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Original Article

Role of Montelukast in the Management of Moderate Inflammatory Acne

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ABSTRACT

Objective: To study the efficacy of montelukast as an adjunct in the treatment of moderate inflammatory acne.
Study Design: Quasi experimental Study.
Place and Duration of Study: Department of Dermatology, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Apr to Oct 2023.
Methodology: This study was conducted on 150 patients with acne who needed systemic therapy. Group A (n=75) received 100 mg doxycycline daily plus placebo and the group B (n=75) received 100 mg daily doxycycline plus 10mg daily montelukast. Both groups also received topical benzoyl peroxide 4% every other night. The patients were evaluated for treatment efficacy by lesion count, Investigator Global Assessment, Global Acne Grading System, and Cardiff Acne Disability Index scoring systems after 12 weeks of intervention.
Results: The study included 150 patients with acne divided into two groups Group A 75(50%) and Group B 75(50%). All 150 patients included in the study showed improvement with the interventions. Individuals from Group B showed significantly superior reduction in the inflammatory as well as non-inflammatory lesion count (p-value <0.001). The decrease in Investigator Global Assessment, Global Acne Grading System, and Cardiff Acne Disability Index scores was also significant (all p-values<0.001) in comparison with group A.
Conclusion: Montelukast can be used as an adjuvant therapy along with other treatments of acne, especially for inflammatory variant.

Keywords: Acne, Adjuvant, Doxycycline, Montelukast, Treatment.

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INTRODUCTION

Acne vulgaris is a chronic inflammatory skin disease that primarily affects a large population of post pubertal adolescents and young adults.[1] The disease involves the pilosebaceous unit and manifests itself in the form of comedones, papules, pustules and nodules or cysts.[2] The condition is regulated by hormones and neuropeptides as well as inflammatory cytokines including interleukins, leukotrienes and prostaglandins.[3] Cutibacterium acne bacteria colonizes the sebaceous glands and is implicated in the complex pathogenesis.[4] Impaired follicular keratinization with concomitant increase in sebum secretion further aggravates the inflammation. Healing often occurs with scarring and pigmentary changes, causing significant psychological morbidity, often in the form of anxiety and depression.[5]

A variety of assessment tools have been used across the years to analyse severity of disease and monitoring treatment response. Global Acne Grading System (GAGS) and Investigator Global Assessment of Acne (IGA) are two well established systems that have been proven to be reliable and most often used by researchers in academic research.[6]

Various treatment modalities have been employed over time to treat this tenacious condition with topical agents including benzoyl peroxide, antibiotics, and retinoids being considered first line therapy.[7] Oral treatment is usually preferred for cases with marked severity and poor prognostic factors. Tetracyclines are the antibiotic of choice for most physicians- apart from oral retinoids.[8] The potential for antibiotic resistance as well as significant side effects remain limitations in these therapies which also affect patient compliance. This has resulted in the recognition of a need for other compounds with safer profiles as alternative or adjuncts to established therapeutic options.

Dapsone and photodynamic therapy have also been considered effective by some authors.[9] Anti-androgen receptor inhibitors like Clascoterone have recently garnered interest by showing substantial

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efficacy[10] while probiotics have also been shown to have a role in the management of acne.[11]

Leukotriene B4 (LT-B4) is a potent leucocyte chemotactic mediator in the pathogenesis of acne.[12] It is possible to affect a therapeutic blockade in the leukotriene pathway by preventing bonding between LT-B4 and its receptor. Montelukast is an antagonist of LT-B4 receptor and also has anti-inflammatory properties. It has been evaluated previously as an option for monotherapy in acne vulgaris in the past with varying results compared to usual first line antibiotic medication,[13] retinoids as well as anti-androgens. Its use as an adjunctive agent has garnered attention recently as a modality to expedite clearance of lesions in patients with moderate acne.[14] Our study was aimed at further exploration of this hypothesis.

METHODOLOGY

This study was conducted at the Department of Dermatology, Pak-Emirates Military Hospital, Rawalpindi Pakistan, between April 2023 and October 2023 on patients with acne who warranted systemic therapy. The study was carried out after written approval of the institutional ethical committee (Ref No. A/28/241 (1) EC/527/2023). A total of 150 patients of moderate inflammatory acne were enrolled in the study as cases using non-probability convenience sampling. The sample size was calculated using WHO sample size calculator using population prevalence of acne vulgaris 5%, margin of error of 5% and confidence interval of 95%.[15] Total sample size came out to be 73. Two groups with 75 individuals each were included in the study and placed in group A receiving placebo and group B receiving montelukast respectively (n=150).

Inclusion Criteria: Equal number of males and females aged 13-35 years with moderate acne who were candidates for systemic therapy and not receiving any topical or systemic treatment for the past 1 month before joining the study.

Exclusion Criteria: Pregnancy and lactation, polycystic ovarian syndrome, severe or aggressive forms of acne (acne conglobata, acne fulminans), age under 13 and over 35 years, and any history of hypersensitivity reaction to the drugs being evaluated. Patients on any type of systemic therapy, including herbal medication and home remedies for any other systemic (inflammatory) diseases like hypertension, diabetes mellitus, familial hyperlipidemia, were also excluded. Seventy-five individuals were included in each group and informed consent was obtained from all 150 patients.

All patients received doxycycline 100mg daily with topical benzoyl peroxide 4% cream applied at night. The patients in the Group A received placebo daily in the evening while those in Group B received montelukast 10mg in identical containers. The duration of the treatment was 3 months. The patients were evaluated at baseline and thereafter on a monthly basis by the same investigator to minimize investigator bias. Neither the participants nor those performing the experiment knew which individuals were receiving the montelukast. Efficacy was assessed by analyzing total, inflammatory, and non-inflammatory lesions count and Global Acne Grading System (GAGS) along with Investigator Global Assessment (IGA) and Cardiff Acne Disability Index (CADI) scoring systems at the beginning and at week 12. In order to evaluate the effect of the therapy, clinical photographs were taken by the same camera and operator at the beginning and end of the treatment.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Normality of data was checked by Shapiro-Wilk test that showed that age was non-normal data. Median (IQR) were calculated for scoring system outcomes Qualitative data was represented by using percentage and frequency. Chi square test (for qualitative variables) and Mann-Whittney U-test was used for Comparisons of scoring system outcomes between placebo and montelukast group. The *p*-value of ≤0.05 was considered as statistically significant".

RESULTS

A total of 150 individuals with moderate acne vulgaris having an IGA score of 3 were enrolled as group A (n=75) and group B (n=75). There was statistical difference found with age (*p*-value =0.042) and not difference found in gender among to groups (*p*-value =0.870) shown in Table-I.

Table-I: Descriptive Variables of the Study Population (n=150)

Parameter		Doxycycline +placebo (n=75)	Doxycycline +montelukast (n=75)	*p*-value
Gender	Male	38(25.3%)	37(24.7%)	0.87
	Female	37(24.7%)	38(25.3%)	0.87
Mean Age (years)		25.00(31.00–19.00)	20.00(28.00–17.00)	0.042

Mann Whitney U test (between Group A and Group B), Wilcoxon test for before and after (baseline and 3 months)

For all variables, significant improvements were observed from baseline to follow-up within both groups (p-value <0.001), indicating the effectiveness of the interventions in reducing acne severity and improving quality of life. However, the group receiving montelukast appeared to be superior in efficacy compared to the placebo group.

Table-II: Comparisons of Scoring System Outcomes between Placebo and Montelukast Group (n=150)

Scoring System	Mean±SD Group A (n=75) (Placebo +Doxycycline)	Mean±SD Group B (n=75) (Montelukast +Doxycycline)	*p*-value
Total Lesion Count Baseline	50.00(51.00–49.00)	50.00(51.00–49.00)	0.800
Total Lesion Count after 3 months	22.00(22.00–19.00)	9.00(11.00–8.00)	<0.001
p-value	<0.001	<0.001	-
Inflammatory Lesion Count Baseline	21.00(22.00–20.00)	21.00(22.00–20.00)	0.923
Inflammatory Lesion Count after 3 months	10.00(15.00–8.00)	4.00(5.00–3.00)	<0.001
p-value	<0.001	<0.001	
Non-Inflammatory Lesion Count Baseline	29.00(30.00–28.00)	29.00(30.00–28.00)	0.627
Non-Inflammatory Lesion after 3 months	16.00(17.00–15.00)	6.00(6.00–5.00)	<0.001
p-value	<0.001	<0.001	
GAGS Baseline	29.00(30.00–28.00)	29.00(30.00–28.00)	0.644
GAGS after 3 months	15.00(19.00–12.00)	10.00(11.00–10.00)	<0.001
p-value	<0.001	<0.001	
IGA Baseline	3.00(3.00–3.00)	3.00(3.00–3.00)	1.00
IGA after 3 months	2.00(2.00–2.00)	2.00(2.00–1.00)	<0.001
p-value	<0.001	<0.001	
CADI Baseline	8.00(8.00–7.00)	8.00(8.00–7.00)	1.00
CADI after 3 months	4.00(5.00–4.00)	3.00(4.00–3.00)	<0.001
p-value	<0.001	<0.001	

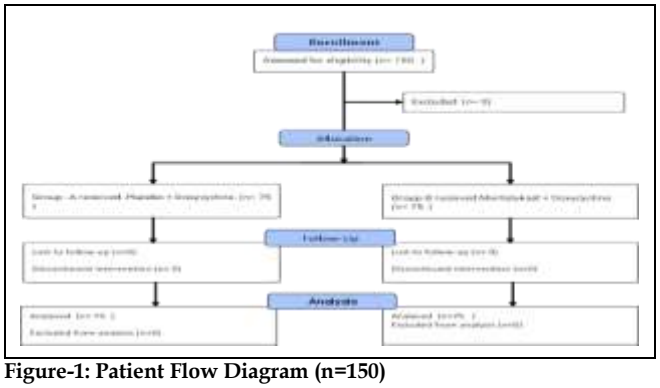

Figure-1: Patient Flow Diagram (n=150)

DISCUSSION

Acne vulgaris affects a significant proportion of the world's adolescent and adult population. The condition causes both physical irritation and psychological debilitation.[16] Since the advent of social media, the psychosocial comorbidity associated with the condition has increased dramatically, rendering affected individuals to depression, anxiety, low self-esteem and even suicidal ideation.[17,18]

Early, robust treatment is now the general principle to prevent sequalae.[19] Topical treatment is recommended as first line whereas oral formulations are used for unresponsive or severe cases. Various agents have been pursued for the suppression of this chronic condition but tetracyclines and retinoids have been the mainstay with good efficacy.[20] However, considering the relapsing and persistent nature of the disease, and the prolonged treatment associated with it, the possibility of resistance[21] and side effects is increased. Tetracyclines pose the risk of photosensitivity, gastrointestinal disturbance and vestibular effects[22] while dyslipidemia, skeletal abnormalities and teratogenicity are major concerns when prescribing oral retinoids.[23] Safer options that may serve as an alternative or help decease the dose of the primary agent are the need of the hour.

Numerous studies have been conducted on the addition of different adjuvant treatment modalities9, including topical therapies, systemic agents, physical therapies like laser, and photodynamic therapy. Administration of such adjuvants to isotretinoin confirmed the improved efficacy of combination therapies and decreased adverse effects of isotretinoin.[24]

Montelukast is a LTB4 inhibitor that has strong anti-inflammatory action.[25] It has the potential to be an effective therapeutic agent in the treatment of acne. In a previous study performed by Aslam *et al.*, on 84 patients with moderate acne in 2016, oral montelukast 5 mg was compared with oral doxycycline 100 mg. After 1 month of treatment, the acne lesions decreased in both groups, but the efficacy of doxycycline 100 mg daily was superior to that of montelukast 5 mg per day. Rokni *et al.*, compared treatment with oral montelukast and oral finasteride in women with moderate acne vulgaris. Both groups were given topical clindamycin 2% concomitantly. The study showed good efficacy of both treatment methods with finasteride depicting better outcome compared to montelukast.[26]

Considering the relatively inferior efficacy of montelukast to other drugs, its use as an adjunct instead of a single treating agent was considered. A study was conducted by Fazelzadeh-Haghighi *et al.*, involving 108 patients with moderate acne vulgaris.

The patients were divided into two groups where one group received 100mg of doxycycline with oral montelukast 10mg per day while the other was administered 100mg of doxycycline with placebo. It was discovered that the combination of montelukast and doxycycline was more effective than doxycycline alone.[14]

Our study also revealed that the addition of montelukast to doxycycline and topical benzoyl peroxide significantly improved IGA and lowered both the inflammatory and non-inflammatory lesion count in patients with moderate acne vulgaris. A significant decrease was observed in the percentage of the total lesion count (p <0.05). The results also showed a noticeable difference between the study groups regarding the decrease in the CADI and GAGS score (p <0.001). Overall, after the three months of intervention, a superior response was observed with the use of adjuvant montelukast compared to placebo.

A limitation of our study was that environmental risk factors that influence inflammatory acne such as diet with high glycemic index and stress could not be entirely excluded. As patients were all from different walks of life with varying lifestyle, we excluded those with a prior history of excessive exposure to such factors to diminish the confounding potential of these factors in this study.

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CONCLUSION

Montelukast has an anti-inflammatory action which helps decrease the inflammatory aspect of acne pathogenesis. Studies have revealed that it is inferior to currently employed first line oral treatments in terms of efficacy as an agent for monotherapy. However, as an adjunctive agent, it can be used in the management of moderate inflammatory acne as part of a combination treatment to achieve good outcome and prevent side effects from prolonged use of other oral medications. The lack of serious side effects makes it a safe treatment modality as well. Moreover, considering the established association of asthma with acne, it can prove to be a promising prospect in treatment of patients of inflammatory acne having concomitant asthma. Further research in this regard is warranted.

Conflict of Interest: None.

Discolure

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

ANM & NI: Data acquisition, data analysis, critical review, approval of the final version to be published.

SSM & FY: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AUB & AA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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