Role of Intercellular Adhesion Molecule -1 in Acne Vulgaris patients: Effect of Montelukast therapy

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Abstract

Background: Acne vulgaris (AV) is the most common inflammatory skin condition. It has complicated pathophysiology.

Objectives: We compared montelukast therapy on AV patients over a three-month period, assessing serum of soluble intercellular adhesion molecule -1 **(**sICAM-1) in AV, comparing it to a control group and its relationship to AV severity.

Patients and method: 40 AV patients were split into two groups based on Investigator's Global Assessment: group 1 was moderate AV, group 2 was severe AV. (sICAM-1) was measured in AV patients before and after montelukast treatment and compared to the control group (group 3).

Results: Moderate AV group outperformed the severe group in clinical improvement: moderate AV: good (55%), excellent (30%), severe AV: good (40%), and excellent (20%). Median s.ICAM-1 level was significantly lower in the control group (1.3 [0.5-3]) compared with both (moderate AV (35.5 [15-45]) ($p < 0.001$) and severe AV (57 [45-78]) ($p < 0.001$). After treatment, there was a significant difference between the three groups in the median level of s.ICAM-1 ($p < 0.001$) i.e., the median level was significantly lower in the control group (1.3 [0.5-3]) compared with (moderate AV (12.5 [6-72]) ($p < 0.001$) and severe AV (54 [39-72]) ($p < 0.001$). Treatment side effects were significant with severe AV ($p = 0.046$) compared with moderate AV.

Conclusion: The study revealed that AV patients had significantly higher serum levels (sICAM-1), an independent predictor of acne severity. Montelukast is a safe, efficient treatment for AV, especially moderate.

Keywords: Acne vulgaris; s.ICAM-1; Montelukast.

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Introduction

One of the ten most prevalent disorders worldwide is acne vulgaris, as well as the most common inflammatory disease **(Chilicka et al., 2022).** Acne is a chronic cutaneous inflammation affecting the upper pilosebaceous unit with a complex pathophysiology (**Huang et al., 2024).** AV is the ninth most common skin disorder globally, affecting 9.38% of all age groups; however, prevalence varies by the country and age group (**Heng et al., 2020).** In Egyptian secondary school adolescents, acne vulgaris was found to be more common in females (41.4%) than in males (31.6%), with mild forms of the condition being the most common (53%), followed by moderate and severe forms, and more common in females, urban dwellers, and those with lower socioeconomic status (**Gabr et al., 2021).**

Acne is a complicated and complex condition, influenced by genetics and diet. The primary lesion is a tiny hyperkeratotic plug known as a microcomedo. It develops into pustules, nodules, blackheads, and whiteheads, among other acne lesions. The following four fundamental pathogenic events are thought to have had a role in the development of microcomedones into various types of acne lesions: Seborrhea (increased production of sebum), follicular hyperkeratinization, Anaerobic diphtheroid C. acnes (formerly Propionibacterium acnes) is naturally present in i skin flora and inflammation (**O'Neill et al., 2018).** Since different interleukins (IL-1, IL-8) have been found in comedones, lymphocytes and also macrophages have been found in early-onset, non-inflammatory acne lesions, inflammation is likely a crucial factor in acne (**Jeremy et al., 2003).** The strongest leukocyte chemotactic regulator in the pathophysiology of acne is leukotriene B4 (LT-B4) (**Alestas et al., 2006).**

Cell adhesion molecules (CAMs) are essential for the formation and maintenance of multicellular tissues, especially epithelia. In the epidermis, they are engaged in cell-cell contact and cellular interactions with the extracellular matrix, therefore contributing to the skin's structural integrity and barrier formation (**D'Arcy et al., 2021**). Intercellular adhesion molecule -1(ICAM-1) is one of the most extensively inducible (CAMs) and is responsible for different immunological processes such as T cell activation, extravasation, and inflammation (**Singh et al., 2021).** There is a correlation between the kind and degree of inflammation and ICAM-1 expression. Increased ICAM-1 expression may promote leukocyte-keratinocyte interaction and is considered a crucial initiator in a range of inflammatory skin diseases (**Huang et al., 2018**). Soluble ICAM-1 is a circulatory form produced constitutively or stimulated on the surface of several cell types (**Witkowska et al., 2004).** It is indicated that serum sICAM-1 level rose significantly with increasing sickness severity, which may be connected with the more obvious proinflammatory response (**Mustafaet al., 2022).** The major acne treatment method is topical therapy, which includes retinoids, benzoyl peroxide, antibiotics, clascoterone, salicylic acid, and azelaic acid. Multimodal therapy is indicated for maximum efficacy and reduced antibiotic resistance. They can be used as monotherapy (except topical antibiotics) (**Reynolds et al., 2024).**

Acne vulgaris ranges from moderate to severe, requesting aggressive therapy. Oral antibiotics, hormone therapy and oral isotretinoin are among the topical and systemic therapies that are available. With the exception of oral isotretinoin, systemic treatment is usually used in conjunction with topical therapy, as mentioned for mild cases (**Sutaria et al., 2023).** Montelukast, a (CysLType1) receptor antagonist, has an anti-inflammatory effect. It is an antagonist of the leukotriene B4 (LT-B4) receptor (**Zhao et al., 2011).** By generating superoxide radicals, free fatty acids,

inflammatory mediators and activating the complement system, leukotriene B4, an important leukotriene derived from arachidonic acid, can result in inflammatory lesions associated with acne. It has been suggested that decreased activity can reduce acne inflammatory lesions (**Bhat et al., 2017).** In the current research, We evaluated blood levels of soluble intercellular adhesion molecule-1 (sICAM-1) in AV patients over a three-month period, compared them to a control group, and examined the association between AV severity and montelukast medication.

Patients and methods

Study design and participants

This prospective randomized clinical trial (RCT) investigation was carried out from March 2024 to November 2024 at the Dermatology, Venereology, and Andrology Department of South Valley University, Qena University Hospital, Outpatient Clinic. Individuals with moderate and severe acne vulgaris of both sexes. The age range covered was 15–35 years old. The following conditions were excluded: vascular dementia, Crohn's disease, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, SAPHO syndrome, diabetes, hypertension, pregnant or lactating women, patients with polycystic ovaries syndrome, thyroid dysfunction, chronic inflammatory or immune-mediated conditions, acne conglobate, acne fulminans and hypersensitivity reaction to the drug under study. At least two months and two weeks before to the research, respectively, no systemic or local acne medications had been utilized by any of the individuals. The control group included healthy individuals with age and sex, BMI matching, no history of acne, or other inflammatory or autoimmune disorders. In addition to a thorough history taking, each patient had a general and dermatological examination. In order to reach 80% power and a 5% level of significance, (type 1 error), we modified the sample size.

Randomization and masking

At random, patients were split into three groups (1:1:1): group 1 had moderate AV, group 2 had severe AV, and group 3 was the control. The process of randomization was carried out with closed envelopes. In contrast to patients and data interpreters, researchers and medical staff weren't blinded to the trial medication assignment.

Sample size calculation

We applied the G*power 3 algorithm **(Faul et al., 2007)** to determine the sample size. To examine the impact of montelukast on AV patients after three months with a measurement of sICAM-1 in AV patients compared with the control group, a sample size of 60 participants was predicted to be necessary, with an 80% power and a 0.05 error probability. For each participant, one of the three collections was assigned. This led to the creation of three groups in the study: 20 patients with moderate AV, 20 patients with severe AV, both of whom received montelukast, and 20 healthy as a control group.

Ethical considerations

The current study was approved by the South Valley University Faculty of Medicine Ethics Committees under approval number SVU, MED, DVA021-1-23-4-610, South Valley University's Faculty of Medicine's Institutional Review Board-Ethics Committee approved the study, which was carried out in compliance with the principles outlined in the Declaration of Helsinki. Identifier: NCT06340984, the experiment was posted on the clinical trial registration website (https://clinicaltrials.gov/). Additionally, a signed consent form was given to each participant. The goal of the study and their ability to join or withdraw at any moment without any obligations were made explicit in the informed consent. Additionally, each participant was given a code number that

was used exclusively for analysis, guaranteeing their privacy and confidentiality. There were no incentives or prizes for the participants in the research.

History and clinical examination

Comprehensive medical history that includes details on age, sex, work, residence, marital status, and unique habits and details about the disease including its onset, course, duration, progression and past history of AV, site of lesions, prior treatment history, and family history of AV or another autoimmune disorders. Complete clinical assessment, general and detailed dermatological assessment with particular attention to the skin (characteristic AV lesions), hair, nails and oral mucosa, calculating BMI. Before starting treatment, AV patients who had not received any systemic or local acne treatments at least two weeks and two months before to the study, respectively were protocol for treatment.

Classification of patients

Based on the Investigator's Global Assessment (IGA) of the degree of acne severity, patients with acne vulgaris will be divided into moderate and severe cases (**Table.1, CDER, 2005).**

The patients will be divided into two group (each group with 20 cases) and a control group (20):

- Group 1: individuals with moderate cases of acne vulgaris
- Group 2: individuals with severe cases of acne vulgaris
- Group 3: control group

Table 1. Investigator's Global Assessment (IGA) (CDER, 2005).

0	Clear	absence of any inflammatory or non-inflammatory lesions and an active illness.
1	Almost clear	Rarely occurring non-inflammatory lesions with only one small inflammatory lesion.
2	Mild	Only a few inflammatory lesions (papules or pustules; no nodular or cystic lesions) combined with some non-inflammatory lesions.
3	Moderate	With a few inflammatory lesions (papules or pustules) but no more than one nodular or cystic lesion, the majority of lesions are non-inflammatory.
4	Severe	Numerous inflammatory and non-inflammatory lesions, along with five or fewer nodular or cystic lesions, comedones, and papules/pustules.
5	Very severe:	With a varied number of comedones, several papules or pustules, and more than five nodular or cystic lesions, highly inflammatory lesions prevail.

Treatment protocol

Sever and moderate acne vulgaris patients received 10 mg of montelukast daily for three months.

Serum collection and analysis

Three milliliters of venous blood from each subject were drawn into plain test tubes under optimal sterile conditions. The isolated serum had been separated and kept at -20°C for further tests of serum sICAM-1 levels using the Human Soluble Intercellular Adhesion Molecule-1 (sICAM-1) ELISA Kit after samples had been centrifuged (at 3000 g för 20 minutes) following coagulation. Sino Gene Clon Biotech Co.,Ltd, Catalog No : SG-11412.

Method Type: Sandwich ELISA Detection. Procedure for the assay: All necessary chemicals, blanks, working standards, and samples were prepared. Next, using the Assay Layout Sheet, determined how many wells should be used. Finally, any leftover wells were put and desiccator back inside the pouch, seal the Ziploc, and

stored any unused wells at 4°C. 50 µl of the typical solution was added to the test well. 40 µl of the sample dilute and 10 µl of the sample to be tested were added to the pipette. Pipette the collected material into the wells, avoiding as much contact with the well wall as possible, and mix gently. Incubated: After covering with the adhesive strip, the mixture was incubated at 37°C for 30 minutes then Liquid configuration: Used pure water to dilute the washing solution thirty times, then Cleaning: the sticky strip removed, pour away the liquid, pipette the cleaning solution into every container, wait 30 seconds, empty, repeat five times, and then add the enzyme. With the exception of the blank well, pipette 50µl of HRP-Conjugate solution into every well. Incubated: Then, washing,then: Color:each well with 50 ul of Chromogen Solution A and 50 ul of Chromogen Solution B. For fifteen minutes at 37°C, avoided light preservation. Put an end to the reaction. Pipette 50µl of the halt solution into each well to stop the reaction. After the blue becomes yellow, the blank well was calculated. the absorbance at 450 nm within fifteen minutes was evaluated at End Solution.

Dermatological evaluation of the included patients

- **Clinical assessments**: at baseline and following treatments, patients will be shot with a 48-megapixel camera set to an aperture of F/1.8, under normal lighting conditions and at a standard distance, Evaluation of clinical improvement based on both lesion count changes and IGA success yields both quantitative and qualitative assessments of acne, providing helpful supplementary data, Assessment of clinical Improvement according to (**Witkowski et al., 2004):** G4 (excellent: 100% reduction), G3 (good: 75-99% reduction), G2 (moderate: 50-74% reduction), G1 (insufficient: 1-49% reduction), G0 (unchanged), G-1 (worse)
- **Clinical Satisfaction:** A three-point evaluation system was used to record patient satisfaction, with grade 3 representing "highly satisfied," grade 2 representing "satisfied," and grade 1 representing "dissatisfied."
- **Assessment of Complications:** Following three months of montelukast medication, follow-up was conducted for every patient.

Statistical analysis

SPSS version 24* was used for data analysis, verification, and coding by the researcher. Descriptive statistics: Percentages, means, and standard deviations (SD) were computed. Test of significance: To examine the variations in frequency distributions between several groups, the Chi square test was employed. For constant variables with more than two categories, the post-hoc test was computed using Bonferroni corrections, and the ANOVA/Kruskal Wallis test was computed to evaluate the mean/median variations of the data (parametric and non-parametric, respectively). A paired sample t-test was employed for repeated measurements (pre- vs. post-treatment). The mean variations in constant variables across groups were tested using a student t-test. To examine the relationship between S. soluble ICAM-1 and illness parameters, Pearson's correlation was computed. A p-value of 0.05, or less was regarded as significant.

Results

Baseline sociodemographic characteristics of the study groups

Controls were significantly ($p < 0.001$) older (24.9 ± 4.6 years) compared with both patients' groups (moderate AV [20.4 ± 3.3 years] and severe AV [20.5 ± 2.4 years]). Also, males represented significantly ($p = 0.040$) a higher percentage of the control group (55%) than the patients' groups

(moderate AV [20%] and severe AV [25%]). The distribution of the sample according to the marital status and residence was non-significant (p = 0.155, = 0.935). The distribution of the sample according to the occupation was as follows: employees represented significantly (p = 0.034) a higher percentage (45%) of the cohort in the control group compared with the moderate (20%) and severe (10%) AV groups. On the other hand, the mean BMI was insignificantly (p = 0.376) different among the groups under study **(Table. 2).**

Table 2. Baseline characteristic differences among the study groups

Variables	Control (n = 20)	Moderate AV (n = 20)	Severe AV (n = 20)	P-value
Age/year	24.90 ± 4.6	20.40 ± 3.3	20.45 ± 2.4	**< 0.001***
P-value**	**I vs. II < 0.001**	II vs. III = 0.965	**I vs. III < 0.001**	
Sex				
Female	9 (45%)	16 (80%)	15 (75%)	**= 0.040*****
Male	11 (55%)	4 (20%)	5 (25%)	
Marital Status				
Single	13 (65%)	18 (90%)	16 (80%)	= 0.155***
Married	7 (35%)	2 (10%)	4 (20%)	
Residence				
Rural	9 (45%)	9 (45%)	10 (50%)	= 0.935***
Urban	11 (55%)	11 (55%)	10 (50%)	
Occupation				
Housewife	2 (10%)	2 (10%)	3 (15%)	
Student	9 (45%)	14 (70%)	15 (75%)	**= 0.034*****
Employed	9 (45%)	4 (20%)	2 (10%)	
BMI	23.79 ± 1.9	24.63 ± 2.5	23.82 ± 1.8	= 0.376*
P-value**	I vs. II = 0.218	II vs. III = 0.236	I vs. III =0.960	

*ANOVA test was used to compare the mean difference between groups; **Post-hoc test was used for pairwise comparison with Bonferroni correction; ***Chi-square test was used to compare the proportion difference between groups

The clinical characteristics of the study groups.

In terms of onset (p = 0.465), course (p = 0.342), duration of disease (p = 0.158), and lesion characteristics (p > 0.05), there was no significant variations in statistics among the two groups; however, the percentage of nodules in severe AV was significantly (p < 0.001) higher than that in moderate AV (n = 9 [45%]). Regarding history, an insignificant difference was found about family history (p = 1.000) and history of previous treatment (p = 0.327). Also, for the past-history, recurrence was insignificant (p = 0.736) higher in severe AV (n = 14 [70%]) than Moderate AV (n = 13 [65%]) (**Table. 3**).

Table 3: Clinical data differences among study groups

Variables	Moderate AV (n = 20)	Severe AV (n = 20)	P-value
Disease Onset			
Acute	4 (20%)	6 (30%)	= 0.465*
Gradual	16 (80%)	14 (70%)	

Disease Course			
Progressive	8 (40%)	11 (55%)	= 0.342*
Intermittent	12 (60%)	9 (45%)	
Disease Duration/months	22.20 ± 4.8	26.25 ± 5.1	= 0.158**
Lesion Characteristics			
Comedones			
✓ **Few**	4 (20%)	8 (40%)	= 0.168*
✓ **Multiple**	16 (80%)	12 (60%)	
Inflammatory Lesions			
✓ **Few**	1 (5%)	3 (15%)	= 0.292*
✓ **Multiple**	19 (95%)	17 (85%)	
Post Acne Scar	12 (60%)	15 (75%)	= 0.311*
Nodules	9 (45%)	20 (100%)	**< 0.001***
Family History			
Negative	9 (45%)	9 (45%)	= 1.000*
Positive	11 (55%)	11 (55%)	
Previous Treatment			
No	6 (30%)	9 (45%)	= 0.327*
Yes	14 (70%)	11 (55%)	
Past-history			
Primary	7 (35%)	6 (30%)	**= 0.736***
Recurrent	13 (65%)	14 (70%)	
Lesion Site (Face)	20 (100%)	20 (100%)	= 1.000*

*Chi-square test was used to compare the proportion difference between groups; **Independent Sample t-test was used to compare the mean difference between groups

The impact of montelukast medication on side effects, patient satisfaction and the extent of disease improvement

There was no significant variations in statistics among the two groups regarding clinical improvement (p = 0.207). For the patients' satisfaction, about three-quarters (n = 15) of the moderate AV was highly satisfied compared with only 5% (n = 1) in severe AV and This has statistical significance, (p < 0.001). For the side effects: cases with severe AV had significantly (p = 0.046) greater rates of adverse effects (n = 6 [30%]) compared with only 5% (n = 1) in moderate AV **(Table.4).**

Table 4. Outcome findings among the study groups

Variables	Moderate AV (n = 20)	Severe AV (n = 20)	P-value
Clinical Improvement			
Insufficient/ Moderate	3 (15%)	8 (40%)	= 0.207*
Good	11 (55%)	8 (40%)	
Excellent	6 (30%)	4 (20%)	
Patients' Satisfaction			
Unsatisfied	4 (20%)	7 (35%)	
Satisfied	1 (5%)	12 (60%)	**< 0.001***
Highly Satisfied	15 (75%)	1 (5%)	
Side Effects			

No	19 (95%)	14 (70%)	**= 0.046***
Yes	1 (5%)	6 (30%)	

*Chi-square test was used to compare the proportion difference between groups

The impact of treating montelukast on the s. soluble ICAM-1 level among cases vs. control

Before treatment: The median amount of serum soluble ICAM-1 varied significantly across the three groups ($p < 0.001$). The control group had a substantially lower median level (1.3 [0.5-3]) compared with cases (46.3 [15-78]) ($p < 0.001$), Severe AV had significantly higher median levels than moderate AV (moderate AV (35.5 [15-45]) ($p < 0.001$) and severe AV (57 [45-78]) ($p < 0.001$).

After treatment: The median amount of serum soluble ICAM-1 varied significantly across the three groups ($p < 0.001$). The control group had a substantially lower median level (1.3 [0.5-3]) compared with both cases (41 [6-72]) ($p < 0.001$), Severe AV had significantly higher median levels than moderate AV (moderate AV (12.5 [6-72]) ($p < 0.001$), severe AV (54 [39-72]) ($p < 0.001$), For within-group comparisons, Following therapy, the moderate AV group's serum soluble ICAM-1 level significantly decreased (17, $p = 0.001$), as did the severe AV group (6, $p = 0.003$) (**Table.5).**

Table 5: Difference in S. Soluble ICAM -1 Level between study groups

Variables	Control (n = 20)	Moderate AV (n = 20)	Severe AV (n = 20)	P-value
S. Soluble ICAM -1 Before Treatment				
Mean ± SD	1.43 ± 0.9	33.55 ± 8.1	59.01 ± 10.6	
Median (Range)	1.3 (0.5-3)	35.5 (15-45)	57 (45-78)	**< 0.001***
P-value**	**I vs. II < 0.001**	**II vs. III < 0.001**	**I vs. III < 0.001**	
S. Soluble ICAM -1 After Treatment				
Mean ± SD	1.43 ± 0.9	18.43 ± 17.2	53.80 ± 8.6	
Median (Range)	1.3 (0.5-3)	12.5 (6-72)	54 (39-72)	**< 0.001***
P-value**	**I vs. II < 0.001**	**II vs. III < 0.001**	**I vs. III < 0.001**	
P-value***	= 1.000	**= 0.001**	**= 0.003**	

*Kruskal Wallis test was used to compare the mean difference between groups; **Post-hoc test was used for pairwise comparison with Bonferroni correction; ***Paired Sample t-test was used to compare the difference in mean within group

Serum soluble ICAM-1 levels before and after montelukast therapy and illness determinants were correlated

For the total sample: there was a significant negative moderate to high moderate correlation between s. soluble ICAM-1 before and after treatment and age, sex, past history, clinical improvement and patients' satisfaction ($r = -0.392$ ($p = 0.001$), -0.248 ($p = 0.028$), -0.300 ($p = 0.030$), -0.437 ($p = 0.002$), and -0.637 ($p < 0.001$) - ($r = -0.385$ ($p = 0.001$), -0.256 ($p = 0.024$), -0.252($p = 0.058$) -0.603 ($p < 0.001$), and -0.612 ($p < 0.001$) respectively), i.e., Before and after therapy, a drop in the s. soluble ICAM-1 level was linked to an increase in the illness correlates.

For the moderate AV group, Prior to treatment, S. ICAM-1 & BMI had a moderately significant statistical relationship ($r = 0.387$, $p = 0.046$), meaning that a rise in BMI was linked to an increase in s. ICAM-1 levels.

For the moderate AV group, was negative high moderate correlation between S. ICAM prior to and after treatment and clinical enhancement (r = -0.483, p = 0.016), (r = -0.619 (p = 0.002), respectively), i.e., a decrease in the s. soluble ICAM-1 level was associated with clinical improvement.

For the severe AV group, there was a significant negative moderate to high correlation among s. soluble ICAM-1 level before and after treatment and both clinical improvement and patients' satisfaction (r = -0.469 (p = 0.018) and -0.520 (p = 0.009), (r = -0.782 and -0.764 (p < 0.001), respectively), i.e., a decrease in the s. soluble ICAM-1 level was associated with better clinical improvement and patients' satisfaction.(**Table.6**).

Table 6. Correlation between S. sICAM-1 and disease determinants

Variables	S. sICAM-1 Before	S. Soluble ICAM-1 After
	r* (P-value**)	
Total Sample		
Age	**-0.392 (p = 0.001)**	**-0.385 (p = 0.001)**
Sex	**-0.248 (p = 0.028)**	**-0.256 (p = 0.024)**
BMI	0.099 (p = 0.225)	0.027 (p = 0.418)
Disease Duration	0.240 (p = 0.068)	0.121 (p = 0.228)
Onset	-0.083 (p = 0.306)	-0.053 (p = 0.374)
Course	-0.132 (p = 0.208)	-0.254 (p = 0.057)
Past-history	**-0.300 (p = 0.030)**	-0.252 (p = 0.058)
Family History	0.019 (p = 0.428)	0.017 (p = 0.415)
Treatment History	-0.157 (p = 0.167)	-0.054 (p = 0.392)
Clinical Improvement	**-0.437 (p = 0.002)**	**-0.603 (p < 0.001)**
Patients' Satisfaction	**-0.637 (p < 0.001)**	**-0.612 (p < 0.001)**
Side Effects	0.248 (p = 0.061)	**0.279 (p = 0.040)**
Moderate AV Group		
Age	-0.344 (p = 0.069)	-0.086 (p = 0.359)
Sex	-0.087 (p = 0.358)	-0.141 (p = 0.267)
BMI	**0.387 (p = 0.046)**	0.118 (p = 0.310)
Disease Duration	0.257 (p = 0.137)	-0.031 (p = 0.228)
Onset	-0.054 (p = 0.410)	-0.185 (p = 0.374)
Course	0.204 (p = 0.194)	-0.213 (p = 0.057)
Family History	0.105 (p = 0.330)	0.149 (p = 0.058)
Treatment History	0.170 (p = 0.236)	0.370 (p = 0.054)
Clinical Improvement	**-0.483 (p = 0.016)**	**-0.619 (p = 0.002)**
Patients' Satisfaction	-0.324 (p = 0.082)	-0.356 (p = 0.062)
Side Effects	0.060 (p = 0.401)	0.040 (p = 0.434)
Severe AV Group		
Age	-0.155 (p = 0.257)	-0.196 (p = 0.204)
Sex	-0.371 (p = 0.054)	-0.281 (p = 0.115)
BMI	0.111 (p = 0.321)	0.052 (p = 0.414)
Disease Duration	0.257 (p = 0.137)	0.264 (p = 0.131)

Onset	0.104 (p = 0.331)	0.199 (p = 0.201)
Course	-0.218 (p = 0.178)	-0.148 (p = 0.267)
Past-history	0.190 (p = 0.212)	-0.209 (p = 0.189)
Family History	0.070 (p = 0.385)	0.070 (p = 0.385)
Treatment History	-0.242 (p = 0.149)	-0.148 (p = 0.266)
Clinical Improvement	**-0.469 (p = 0.018)**	**-0.782 (p < 0.001)**
Patients' Satisfaction	**-0.520 (p = 0.009)**	**-0.764 (p < 0.001)**
Side Effects	-0.152 (p = 0.262)	0.076 (p = 0.357)

*Pearson's correlation coefficient **Based on normal approximation

The AV disease predictors' multivariable logistic regression model for the total sample, moderate AV and severe AV prediction

There were three predictors after adjusting for all variables. With a one-year increase in age, there was a 26% (OR=0.738, 95% CI: 0.612–0.890, p = 0.001) decrease in liability for AV, there was a 22% (OR = 0.777, 95% CI: 0.637–0.947, p = 0.013) decrease in the probability for moderate AV affection, and there was a 28% (OR=0.722, 95% CI: 0.568–0.919, p = 0.008) reduction in the possibility for severe AV affection.

For the total sample, Also, with a one-ng/ml rise in the level of s. soluble ICAM-1 before treatment, there was a 10 times (OR=9.987, 95% CI; 1.989–21.351, p < 0.001) rise in the risk of developing AV disease. **For total sample,** likewise, with a one-ng/ml rise in the level of s. soluble ICAM-1 after treatment, there was a 5 times, (OR=5.395, 95% CI: 1.305 – 9.064, p < 0.001). rise in the risk of developing AV disease. **For moderate AV and severe AV prediction** additionally, with a one-ng/dl increase in the level of serum soluble ICAM-1 before treatment, the risk of moderate AV increased by 2.5 times (OR=2.454, 95% CI: 1.031–7.271, p=0.006), the hazards of severe AV increased by 13.5 times (OR = 13.441, 95% CI: 2.157–30.635, p < 0.001). Likely, with a one-ng/dl rise in the level of serum soluble ICAM-1 after treatment, there was double (OR = 2.084, 95% CI: 1.001–6.894, p = 0.024) rise in the risk of moderate AV disease, there was 8.6 times (OR = 8.584, 95% CI: 2.015–16.001, p < 0.001) rise in the risk of severe AV disease (**Table.7**).

Table 7. Independent predictors of AV: multivariable logistic regression model

Variables	OR (95% CI) *	P-value
Total Sample		
Age	0.738 (0.612 – 0.890)	**= 0.001**
Sex (Male)	0.277 (0.074 – 1.039)	= 0.057
S. soluble ICAM-1 Before	9.987 (1.989 – 21.351)	**< 0.001**
S. soluble ICAM-1 After	5.395 (1.305 – 9.064)	**< 0.001**
Moderate AV		
Age	0.777 (0.637 – 0.947)	**= 0.013**
Sex	0.265 (0.067 – 1.251)	= 0.094
S. soluble ICAM-1 Before	2.454 (1.031 – 7.271)	**= 0.006**
S. soluble ICAM-1 After	2.084 (1.001 – 6.894)	**= 0.024**
Severe AV		
Age	0.722 (0.568 – 0.919)	**= 0.008**

Sex	0.327 (0.070 – 1.538)	= 0.157
S. soluble ICAM-1 Before	13.441 (2.157 – 30.635)	**< 0.001**
S. soluble ICAM-1 After	8.584 (2.015 – 16.001)	**< 0.001**

OR=Odds Ratio; CI, Confidence Interval

Cases

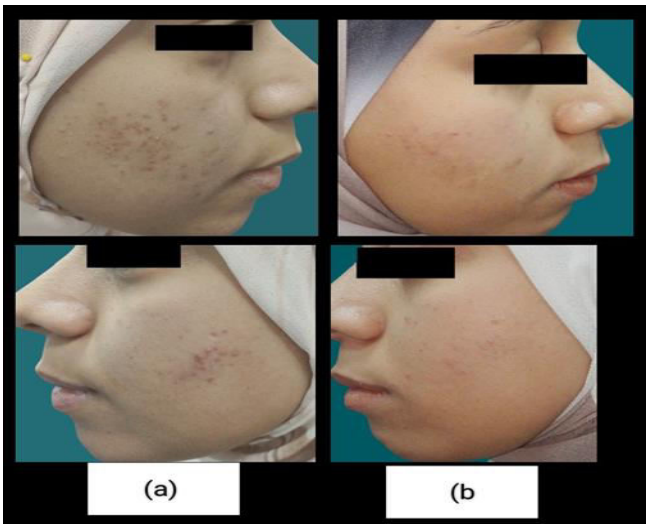

Fig. 1. The 19-year-old female patient with moderate AV (a) prior to montelukast and (b) after receiving montelukast showed good clinical improvement.

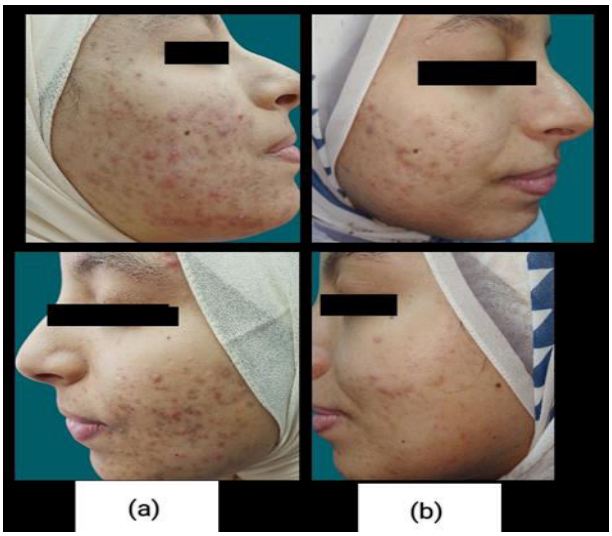

Fig. 2. The 19-year-old female patient with severe AV (a) prior to montelukast and (b) after receiving montelukast showed good clinical improvement.

Discussion

Acne vulgaris, a chronic, inflammatory condition causing increased sebum production, follicle hyperkeratinization, bacterial colonization, and inflammation, is a benign, self-limiting illness that can cause disfiguring scars and serious psychological issues **(Leung et al., 2021).** Acne vulgaris is believed to affect approximately 9.4% of the global general population **(Vos et al., 2012).** Acne, due to its prolonged duration and exposure to

affected areas, significantly impacts a patient's quality of life and well-being **(Andersen et al., 2022).** Intercellular adhesion molecule-1, a transmembrane glycoprotein in the immunoglobulin superfamily, increases in response to inflammatory stimuli, enabling trans-endothelial migration to inflammatory areas (**Roebucket al., 1999).** Cell adhesion molecules, a type of glycoprotein, are crucial for cell connectivity and migration of defense cells to the injury site **(Janiszewska et al., 2020)**. ICAM-1 release regulates circulating substances and cellular adhesion, a key feature of inflammation, and may be linked to variations in cell adhesion molecule expression **(Habas et al., 2018).** Recently, several groups have identified ICAM-1 as a potential target molecule for various disorders due to its significant role **(Brown et al., 2013)**. A multimodal approach is recommended to tackle acne pathogenesis, avoiding topical and oral antibiotic therapy due to global bacterial resistance **(Zaenglein et al., 2016).** Common topical and systemic acne treatments are still effective, but new approaches are needed. Initial treatment varies based on severity, and long-term therapy is necessary for specific goals **(Hester et al., 2016).** The LT-B4 receptor is antagonistic to montelukast **(Grice et al., 2008)** Of all the leukotrienes, LT-B4 is the most potent modulator of leukocyte chemotaxis **(Zouboulis et al., 2008).** Increased neutrophil adhesion triggers an inflammatory response, activating the complement cascade, generating superoxide radicals, releasing inflammatory cell lysosome products, and causing interleukins production **(Bubna et al., 2021).** Therapeutically stopping the leukotriene pathway can be achieved by blocking 5-lipooxygenase (5-LOX) or the link between LT-B4 and its receptor **(Grice et al., 2008).**

The study demonstrated how montelukast therapy (10mg\day) affects moderate and severe individuals over a three-month period. Before and after treatment, AV patients' levels of sICAM-1 were measured as a measure of acne severity and potential for AV.

The two groups (moderate and severe) did not vary statistically significantly in terms of clinical improvement ($p = 0.207$). That indicates the effectiveness of montelukast in treatment of acne vulgaris. The following clinical improvements were more noticeable in the moderate group than in the severe group:

Moderate AV insufficient/ moderate (15%), good (55%), excellent (30%), Severe AV insufficient/ moderate (40%), good (40%), excellent (20%).

This is in agreement with research by **(Behrangi et al. (2015),** which demonstrated that montelukast had an impact comparable to that of doxycycline. 52 people with moderate acne in all were evaluated. Group 1 consisted of 100 mg of doxycycline per day in addition to 1% clindamycin solution, while Group 2 consisted of 5 mg of montelukast per day in addition to 1% clindamycin solution. In the beginning, the mean severity of the acne index for the montelukast and doxycycline groups was 18.2 ± 6.1 and 19 ± 4.2, respectively ($P = 0.679$). After three months, the mean severity of the acne index for the montelukast group was 8.6 ± 4.8, whereas the doxycycline group's was 8.2 ± 1.2. The values of P are 0.001 and 0.001. During follow-up, the acne severity index significantly lowered for each group ($P = 0.001$). Both medications are beneficial, based on the study, and no appreciable variation was seen. Montelukast is therefore advised, especially for moderate-level acne. This is against the results reported by **(Aslam et al., 2020),** which found that doxycycline was more effective than montelukast. There were 84 patients in the trial. Group A received 100 mg of doxycycline and topical 10% benzoyl

peroxide, whereas Group B received 5 mg of montelukast and topical 10% benzoyl peroxide. After treatment, the Acne Severity Index (ASI) changed by an average of 5.45±1.29 for Group A and 1.80±0.59 for Group B ($p<0.001$). While montelukast demonstrated its effectiveness in treating acne by reducing the mean ASI from baseline, doxycycline was noticeably more effective, and the two medicines' effectiveness differences were of statistical significance.

Similarly, the research by **(Rokni et al., 2021**) A study of 65 female patients with moderate AV found that finasteride combined with clindamycin topical had a more significant effect than montelukast alone, with 30 receiving oral montelukast (10 mg PO daily) and 25 receiving clindamycin 2% solution and oral finasteride (2.5 mg PO daily). The montelukast group experienced a significant reduction in acne severity, dropping from 33.93 to 20.6 by the end of a 12-week treatment, while the finasteride group experienced a drop from 35.71 to 16.43. Nearly complete acne resolution was accomplished by 79.6% of patients in the montelukast group and 88.6% of patients in the finasteride group. The study found finasteride and montelukast are safe, effective, and tolerable for acne treatment, with finasteride showing a 2% better performance when combined with clindamycin solution.

For the patients' satisfaction, about 75% (n = 15) of the moderate AV were highly satisfied. Compared with only 5% (n = 1) in severe AV, this was a significant statistical finding. ($p < 0.001$). This agrees with the research by (**Rokni et al., 2021),** where At the conclusion of 12 weeks, 63.3% of patients in the montelukast group reported feeling satisfied with their doctors.

For the side effects: cases with severe AV had significantly, ($p = 0.046$) greater rates of adverse effects (n = 6 [30%]) compared with only 5% (n = 1) in moderate AV. This agrees with the study by (**Rokni et al., 2021),** In the montelukast group, a few adverse symptoms were reported, such as headache, feeling dizzy, and gastrointestinal distress. This is against (**Behrangi et al., 2015),** Where In the Montelukast group, no patient had any negative medication effects.

The effect of treatment on the s. soluble ICAM-1 level among cases vs. control and among case groups, Before treatment: There was a significant distinction among the three groups in the median level of serum soluble ICAM-1 ($p < 0.001$). The control group's median level was noticeably lower. (1.3 [0.5-3]) compared with cases (46.3 [15-78]) ($p < 0.001$), Severe AV had significantly higher median levels than moderate AV (moderate AV (35.5 [15-45]) ($p < 0.001$) and severe AV (57 [45-78]) ($p < 0.001$). This is consistent with the research by **(F Abdou et al., 2022; Mustafa et al., 2022)**, Where the Serum sICAM-1 levels were substantially greater in acne patients than in controls ($P < 0.001$). Serum sICAM-1 level increased significantly with increased disease severity

After treatment: The median amount of serum soluble ICAM-1 varied significantly across the three groups ($p < 0.001$). The control group's median level was noticeably lower. (1.3 [0.5-3]) compared with both cases (41 [6-72]) ($p < 0.001$), Severe AV had significantly higher median levels than moderate AV (moderate AV (12.5 [6-72]) ($p < 0.001$) and severe AV (54 [39-72]) ($p < 0.001$), For within-group comparisons, there was a significant drop in level of serum soluble ICAM-1 after treatment for the moderate AV group (17, $p = 0.001$) and the severe AV group (6, $p = 0.003$). This agrees with (**Mustafa et al., 2022)** where the serum sICAM-1 levels were substantially higher in individuals with severe AV than those with mild to moderate acne vulgaris (AV). Studies show that sICAM-1 levels rise significantly with increasing disease severity, which may be

linked to a more obvious proinflammatory response.

The relationship between soluble serum ICAM-1 level before and after treatment and disease determinants, For the total sample**:** there was a significant negative moderate to high moderate correlation between s. soluble ICAM-1 before and after treatment and age, sex, past history, clinical improvement and patients' satisfaction (r = -0.392 (p = 0.001), -0.248 (p = 0.028), -0.300 (p = 0.030), -0.437 (p = 0.002), and -0.637 (p < 0.001) - (r = -0.385 (p = 0.001), -0.256 (p = 0.024), -0.252(p =0.058) -0.603 (p < 0.001), and -0.612 (p < 0.001) respectively), i.e., an increase in the disease correlates was linked to a decline in the s. soluble ICAM-1 level before and after treatment. This demonstrates the increase of S. ICAM-1 level before or after treatment connected with young people who are more prone to acne vulgaris, and the reduction in S. ICAM-1 level before or after treatment related with higher clinical improvement and patient satisfaction. This agrees with (**Sutaria et al., 2023)** Where AV can appear as early as 7-12 years old and mostly disappear by the third decade and with **(Mustafa et al., 2022)** Where the severity of the inflammation determines the level of sICAM-1 expression. Thus, the less inflammation, the higher clinical improvement and patient satisfaction**.**

Notably, the presence of side effects was positively correlated with S. ICAM-1 after treatment (r = 0.279 (p = 0.040) This suggests a relationship between montelukast side effects and the level of s. soluble ICAM-1, and that an increase in the s. soluble ICAM-1 level after therapy increases the liability to side effects.

For the moderate AV group: Prior to treatment, there was a substantial positive moderate connection between S. ICAM-1 & BMI (r = 0.387, p = 0.046), meaning that a rise in BMI was linked to an increase in s. ICAM-1 levels. This agrees with (**Lin et al., 2019),** who discovered strong connections between ICAM polymorphism and acne patients' BMI, with the greatest Body mass index (BMI) among those with the highly expressed GG genotype, implying that obesity increases ICAM-1 expression.

For the moderate AV group: was negative high moderate correlation between S. ICAM prior to and following after treatment and clinical enhancement (r = -0.483, p = 0.016), (r = -0.619 (p = 0.002), respectively), i.e., a decrease in the s. soluble ICAM-1 level was associated with clinical improvement. For the severe AV group**:** there was a significant negative moderate to high collaboration between s. soluble ICAM-1 level prior to & after treatment and both clinical enhancement & patients' satisfaction (r = -0.469 (p = 0.018) and -0.520 (p = 0.009), (r = -0.782 and -0.764 (p < 0.001), respectively), i.e., a decrease in the s. soluble ICAM-1 level was associated with better clinical improvement and patients' satisfaction. This agrees with (**Mustafa et al., 2022),** where The expression of sICAM-1 will increase with the severity of the inflammation. So the less inflammation, the better clinical improvement and patients' satisfaction**.**

The AV disease predictors' multivariable logistic regression model, for the total sample, moderate AV prediction and severe AV prediction**,** had three predictors after adjusting for all variables. With a one-year increase in age, there was a 26% (OR=0.738, 95% CI: 0.612–0.890, p = 0.001) lower liability for AV, there was a 22% (OR = 0.777, 95% CI: 0.637–0.947, p = 0.013) decrease in the probability for moderate AV affection, and there was a 28% (OR=0.722, 95% CI: 0.568–0.919, p = 0.008) lowering in the possibility for severe AV affection. This indicates that the older the age, the less liable to AV and decrease in the probability for severe more than moderate AV. This agrees with (**Sutaria et al., 2023),** Where AV can appear as early as

7-12 years old and mostly disappear by the third decade but it can also continue throughout adulthood or occur for the first time.

For the total sample**,** Also, he probability of developing AV illness increased tenfold (OR=9.987, 95% CI: 1.989–21.351, $p < 0.001$) with a one-ng/ml rise in the amount of s. soluble ICAM-1 prior to therapy. Similarly, there was a five-fold rise (OR=5.395, 95% CI: 1.305 – 9.064, $p < 0.001$) in the amount of s. soluble ICAM-1 following treatment with a one-ng/ml increase. a higher chance of developing AV illness. Study data showing The level of s. soluble ICAM-1 is higher before more than after the treatment, As a result, the higher the amount of s. soluble ICAM-1, the greater the chance of developing AV illness, and the risk increases before therapy rather than after treatment. This agrees with (**Mustafa et al., 2022),** where An elevated risk of AV susceptibility was linked to greater serum sICAM-1 levels.

Additionally, with a one-ng/dl increase in the level of serum soluble ICAM-1 before treatment, the risk of moderate AV increased by 2.5 times (OR=2.454, 95% CI: 1.031–7.271, p=0.006), the risk of severe AV increased by 13.5 times (OR = 13.441, 95% CI: 2.157–30.635, $p < 0.001$). This suggests that the higher the amount of serum soluble ICAM-1, the greater the risk of severe more than moderate AV. This is agrees with (**F Abdou et al., 2022**; **Mustafa et al., 2022),** where As the severity of the condition grew, the serum sICAM-1 level rose noticeably.

After therapy, the level of serum soluble ICAM-1 is probably going to rise by one ng/dl. there was double (OR = 2.084, 95% CI: 1.001–6.894, p = 0.024) rise in the risk of moderate AV disease, there was 8.6 times (OR = 8.584, 95% CI: 2.015–16.001, $p < 0.001$) rise in the risk of severe AV disease. This implies a decrease in the amount of serum-soluble ICAM-1 following therapy in the moderate group more than in the severe group. That suggesting effect of Montelukast on moderate AV group more than severe AV group. This agrees with (**Fazelzadeh et al., 2022; Rokni et al., 2021**; **Behrangi et al., 2015),** where For the treatment of moderate AV, montelukast is a safe and efficient drug.

Limitations: The study was limited by its brief follow-up time and small sample size. Therefore, it might be required to carry out more extensive research in the future, and longer follow-up sessions would allow for a more informed decision regarding the safety and effectiveness of Montelukast.

Conclusion

The study's findings indicated that AV patients had a considerably greater serum level of sICAM-1 than the controls group. Levels of serum sICAM-1 have been proposed as an independent predictor of acne severity and susceptibility, early evaluation of this biomarker level may help control acne, a prevalent condition that is problematic during adolescence. A better understanding of the pathophysiology of acne may help direct future therapeutic approaches. Early identification of increased serum levels of ICAM-1 may be beneficial for adolescents with acne.

Finally, based on the findings of this investigation, it can be said that Montelukast is a medication that effectively and safely treats acne. Therefore, it is advised to use this medication, particularly if you have moderate acne. Following treatment, The moderate group observed a greater reduction in serum sICAM-1 expression following montelukast than did the severe group.

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