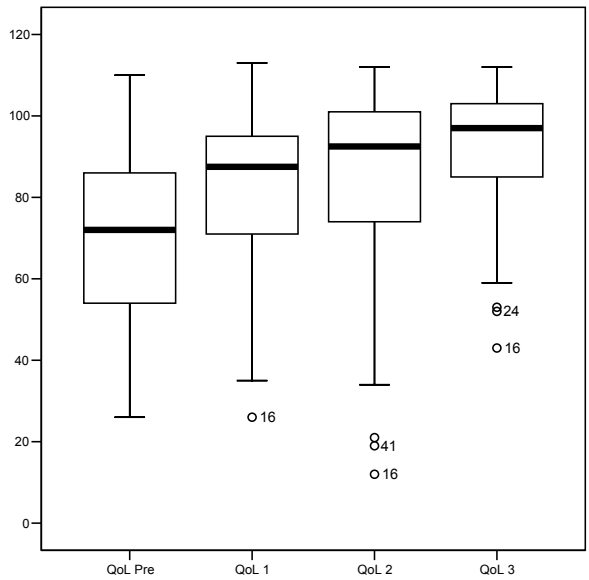

Figure 2. Average Acne Quality of Life (AQoL) in 46 patients

Table 2. Spearman correlation coefficients between Acne Quality of Life (AQoL) and Global Acne Grading System (GAGS) over time in patients with moderate acne vulgaris

Time	Spearman rho	P
Before	0.093	0.540
4 weeks	0.092	0.545
8 weeks	-0.230	0.124
12 weeks	-0.103	0.496

CONCLUSION

Each clinical form of acne necessitates a specific treatment, which should redress all four major pathogenic factors, as recommended by a recent therapeutic algorithm (2,6,7). Combination therapy is the treatment of choice and should be initiated as early as possible to simultaneously attack two or more of the pathogenic factors. Antibiotics are an affective treatment for inflammatory acne lesions because of their anti-inflammatory and anti-microbial properties. Azithromycin has many advantages when compared to other antimicrobials used in acne treatment. This study focused especially on the use of antibiotics in acne therapy and examined the efficacy, safety and compliance of 500 mg oral azithromycin given thrice weekly over a 12-week period. This antibiotic was coadministered with local therapy, adapalene 0.1% (in the morning) and benzoyl peroxide 5% (in the evening). Both clinical (GAGS) and quality of life (AQoL) improvements were evident from the beginning of week 4 of therapy and continued to be evident at weeks 8 and 12 of treatment.

The results recorded at the end of the study demonstrate that azithromycin, 500 mg, administered orally thrice weekly for 12 weeks, is a good and safe therapeutic choice in the treatment of moderate inflammatory acne. The clinical improvement obtained from week 8 to week 12 suggests that systemic antibiotics in acne therapy have to be taken for 3 months in order to achieve the best therapeutic results and to decrease the risk of bacterial resistance. The mode of administration, good compliance, enhanced spectrum of activity against gram-positive and gram-negative pathogens, and longer serum and tissue half-lives make azithromycin an important adjunct for the dermatologist in the treatment of gram-positive and gram-negative infections. Up to now, cases of *Propionibacterium acnes* resistance to azithromycin have never been reported. Moreover, this antibiotic was well tolerated by the great majority of patients with only six of 57 (10.5%) patients enrolled dropping out from the study because of side effects.

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Spring is time for Nivea cream and Nivea oil; year 1936.
(from the collection of Mr. Zlatko Puntijar)