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 is one of the crucial mechanisms, amongst others. Of the various cytokines, leukotriene B4 (LTB4) is the most potent leukocyte chemo tactic mediator. Montelukast is an antagonist of the LTB4 receptor. Finasteride is an antiandrogen which specifically inhibits the 5α-reductase enzyme.

Aims: This study aimed at comparing the efficacy, tolerability and safety of montelukast versus finasteride in the treatment of 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 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 montelukast 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. The pilosebaceous unit is the primary target in acne, with highest concentration on the face, chest, and upper back. Acne affects approximately 80% of adults between the ages of 11 and 30 years. The residual scars from acne can affect a patient's self-esteem leading to psychological issues like depression, anxiety, and even suicidal ideation. 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. Other pro-inflammatory mediators, such as leukotrienes (LTs) and prostaglandins (PGs), are implicated in the initiation and progression of acne. Leukotriene B4 (LT-B4) is the most potent leukocyte chemotactic mediator in the pathogenesis of acne. It is possible to affect a therapeutic blockade in the leukotriene pathway by either inhibition of 5-lipoxygenase (5-LOX) to reduce leukotriene synthesis, or by preventing bonding between LT-B4 and its receptor. Montelukast is an antagonist of LT-B4 receptor. It is a selective antagonist of cysteinyl leukotriene receptor that is employed in bronchial asthma as an adjuvant therapy. Montelukast prevents airway remodeling due to its anti-inflammatory effect. 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. The 5α-reductase enzyme converts testosterones 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. Finasteride is an antiandrogen which specifically inhibits the type-2 isoenzyme of 5α-reductase enzyme. 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 5α-reductase enzyme in peripheral tissue in these patients. In a study by Carmina in 2001, finasteride was effective in treating acne in hyperandrogenic women with polycystic ovarian disease. In a clinical trial study in 2015, the efficacy of finasteride on severe nodulocystic acne in men was evaluated and delineated. 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. 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/m² 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
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 finas-
teride 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 finas-
teride 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, in-
cluding 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 pa-
tients in the finasteride group reported improvement in alopecia
while taking the drug.
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%        |         |
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. 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. Kelidari et al., while studying a new formulation of nanoparticles for use in acne, had nearly 90% female volunteers. 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. 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. The study by Carmina et al. documented finasteride to be effective in treating acne in hyperandrogenic women. 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 dyspepsia 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.

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REFERENCES

1. Lynn DD, Umari T, Dunnick CA, Dellavalle RP. The epidemiology of acne vulgaris in late adolescence. Adolesc Health Med Ther. 2016;7:13-25.

2. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol. 2003;49:51-S37.

3. Plevig G, Kligman AM. Acne and rosacea, 3rd edn. Springer Verlag; 2000: 460.

4. Guzman AK, Choi JK, James WD. Safety and effectiveness of amoxicillin in the treatment of inflammatory acne. Int J Womens Dermatol. 2018;4:174-175.

5. Kucharska A, Szmurło A, Sínska B. Significance of diet in treated and untreated acne vulgaris. Postepy Dermatol Alergol. 2016;33:81-86.

6. Collier CN, Harper JC, Cafardi JA, et al. The prevalence of acne in adults 20 years and older. J Am Acad Dermatol. 2008;58:56-59.

7. Zouboulis CC. Is acne vulgaris a genuine inflammatory disease? Dermatology. 2001;203:277-279.

8. Zouboulis CC, Eady A, Philpott M, et al. What is the pathogenesis of acne? Exp Dermatol. 2005;14:143-152.

9. Behranghi E, Arasteh E, Tavakoli T, et al. Comparing efficacy of montelukast versus doxycycline in treatment of moderate acne. J Res Med Sci. 2015;20:379-382.

10. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol. 2003;121:20-27.

11. Zouboulis CC. Zileuton, a new efficient and safe systemic anti-acne drug. Dermato Endocrinol. 2009;1:188-192.

12. Aletas T, Ganceviciene R, Fimmel S, Müller-Decker K, Zouboulis CC. Enzymes involved in the biosynthesis of leukotriene B4 and prostaglandin E2 are active in sebaceous glands. J Mol Med (Berl). 2006;84:75-87.

13. Grice CA, Tays KL, Savall BM, et al. Identification of a potent, selective, and orally active leukotriene A4 hydrolase inhibitor with anti-inflammatory activity. J Med Chem. 2008;51:4150-4169.

14. Al Saadi MM, Meo SA, Mustafa A, Shafi A, Tuwajri AS. Effects of montelukast on free radical production in whole blood and isolated human polymorphonuclear neutrophils (PMNs) in asthmatic children. Saudi Pharm J. 2011;19:215-220.

15. Muz MH, Deveci F, Bulut Y, İlhan N, Yekeler H, Turgut T. The effects of low dose leukotriene receptor antagonist therapy on airway remodeling and cysteinyl leukotriene expression in a mouse asthma model. Exp Mol Med. 2006;38:109-118.

16. Okeigwe I, Kuohung W. 5-Alphareductase deficiency: a 40-year retrospective review. Curr Opin Endocrinol Diabetes Obes. 2014;21:483-487.

17. Motofei IG, Rowland DL, Tampa M, et al. Finasteride and androgenic alopecia; from therapeutic options to medical implications. J Dermatolog Treat. 2020;31:415-421.

18. Zouboulis CC, Dessinioti C, Tsatsou F, Gollnick HPM. Anti-acne drugs in phase 1 and 2 clinical trials. Expert Opin Investig Drugs. 2017;26:813-823.

19. Carmina E, Lobo RA. A comparison of the relative efficacy of antiandrogens for the treatment of acne in hyperandrogenic women. Clin Endocrinol (Oxf). 2002;57:231-234.

20. Kohler C, Tschumi K, Bodmer C, Schneider M, Birkhaeuser M. Effect of finasteride 5 mg (Proscar) on acne and alopecia in female patients with normal serum levels of free testosterone. Gynecol Endocrinol. 2007;23:142-145.

21. Carmina E, Lobo RA. Treatment of hyperandrogenic alopecia in women. Fertil Steril. 2003;79:91-95.

22. Hazarika N. Acne vulgaris: new evidence in pathogenesis and future modalities of treatment. J Dermatolog Treat. 2021;32:277-285.

23. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol. 1997;36:416-418.

24. Babayeva L, Akarsu S, Fetil E, Güneş AT. Comparison of tretinoin 0.05% cream and 3% alcohol-based salicylic acid preparation in the treatment of acne vulgaris. J Eur Acad Dermatol Venereol. 2011;25:328-333.

25. Kelidari HR, Saeedi M, Hajheydari Z, et al. Spironolactone loaded nanostructured lipid carrier gel for effective treatment of mild and moderate acne vulgaris: a randomized, double-blind, prospective trial. Colloids Surf B Biointerfaces. 2016;146:47-53.

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