Received: 13 July 2021 | Revised: 23 July 2021 | Accepted: 30 July 2021

DOI: 10.1111/jocd.14462

ORIGINAL CONTRIBUTIONS

JCD Journal of Cosmetic Dermatology WILEY

Efficacy, tolerability, and safety of montelukast versus finasteride for the treatment of moderate acne in women: A prospective, randomized, single-blinded, active-controlled trial

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Abstract

Background: Acne is a chronic inflammatory skin disease which involves the pilosebaceous unit. Tissue inflammation isone of the crucial mechanisms, amongst others. Of the various cytokines, leukotriene B4 (LT-B4) is the most potentleucocyte chemotactic mediator. Montelukast is an antagonist of the LT-B4 receptor. Finasteride is an antiandrogen whichspecifically inhibits the 5α-reductase enzyme.

Aims: This study aimed at comparing the efficacy, tolerability and safety of montelukast versus finasteride in the treatmentof moderate acne in women.

Patients/Method: This randomized, single-blinded, prospective trial over 12 weeks recruited 65 female subjects with moderate acne vulgaris (Global Acne Grading System Scale) for evaluation. One group (n = 30) received oral montelukast (10 mg PO daily), while the second group (n = 25) received oral finasteride (2.5 mg PO daily) in combination with topical clindamycin 2% solution. Lesion count and acne severity were evaluated at time intervals of 0 (baseline), 4, 8, and 12 weeks. Adverse effects of the drugs were noted.

Results: Both lesion count and severity of acne decreased significantly after treatment in both the groups as compared to the baseline. The acne severity score reached from 33.93 in time zero to 20.6 in the 12th week and 35.71 at baseline to 16.43 at the end of treatment in the Montelukast and Finasteride groups, respectively. Side effects were noted in 3 patients and 2 patients in the monteleukast and finasteride group, respectively, which were transient and non-serious in nature proving the satisfactory tolerability and safety of these two drugs.

Conclusion: The results of this study show that both montelukast and finasteride have good efficacy in the treatment of acne. Finasteride has more efficacy than montelukast for treating moderate acne in normo-androgenic women.

KEYWORDS
acne, acne severity index, finasteride, montelukast

1 | INTRODUCTION

Acne is a chronic inflammatory skin disease which is mediated by complex pathogenic mechanisms. Four major factors play a role in its etiopathogenesis: hyperkeratinization, colonization by *Propionibacterium acnes*, inflammation, and an increase in sebum production.[1] The pilosebaceous unit is the primary target in acne, with highest concentration on the face, chest, and upper back.[2–4] Acne affects approximately 80% of adults between the ages of 11 and 30 years.[5] The residual scars from acne can affect a patient's self-esteem leading to psychological issues like depression, anxiety, and even suicidal ideation.[6] Inflammation is one of the major factors involved in acne which is proven by the detection of many interleukins (IL-1, IL-8) in comedones and the presence of lymphocytes and macrophages in early, non-inflammatory acne lesions.[7–10] Other pro-inflammatory mediators, such as leukotrienes (LTs) and prostaglandins (PGs), are implicated in the initiation and progression of acne.[11] Leukotriene B4 (LT-B4) is the most potent leucocyte chemotactic mediator in the pathogenesis of acne.[12] It is possible to affect a therapeutic blockade in the leukotriene pathway by either inhibition of 5-lipooxygenase (5-LOX) to reduce leukotriene synthesis, or by preventing bonding between LT-B4 and its receptor. Montelukast is an antagonist of LT-B4 receptor.[13] It is a selective antagonist of cysteinyl leukotriene receptor that is employed in bronchial asthma as an adjuvant therapy.[14] Additionally, montelukast prevents airway remodeling due to its anti-inflammatory effect.[15] In 2015, Behrangi et al. compared the efficacy of montelukast versus doxycycline for the treatment of moderate acne. The efficacy was same across the groups, and there was no statistically significant difference.[9] The 5α-reductase enzyme converts testosterone to its active form 5α dihydrotestosterone (DHT) in peripheral tissues. There are three isoenzymes in this family: type 1 distributed in the scalp and skin, type 2 in prostate, and type 3 being found abundantly in skin and brain.[16,17] Finasteride is an antiandrogen which specifically inhibits the type-2 isoenzyme of 5α-reductase enzyme.[18,19] In 2007, Kohler et al. studied the effect of finasteride 5 mg on acne and alopecia in female patients with normal serum levels of free testosterone. This was a retrospective study evaluating a questionnaire filled out by 12 patients, six of whom had acne and six had alopecia. Of these, symptoms in nine patients decreased significantly. This supports the hypothesis of an excessive activity or high affinity of 5a-reductase enzyme in peripheral tissue in these patients.[20] In a study by Carmina in 2001, finasteride was effective in treating acne in hyperandrogenic women with polycystic ovarian disease.[21] In a clinical trial study in 2015, the efficacy of finasteride on severe nodulocystic acne in men was evaluated and delineated.[22] We conducted this study owing to paucity of literature regarding the efficacy of montelukast and finasteride in treating moderate acne.

2 | METHODS

This was a prospective, randomized, active-controlled clinical trial that was conducted from September 2018 to September 2020. Seventy female subjects, between 14 to 50 years of age with moderate acne based on global acne evaluation and normal androgens (total and free testosterone, sex hormone binding globulin (SHBG), and dehydroepiandrosterone (DHEAS)), were included. The study was approved by the ethical review committee of Mazandaran University of Medical sciences. Written consent was obtained from all the patients. Single women who did not want to conceive during the study were recruited in this study. Patients were randomly allocated to receive oral montelukast 5 mg daily per os (PO) plus 2% clindamycin solution or finasteride 2.5 mg/day PO plus 2% clindamycin solution for a total duration of 12 weeks. Patients were followed up at time intervals of 4, 8, and 12 weeks. The efficacy, patient's satisfaction, side effects, and tolerability were recorded and evaluated. The acne severity index measurement was single-blinded being done by an independent dermatologist comparing the efficacy parameters between the two study groups. Acne vulgaris was graded based on a score designed by Indian authors, which classifies acne lesions into 4 groups. Each type of lesion is given a value depending on severity: No lesions = 0, comedones = 1, papules = 2, pustules = 3, and nodules = 4. The factor for each area includes forehead: 2, right cheek: 2, left cheek: 2, nose: 1, chin: 1, chest and upper back: 3. Local score is calculated using the formula: Local score = Factor × Grade (0–4). The global score defining the severity of acne is the sum of local scores. A score of 1–18 is considered mild; 19–30 as moderate; 31–38 as severe; and >39 as very severe.[23] Tolerability and safety of both the drugs was assessed through side effect profile seen in the patients leading to drug discontinuation. Statistical Package for the Social Sciences (SPSS) version 24 was used for analysis. Non-parametric test (Wilcoxon) and Coupled *t* test were used for the comparison between pretreatment and post-treatment results. Variance analysis test (for repeated measurements) was used for data analysis. Satisfaction rate was determined using Kappa agreed coefficients and chi-square test. A *p*-value of <0.05 was considered statistically significant.

3 | RESULT

There were 35 female patients in each group. Five patients from the montelukast group withdrew from the study citing personal reasons. The mean age of patients (in years) in the montelukast group was 23.87 ± 6.51 (Max - 38 and Min - 16) and in the finasteride group was 23.63 ± 5.16 (Max - 35 and Min - 15). Mean body mass index (BMI) in kg/m^2 in the montelukast group was 22.21 ± 2.577 (Max 27 and Min 17.9) and in the finasteride group was 22.94 ± 2.79 (Max 29.09 and Min 18.2). Overall, 60% patients were single while 40% were married. The mean duration of disease (in years) in montelukast group was 2.80 ± 2.23 and in finasteride group was 2.63 ± 2.52. Hormonal evaluations with total and free testosterone, SHBG, and DHEAS were done in all patients prior to starting the treatment which were in normal range. The average acne severity index in the montelukast and finasteride groups, in the initial visit, was 33.93 and 35.71, which reached to 20.6 and 16.43 at the end of 12 weeks, respectively (Table 1). During patient assessment, in the first follow-up

TABLE 1 The average acne severity index in both groups

Average acne severity index	Montelukast	Finasteride	*p*-value
Initial visit	33.93	35.71	0.186
Fourth week visit	26.63	27.74	0.448
Eighth week visit	22.27	21.94	0.823
Twelfth week visit	20.6	16.43	0.042

at 4 weeks, only 28.6 percent of patients in the finasteride group and 16.7 percent in the montelukast group found their condition improving (Table 2). At the end of 12 weeks, 88.6% patients in the finasteride group and 79.6% patients in the montelukast group had near-total clarity of acne (Figures 1 and 2). Patient satisfaction at the end of the 12 weeks was reported in 80% patients in the finasteride group while 66.7% in the montelukast group (Table 3). (Patient satisfaction rate was measured as complete, marked, and moderate in a subjective questionnaire). Physician assessment, at week 4, showed some level of improvement in 34.3% patients in the finasteride group and 30% patients in the montelukast group (Table 4). At the end of the study period, the incidence of "mild, almost clear and clear" reached 94.3% in the finasteride group and 86.7% in the montelukast group. Physician satisfaction at the end of 12 weeks was recorded in 79.9% patients in the finasteride group and 63.3% patients in the montelukast group (Table 5).

Three people had complications in montelukast group, including headache, dizziness, and gastrointestinal upset, while in finasteride group, two patients reported side effects, including menstrual irregularities and dyspepsia. These were transient and non-serious in nature proving the satisfactory tolerability and safety of these two drugs. As a non-primary outcome, two patients in the finasteride group reported improvement in alopecia while taking the drug.

Patient assessment	Severity grade	Montelukast	Finasteride	*p*-value
Initial visit	Mild	16.7%	28.6%	0.977
	Moderate	70%	45.7%	
	Severe	13.3%	25.7%	
Fourth week visit	Almost clear	10%	5.7%	0.183
	Mild	36.7%	65.7%	
	Moderate	53.3%	28.6%	
Eighth week visit	Almost clear	16.7%	40%	0.012
	Mild	63.3%	57.1%	
	Moderate	16.7%	2.9%	
	Severe	3.3%	0%	
Twelfth week visit	Clear	0%	34.3%	0.000
	Almost clear	36.7%	40%	
	Mild	43.3%	14.3%	
	Moderate	20%	11.4%	

TABLE 2 Patient assessment of severity in 2 groups

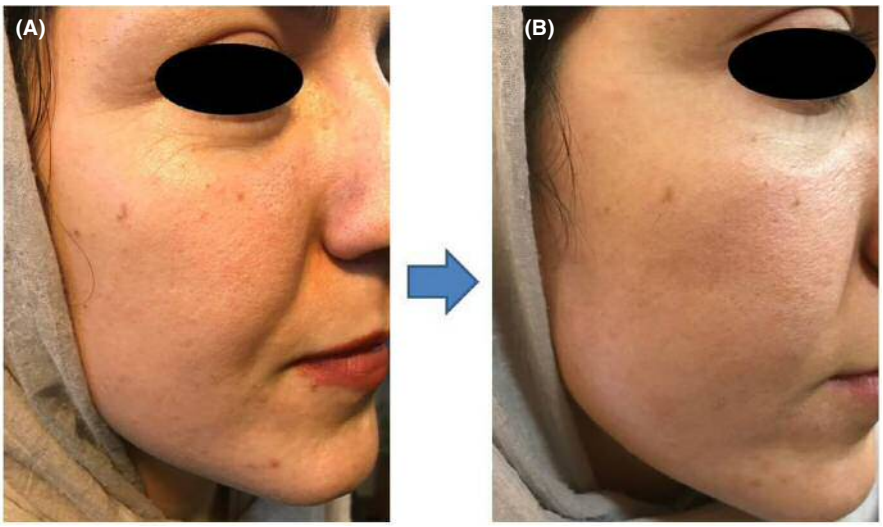

FIGURE 1 Clinical improvement at 12 weeks in finasteride group

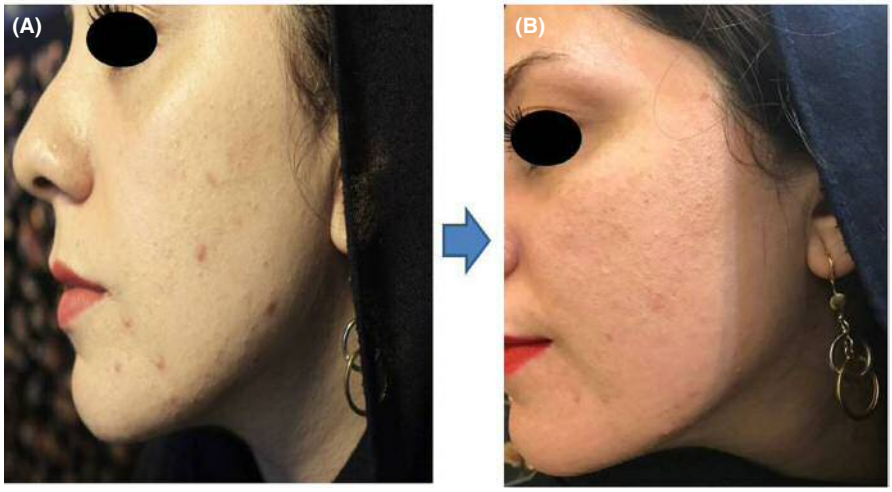

FIGURE 2 Clinical improvement at 12 weeks in montelukast group

TABLE 3 Patient satisfaction in 2 groups

Patient satisfaction	Satisfaction parameters	Montelukast	Finasteride	*p*-value
Fourth week visit	Complete	3.3%	0	0.263
	Marked	10%	8.6%	
	Moderate	53.3%	82.9%	
	Slight	33.3%	8.6%	
Eighth week visit	Marked	36.7%	57.1%	0.049
	Moderate	26.7%	28.6%	
	Slight	33.3%	11.4%	
	Worsening	3.3%	2.9%	
Twelfth week visit	Complete	0	34.3%	0.009
	Marked	36.7%	31.4%	
	Moderate	30%	14.3%	
	Slight	30%	14.3%	
	Worsening	3.3%	5.7%	

TABLE 4 Physician assessment in 2 groups

Physician assessment	Severity grades	Montelukast	Finasteride	*p*-value
Initial visit	Mild	30%	34.3%	0.717
	Moderate	66.7%	62.9%	
	Severe	3.3%	3.9%	
Fourth week visit	Almost clear	6.7%	0	0.189
	Mild	60%	88.6%	
	Moderate	33.3%	11.4%	
Eighth week visit	Almost clear	10%	40%	0.012
	Mild	80%	54.3%	
	Moderate	10%	5.7%	
Twelfth week visit	Clear	0%	34.3%	0.000
	Almost clear	16.7%	34.3%	
	Mild	70%	25.7%	
	Moderate	13.3%	5.7%	

TABLE 5 Physician satisfaction in both groups

Physician satisfaction	Satisfaction parameters	Montelukast	Finasteride	*p*-value
Fourth week visit	Marked	16.7%	8.6%	0.339
	Moderate	53.3%	82.9%	
	Slight	30%	8.6%	
Eighth week visit	Marked	30%	57.1%	0.016
	Moderate	40%	31.4%	
	Slight	30%	11.4%	
Twelfth week visit	Complete	0	37.1%	0.002
	Marked	30%	25.7%	
	Moderate	33.3%	17.1%	
	Slight	33.3%	17.1%	
	Worsening	3.3%	2.9%	

4 | DISCUSSION

Acne is a chronic inflammatory skin disease wherein IL-1 is detected in comedones and in early non-inflammatory acne lesions, including other pro-inflammatory mediators.[1] Of the later, LT-B4 is the most potent mediator. In the present study, all patients included were women which could be one of the limitations of our research. In a study conducted by Babayeva et al. on patients with acne, around 80% of patients were women.[24] Kelidari et al., while studying a new formulation of nanoparticles for use in acne, had nearly 90% female volunteers.[25] The age distribution among the study samples in both the groups was comparable with an average age of 23 years in both the groups. A similar trend was observed in the study by Kelidari et al. There was also similarity of the patient demographics in terms of marital status, BMI status, and duration of the disease ($p > 0.05$). To reduce the impact of intervening variables, serum samples were examined for hyperandrogenism that were shown to be within normal range and there was no difference between the two groups ($p > 0.05$). Assessing the severity of acne with global acne severity index, in four time periods (initial examination, end of the fourth, eighth, and twelfth week), showed a significant decrease in the severity of acne after 4 weeks of treatment in both the groups ($p < 0.0001$). These results indicate the effectiveness of both treatment regimens. There was no statistical difference between the two study groups at the end of eighth week. However, by the end of the twelfth week, patients receiving finasteride showed a better therapeutic efficacy (in terms of both lesion count and severity) than those receiving montelukast. Clinical evaluation and satisfaction by physician and patients showed equivocal results. Overall, a reduction in the average global acne severity index was seen in both groups. In the montelukast group, this index at the initial visit was 33.93, which reached 20.6 at the end of the twelfth week. In the finasteride group, the index at baseline was 35.71, which reached 16.43 after 12 weeks. This decrease was more in the finasteride group. In the study by Behrangi et al., global acne severity index in the montelukast group decreased from 18.2 to 8.6 and in the doxycycline group from 19 to 8.2, which corroborates the effectiveness of montelukast in the treatment of acne.[9] Additionally, in the study by Kohler et al., treatment with 5 mg finasteride was effective in controlling disease progression in acne which is similar to our study.[20] The study by Carmina et al. documented finasteride to be effective in treating acne in hyperandrogenic women.[21] By the end of the week 12, both the patients and the physician in the finasteride group were more satisfied with this regimen. A few side effects were documented, including headache, dizziness, and gastrointestinal upset in the montelukast group while menstrual irregularities and dyspepsis in the finasteride group which were transient and non-serious in nature proving the satisfactory tolerability and safety of these two drugs.

5 | CONCLUSION

The results of this study showed that both montelukast and finasteride have good efficacy, tolerability, and safety in the treatment of acne. Finasteride is more efficacious than montelukast in combination therapy with clindamycin solution 2% which was statistically significant.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Ghasem Rahmatpour Rokni involved in study design, data acquisition, and Final proof. Farzaneh Mohammadnezhad involved in data acquisition and writing the draft. Majid Saeedi, Aseem Sharma, Sunmeet Sandhu, and Atula Gupta involved in review and revising the manuscript. Shiva Shadi and Mohamad Goldust involved in data acquisition, review, and revising the manuscript.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

ETHICS STATEMENT

The study was approved by the ethic committee of Mazandaran University of Medical sciences.

DISCLAIMER

We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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How to cite this article: Rokni GR, Mohammadnezhad F, Saeedi M, et al. Efficacy, tolerability, and safety of montelukast versus finasteride for the treatment of moderate acne in women: A prospective, randomized, single-blinded, active-controlled trial. *J Cosmet Dermatol*. 2021;20:3580–3585. https://doi.org/10.1111/jocd.14462