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Original Article

Angiotensin-converting enzyme gene insertion/deletion polymorphism and its impact on response to azithromycin and doxycycline treatment in acne vulgaris patients

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Abstract

Background: Acne vulgaris (AV) is a common inflammatory skin disorder. Systemic treatments like azithromycin and doxycycline are frequently used. The Angiotensin-Converting Enzyme (ACE) has been implicated in inflammation and skin diseases. This study investigated the association between ACE I/D polymorphism and therapeutic response to azithromycin versus doxycycline in moderate AV.

Methods: This clinical trial enrolled 54 moderate AV patients divided equally into two groups: one received 100 mg/day doxycycline, the other 250 mg/day azithromycin for 3 months. DNA was extracted via salting-out method, and ACE I/D polymorphism was analyzed by PCR and electrophoresis. Treatment efficacy was assessed using Michelson's acne score and standardized photography. Post-treatment, genotype-phenotype correlations were evaluated.

Results: The doxycycline group showed significantly higher recovery rates (59.3%) compared to azithromycin (18.5%) ($p<0.001$). However, no statistically significant association was observed between improvement percentages and genotypes in either the doxycycline (($P = 0.567$) or azithromycin ($P = 0.533$) groups.

Conclusion: Doxycycline was significantly more effective than azithromycin for moderate AV. However, no significant association was found between ACE I/D polymorphism and treatment response for either antibiotic. These findings guide therapeutic selection while suggesting that ACE genotyping may not predict treatment response in moderate AV.

Keywords: Acne vulgaris, Doxycycline, Azithromycin, Polymorphism.

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Acne vulgaris (AV) is a common, chronic inflammatory skin disease that affects approximately 9.4% of the global population. It primarily manifests in individuals between the ages of 11 and 30, a prevalence strongly linked to the onset of puberty. Potential complications of the condition extend beyond the physical, often including psychological effects such as anxiety, depression, social isolation, and diminished self-esteem (1, 2). Acne vulgaris (AV) is a prevalent skin disorder affecting approximately 9.4% of the global population. It ranks as the eighth most common disorder worldwide, with its prevalence among teenagers reaching up to 90%. In many instances, acne can persist into adulthood. Based on the type of acne lesions present, the severity of the condition is generally categorized into three main types: mild, moderate, and severe. Mild acne typically manifests with non-inflammatory lesions, while moderate to severe acne involves both inflammatory and non-inflammatory lesions. Severe cases may exhibit nodules and cysts, which are inflamed, swollen lesions larger than 5 mm (3). Some of the risk factors for acne include family history, high fat intake, genetic factors, alcohol consumption, overweight or obese BMI, mental stress, smoking status, and sun exposure (4).

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One of the crucial factors in the pathophysiology of AV is inflammation (5). In acne vulgaris, inflammation triggered by oxidative stress and its persistence within the pilosebaceous unit are critical early stages that lead to subsequent pathogenic processes (6). The secretion of sebum by pilosebaceous units undergoes compositional changes, potentially releasing reactive oxygen species (ROS) from follicular walls. This oxidative stress is considered a primary contributor to the development of inflammatory responses in acne (7). The renin-angiotensin system (RAS) is known for its regulatory effects across various organs. Angiotensin II, a key molecule in the RAS, plays a significant role in increasing inflammation. Studies have demonstrated that NF-κB-mediated activation induced by angiotensin II triggers a proinflammatory cascade. Furthermore, inhibiting angiotensin II production with Angiotensin-Converting Enzyme (ACE) inhibitors has been shown to mitigate oxidative stress (9 ,8). Angiotensin-converting enzyme (ACE) is a zinc- and chloride-dependent dipeptidase that is expressed in epithelial and endothelial cells. It plays a critical role in blood pressure regulation and fluid homeostasis by catalyzing the conversion of angiotensin I (Ang I) to the potent vasoconstrictor angiotensin II (Ang II) within the renin-angiotensin system (RAS) (10, 11). The ACE gene is located on the long arm of chromosome 17 and spans 21 kb, comprising 26 exons and 25 introns. Due to its widespread distribution and diverse functions, ACE is implicated in various pathological conditions. Genetic variations in the ACE gene, such as the insertion/deletion (I/D) polymorphism in intron 16, are particularly studied for their functional implications (12). The I/D polymorphism has been examined in a number of skin disorders (13, 14).

Numerous systemic and topical treatments are available for acne. Systemic treatments include antibiotics, hormone therapy, and isotretinoin, selected based on acne severity, type, and prior treatments (15). Topical medications include keratolytics, alpha hydroxy acids, benzoyl peroxide, retinoid analogs, azelaic acid, and topical antibiotics. Oral antibiotics such as tetracyclines, erythromycin, and trimethoprim/sulfamethoxazole are effective for patients with locally resistant or severe acne (16). However, the excessive and prolonged use of certain antibiotics has driven the emergence and global spread of resistant bacterial strains (17). Given the high prevalence of AV in young populations and its associated complications such as scarring and psychological distress from inadequate treatment, there is a critical need for effective therapeutic approaches. Understanding ACE's role in immune responses and inflammation prompts investigation into ACE gene polymorphism and it impact on response to antibiotics like doxycycline and azithromycin. This research aimed to investigate the association between the ACE gene insertion/deletion polymorphism (I/D) (rs4646994) and the effectiveness of treatments with doxycycline and azithromycin in patients diagnosed with moderate acne vulgaris.

Methods

Subjects: This research was designed as a open-label, parallel-group, randomized clinical trial (IRCT code: IRCT20230305057628N1). Patients with AV were selected from January 2022 to June 2022 at the Gonabad Skin Clinics. The sample size was determined via a formula based on the mean and standard deviation of inflammatory papules reported in a previous study (18), with a confidence level of 95% and 90% power. Initially, a minimum of 25 participants per group was calculated. To mitigate potential issues such as dropout, an additional eight percent was added to each group, resulting in a final sample size of 27 participants per group (Mean 1= 10.8, SD1= *7.4*, Mean 2= 4.7, SD2=*5.8*)

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-B}\right)^2 (\delta_1^2 + \delta_2^2)}{(\mu_1 - \mu_2)^2}$$

This study conforms to the Declaration of Helsinki regarding research involving human subjects and is approved by the Ethics Committee of Gonabad University of Medical Sciences (IR.GMU.REC.1401.182). In this, a dermatologist selected 54 individuals with moderate acne, meeting the inclusion and exclusion criteria, from among those who visited the Gonabad Skin Clinic. Informed consent was obtained from the participants in the study. Patients were randomly assigned to study groups using block randomization. The inclusion criteria were moderate acne vulgaris, based on the Vaishampayan classification system, and age over 12 years. Exclusion criteria included the occurrence of unusual complications during treatment, withdrawal from the treatment process, failure to complete the treatment, breastfeeding, and pregnancy.

The 54 patients were divided into two groups of 27. One group received doxycycline 100 mg daily along with topical treatments (benzoyl peroxide and tretinoin), while the other group received azithromycin 250 mg every other day, also combined with the same topical treatments. Given that the patients enrolled in the study were predominantly adolescents, they were not taking any other medications over the past 30 days. Patients with moderate acne vulgaris who met the study's inclusion and exclusion criteria were

selected via purposive non-probability sampling by a dermatologist. Subsequently, permuted block randomization with a block size of four was employed to allocate participants into the two treatment groups. This process involved listing all six possible block sequences (BAAB, ABBA, BABA, BBAA, ABAB, AABB) and assigning each a unique number from 1 to 6. A random number between 1 and 6 was then generated using a random number table, and participants were allocated to the groups according to the block sequence corresponding to the selected number. After three months of pharmacological treatment, the Michelson acne score was reassessed. Standardized photography was performed, patient satisfaction was obtained, and the response to drug therapy was evaluated. The Michelson acne score is a method for evaluating patients' response to treatment. The final score is determined based on the count of different types of skin lesions (papules, pustules, etc.) and their assigned weighting coefficients. According to this scoring system, comedones are assigned a coefficient of 0.5, papules a coefficient of 1, and pustules a coefficient of 2. To calculate the final Michelson acne score, we used the following formula: (Number of comedones × 0.5) + (Number of papules × 1) + (Number of pustules × 2) = Final acne score. Also known as the Michaelson's Acne Severity Index (MASI), this scoring system is widely used to assess acne severity (19, 20).This is a grading system for acne severity, which classifies acne as follows:

a) Grade 1 (Mild): Comedones and a small number of papules.

b) Grade 2 (Moderate): Comedones, a large number of papules, and a small number of pustules.

c) Grade 3 (Severe): Mostly pustular lesions, along with nodules and cysts.

d) Grade 4 (Cystic): Numerous cysts or abscesses, with extensive scarring observed.

Based on this classification system, we enrolled patients who met the criteria for Grade 2 and were classified as having moderate acne (20). The response to drug treatment was then evaluated.

Samples and data collection: Demographic and clinical information of patients, including age, gender, duration of acne, and family history of acne, were recorded using a checklist. Michelson's acne score and standard photographs were documented prior to starting acne treatment. Two milliliters (2 mL) of blood were drawn from each patient and collected in EDTA-containing tubes. The blood samples were stored at -20°C.

Genotype determination: DNA was extracted using the salting-out method, and the quality and quantity of the extracted DNA were evaluated using nanodrop spectrophotometry and electrophoresis. The optimal OD ratio for A260/280 was between 1.6 and 1.8. The I/D polymorphism was detected by a polymerase chain reaction (PCR) using following primers: Forward: 5′-CTGGAGACCACTCCCATCC1TTCT-3′, Reverse: 5′-GATGTGGCCATCACATTCGTCAGAT-3′. Primer design was carried out using Oligo7 software, with quality control conducted through the NCBI BLAST primer tool.

For PCR amplification of the target fragment, a mixture was prepared consisting of 1 µL of forward primer, 1 µL of reverse primer, 1 µL of extracted DNA, and Master mix (Ampliqon Company, Denmark). This mixture was placed in a Bio-Rad thermal cycler, with the thermal settings for ACE gene amplification as outlined in Table 1. After PCR, 2% agarose gel electrophoresis was performed to identify the target gene fragments and genotypes. Electrophoresis results were used to detect the presence of mutations (homozygous and heterozygous) or the absence of mutations (homozygous) in the ACE gene. The PCR temperature program is shown in table 1.

Statistical analysis: Statistical analysis was performed using SPSS software, Version 22. A significance level (*P-value*) of less than 0.05 was considered for all tests. First, the normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Since the data did not follow a normal distribution, non-parametric tests such as the Mann-Whitney and Kruskal-Wallis tests, along with Spearman's correlation coefficient, were used. The chi-square test and Fisher's exact test were used to assess qualitative variables. To adjust for the confounding effects of variables, linear regression analysis was performed. In univariate linear regression, the response to treatment was examined in relation to each variable. Variables with a significance level of less than 0.2 were then included in a multivariable regression model.

Table 1. The PCR temperature program used to amplify the target fragment

Cycles	Temperature (°C)	Times (sec)	N Cycles
Initial Denaturation	95	300	1
Denaturation	95	30	
Annealing	58	30	30
Elongation	72	30	
Final Elongation	72	300	1

Results

The flow diagram of the trial is displayed in figure 1. One hundred and three patients with AV were selected and 29 of them were eliminated. Fifty-four patients completed the research. Randomly, they were divided into two groups of treatment with azithromycin (n=27) and doxycycline (n=27). Table 2 presents the subject's demographic. According to the table, 12 (22.2%) participants were males and 42 (77.8%) participants were females. In both groups, the highest frequency was among females, comprising 85.2% in the doxycycline group and 70.4% in the azithromycin group. The duration of disease in the doxycycline group had a median of 24 months with an interquartile range (IQR) of 24 months, while in the azithromycin group, it had a median of 24 months with an IQR of 36 months.

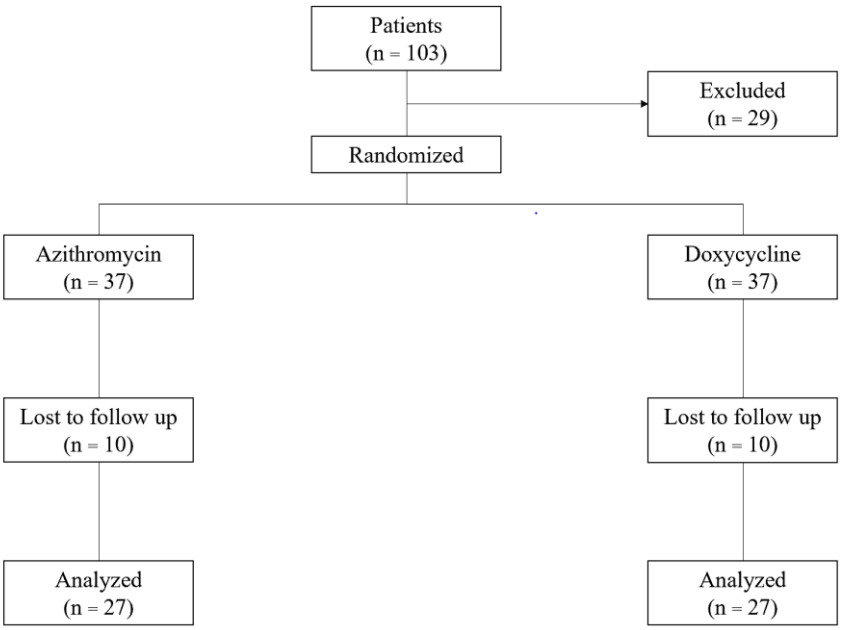

Figure 1. Study design illustration

There was no statistically significant difference in MSA score between the groups before treatment (P = 0.264). Table 3 illustrates the relationship between improvement percentages and genotypes in the two treatment groups. In total, recovery rate in the doxycycline group (59.3%) was significantly more than azithromycin group (18.5%) ($p < 0.001$). According to the table, in each group, the recovery percentage varies among different genotypes, but this difference is not statistically significant. Table 4 presents the results of univariate and multivariable linear regression. In the univariate regression analysis, drug group ($P = 0.021$), and gender ($P = 0.044$) showed significance impact on the difference of the MSA score. After adjusting for confounding variables, drug group ($P = 0.008$) and gender ($P = 0.011$) remained statistically significant.

This suggests that compared to azithromycin, the doxycycline group showed a 0.35-unit decrease in the difference of the MSA score, indicating a more favorable effect of doxycycline over azithromycin. Additionally, women had a 0.33-unit increase in the difference of the MSA score compared to men, indicating a less favorable treatment response in women.

Table 2. Demographics parameters of subjects among the two groups

Variables		Doxycycline (N=27)	Azithromycin (N=27)
Gender	Male [Frequency (%)]	4 (14.8%)	8 (29.6%)
	Female [Frequency (%)]	23 (85.2%)	19 (70.4%)
Family history	No [Frequency (%)]	15 (68.2)	7 (31.8)
	Yes [Frequency (%)]	12 (37.5)	20 (62.5)
Age	Median (IQR)	18 (4)	19 (7)

Variables		Doxycycline (N=27)	Azithromycin (N=27)
Duration of illness	Median (IQR)	24 (24)	24 (36)
Michaelson's acne severity score before treatment	Median (IQR)	72 (49)	65 (43)

Abbreviations: IQR, Interquartile Range.

Table 3. Correlation between improvement percentages and genotypes in the two treatment groups

Groups	Genotypes	Improvement %				*p-value (Within Groups)*
		0-25	25-50	50-75	75-100	
Azithromycin	Homozygote 490	2 (28.6)	3 (42.9)	2 (28.6)	0 (0.0)	0.533
	Homozygote 190	1 (25.0)	2 (50.0)	0 (0.0)	1 (25.0)	
	Heterozygote	2 (12.5)	4 (25.0)	6 (37.5)	4 (25.0)	
	All	5 (18.5)	9 (33.3)	8 (26.9)	5 (18.5)	
Doxycycline	Homozygote 490	0 (0.0)	0 (0.0)	2 (25.0)	6 (75.0)	0.567
	Homozygote 190	1 (12.5)	0 (0.0)	3 (37.5)	4 (50.0)	
	Heterozygote	0 (0.0)	0 (0.0)	5 (45.5)	6 (54.5)	
	All	1 (3.5)	0 (0.0)	10 (37.0)	16 (59.3)	
p-value (Between Groups)		<0.001				

Table 4. Univariate and multivariate linear regression in relation with the difference of the MSA score

Variables	Linear Regression			
	Univariate		Multivariate	
	Beta coefficient	*p-value*	Beta coefficient	*p-value*
Drugs	-0.313	0.021	-0.351	0.008
Age	0.237	0.085	0.182	0.148
Sex	0.276	0.044	0.330	0.011
Duration of illness	0.044	0.750	-	-
Family history	0.020	0.888	-	-
Genotypes	0.010	0.941	-	-

Discussion

This study aimed to investigate the response to doxycycline and azithromycin treatments in moderate acne vulgaris, as well as the relationship between treatment response and ACE gene polymorphism alongside demographic variables. To the best of the authors' knowledge, no prior research has explored the connection between response to doxycycline and azithromycin treatment and ACE gene polymorphism in individuals with acne vulgaris. In this study, 54 patients with moderate acne, classified according to the Vaishampayan classification, were enrolled. The patients were divided into two treatment groups: one group (n=27) received 100 mg of doxycycline daily, combined with topical treatments (benzoyl peroxide and tretinoin), while the other group (n=27) was treated with 250 mg of azithromycin every other day, also combined with the same topical regimen, for a duration of three months. To assess treatment efficacy, Michelson's acne score was calculated both before and after the treatment. The standard photography method was used to evaluate the percentage of recovery. Again, to the authors' knowledge, no previous research has examined the relationship between

ACE gene polymorphism and treatment response to doxycycline and azithromycin in the AV patients. The results of this study showed a decreasing trend in the Michelson acne score in both treatment groups after therapy, with a greater reduction observed in the doxycycline group compared to the azithromycin group, indicating a better response to doxycycline. No significant relationship was found between recovery percentage and genotype, though increasing the sample size may help clarify this result. Additionally, there was no significant association between changes in Michelson's acne score and family history of acne. However, a significant relationship was found between treatment response and age, with older individuals showing a weaker response to treatment. After controlling for confounding variables, a significant relationship between gender and treatment response was observed: women showed an increase of 0.33 units in the score difference before and after treatment, indicating that they responded less favorably to treatment than men. Moreover, 59.3% of participants had a positive family history of acne, consistent with previous studies showing that family history influences the development of acne. Despite this, the statistical analysis revealed no significant relationship between ACE gene polymorphism and treatment outcomes in moderate acne patients treated with doxycycline and azithromycin in Gonabad.

AV is a prevalent inflammatory skin disorder, and oral antibiotics are known to be effective in its treatment. These antibiotics are a cornerstone of acne management due to their anti-inflammatory and antimicrobial properties (21). Among the various antibiotics, tetracyclines and their derivatives are commonly used to treat acne vulgaris. Doxycycline, a preferred tetracycline, is favored for its relatively safer side effect profile and is frequently prescribed for acne management. However, increasing global antibiotic resistance among Propionibacterium acnes poses a significant challenge and can contribute to treatment failure. Within macrolide antibiotics, P. acnes generally exhibit resistance to erythromycin and clindamycin, but is less resistant to azithromycin (22). In the present study, when comparing the response to drug treatment in acne vulgaris, doxycycline demonstrated a better response than azithromycin, and this difference was statistically significant. This finding is consistent with the study by Ullah et al., which found doxycycline to be a superior option compared to azithromycin for the treatment of moderate acne vulgaris (23). In another study, both the azithromycin and doxycycline groups showed reduced acne symptoms after 6 weeks of treatment, with no statistically significant difference between the groups. However, after 12 weeks, patients receiving doxycycline exhibited significantly greater improvement compared to those receiving azithromycin (24). Similarly, a study by Moravvej et al., involving 60 patients with moderate acne, showed that both drugs improved inflammatory lesions and comedones, with azithromycin having an equivalent effect to doxycycline in reducing acne lesions (25) Additionally, another study reported that both azithromycin and doxycycline improved facial lesions, and neither drug was found to be more effective than the other (26). In a study by Haider et al. involving 200 patients with acne vulgaris, azithromycin was found to be more effective than doxycycline, with fewer side effects reported for azithromycin (27). Conversely, another study with 40 participants found no significant difference in effectiveness between doxycycline and azithromycin, indicating that doxycycline is as effective as azithromycin for moderate to severe acne (28). The discrepancies among these studies may be attributed to factors such as racial differences, varying durations of drug use, and sample sizes. Additionally, the influence of other medications and supplements, which may interact synergistically or antagonistically with antibiotics, was not considered. Such conflicting results highlight the impact of population diversity, methodological variations, and differing interpretations in research outcomes.

ACE is expressed in several tissues, including the lungs, kidneys, and heart, as well as in skin tissue cells (29). This enzyme facilitates the conversion of angiotensin I to angiotensin II (30), which has multiple effects in the body. Angiotensin II can increase reactive ROS and elevate pro-inflammatory cytokines, such as interleukin-6 (31, 32). Consequently, ACE may contribute to the development of inflammatory lesions in AV by increasing inflammatory cytokines and oxidative stress. In this study, we investigated the response to doxycycline and azithromycin treatment in relation to the I/D polymorphism of the ACE gene in patients with moderate acne vulgaris. Data analysis revealed no statistically significant relationship between the ACE gene I/D polymorphism and treatment response in either the azithromycin or doxycycline groups, nor was there a significant difference in treatment outcomes before and after therapy. In a study by Neveen et al. involving 100 AV patients, it was suggested that the D allele of the ACE I/D gene polymorphism may increase the risk of developing acne vulgaris. Additionally, a positive family history and ACE gene polymorphism (DD + ID genotypes) were identified as independent predictors of severe acne grades (33). The discrepancy between these findings and ours may be attributed to differences in ethnicity, patient gender, and sample size. Overall, a more comprehensive understanding

of the role of ACE gene polymorphism in AV will require larger-scale, more detailed studies. A number of limitations should be considered when interpreting the present results. First, the sample size is small to interpret the polymorphism results. Additionally, some confounding factors that can affect acne severity were not controlled, such as temporary severe stress in patients, the exacerbation of acne during the premenstrual period in women, and the failure to monitor acne-triggering diets, such as those high in glycemic index. Furthermore, this study did not investigate the potential side effects of the medications used. The results of this research presented a decreasing trend in the Michelson acne score in both treatment groups, with a greater reduction in the doxycycline group compared to the azithromycin group, indicating that doxycycline was more effective. Additionally, no significant relationship was found between ACE gene polymorphism and treatment outcomes in moderate acne patients in Gonabad who were treated with doxycycline and azithromycin.

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Authors' contribution: MM, HM & MK set up the study design and interpreted the data. MM & AM performed the statistical analyses interpreted the data and drafted the manuscript. AT, YK, ZS & ZR collecting the data and do the experiments. All authors read and approved the final manuscript.

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