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ORIGINAL ARTICLE

Comparing efficacy of Montelukast versus doxycycline in treatment of moderate acne

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Background: Treatment of acne is an important issue for reducing the cosmetic and psychological burden of disease. Regarding the inflammatory effect of LT-B4 in acne lesions and action mechanism of Montelukast, this study was performed to determine the efficacy of Montelukastin acne treatment comparison with doxycycline. **Materials and Methods:** In a randomized clinical trial that was performed in Dermatology Clinic in a Training Tertiary Health Care Center in Tehran, Iran since January 2012 to May 2014, 52 patients with moderate acne were evaluated. The included patients were randomly assigned to receive doxycycline 100 mg/day plus 1% Clindamycin solution (Group 1) or Montelukast 5 mg daily plus 1% clindamycin solution (Group 2). The acne severity index was measured and compared between two groups at baseline (on admission), 1-month and 3 months later. Independent-Sample-T, Chi-Square, and Repeated-Measure ANOVA tests were used and were considered statistically significant at $P < 0.05$. **Results:** The mean age was 26.8 ± 7.1 in Group 1 and25 ± 4.8 in Group 2 ($P = 0.1$). 73% women and 26.7% 4 men in Group 1 and 86.7% women, and 13.3% men in Group 2 ($P = 0.01$). The mean acne severity index at baseline was 18.2 ± 6.1 and 19 ± 4.2 in Montelukast and doxycycline group, respectively ($P = 0.679$). The mean acne severity index after 1-month was 10.5 ± 6.2 and 12.9 ± 3.3 in Montelukast and doxycycline group, respectively ($P = 0$). Finally, the mean acne severity index after 3 months follow-up was 8.6 ± 4.8 and 8.2 ± 1.2 in Montelukast and doxycycline group, respectively ($P = 0.01$). There was no significant difference between two groups regarding the amount of decrease in acne severity index across the study ($P = 0.186$). However, each groups showed a significant reduction in the acne severity index, separately ($P = 0.001$). **Conclusion**: It may be concluded that Montelukast is an effective and safe medication for moderate-level acne treatment.

Key words: Acne, inflammation, montelukast, treatment

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INTRODUCTION

Acne lesions are papulopustular affecting mainly the face, chest, and back regions. Acne is usually initiated in age range from 10 to 15 years lasting for 5 to 10 years.[1] However, it may be extended to later ages. The sebaceous glands obstruction, increased sebum formation, and propionibacterium acne are the most important contributing factors. Current medications for acne include Tretinoin and its preparations, benzoyl peroxide, and local and systemic antibiotics.[1]

Doxycycline acts on inflammatory acne. The bacteria are usually present in small numbers. Propionibacterium acne proliferates in the lipid rich environment of the microcomedo and produces proinflammatory mediators that cause papules, pustules and cysts. Propionibacterium acnes are highly sensitive to many antibiotics such as doxycycline, tetracycline, minocycline.[2]

Tissue inflammation is also an important part of acne development and progressions.[3-6] On the other hand, the enzymes contributing for Leukotriene-B4 (LT-B4) and prostaglandin-E2, are active in acne lesions.[7] LT-B4 is the product of arachidonic acid pathway.[8-10] Arachidonic acid would result in LT-B4 and IL-6 secretion and increase in lipid synthesis in sebaceous glands.[9] Also, LT-B4 is a natural ligand for proxisome proliferation activated receptor α (PPAR).[11,12] PPAR may modifies the inflammatory response in different cells with inhibition of proinflammatory genes such as cytokines, metaloproteins, and acute phase reactants.[12,13] There are two ways to interrupt the leukotriene

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pathway and prevention from its effect; first inhibition of 5-lipooxygenase and reduction of leukotriene synthesis and the second way is prevention of bonding between LT-B4 and related receptor on target organs. Drugs such as zafirlukast and Montelukast are antagonists of LT-B4 receptor.[14] Many studies demonstrated the effectiveness of Montelukast in allergic disorders due its immunomodulatory effect.[15-17] In addition, some evidence showed Montelukast therapy can be useful in the treatment of some skin disorder such as atopic dermatitis, chronic idiopathic urticarial and pemphigoid nodularis.[18-20]

Although many studies have shown the efficacy of doxycycline in the treatment of acne, it is associate with some side effects. Side effects caused by doxycycline are gastrointestinal irritation with diarrhea, vomiting, and dyspepsia. Vaginal candidiasis may occur in women and the influence when on the pill is not certain, giving recommendations to be extra cautious with contraceptives during therapy.[21,22] One particularly evident side effect in children is the potential yellowish discoloration and enamel hypoplasia of the developing teeth's.[21,23] Rare adverse effects are benign intracranial hypertension and photosensitivity.[23] Regarding the inflammatory effect of LT-B4 in acne lesions and action mechanism of Montelukast, this study was performed to determine the efficacy of this drug in acne treatment and comparison with doxycycline as a pilot study.

MATERIALS AND METHODS

In this randomized clinical trial that was performed as pilot study, 52 consecutive patients attending to Dermatology Clinic in a Training Tertiary Health Care Center in Tehran, Iran since January 2012 to May 2014 were enrolled. This study was approved by Local Ethical Committee with number 1076 and Helsinki declaration was respected all over the study course. Patients were randomly allocated to receive doxycycline Hakim factory, Iran.100 mg/day plus 1% Clindamycin solution (Pakdaro factory, Iran) or Montelukast 5 mg (Aboreyhan factory, Iran) daily plus 1% Clindamycin solution for 3 months. The duration of treatment was 3 months). The dose of 5 mg Montulukast was selected (half dose of routine dosage of asthma) in this pilot study.[15]

Patients were evaluated on admission, both 1-month and 3-months after treatment. The moderate acne severity, lack of background disease, and lack of other treatments in previous month were the inclusion criteria and major drug reaction and impossibility of follow-up and lack of satisfaction for incorporation in the study were the exclusion criteria. The acne severity index[2] was measured and recoded by single, blind dermatologist and was compared across the study between two groups. Acne vulgaris was graded by Indian authors[16] using a grading system, which classifies acne lesions to 4 groups. Each type of lesion is given a value depending on severity: Nolesions = 0, comedones = 1, papules = 2, pustules = 3 and nodules = 4. The factor for each area include (Forehead: 2, Right cheek: 2, Left cheek: 2, Nose: 1 Chin: 1, Chest and upper back: 3. (Local score) is calculated using the formula: Localscore = Factor × Grade (0-4). The global score is the sum of local scores, acne severity was graded using the global score. A score of 1-18 is considered mild; 19-30, moderate; 31-38, severe; and >39, very severe. The mean acne index before treatment, The mean in case group 12.8 and 10.5 in control group 1-month after treatment and 8.2 in case group, 8.6 in control group 3 months after treatment ($P = 0.01$) in case group was 19.2 and in control group 18.2 ($P = 0.01$). Liver function test was performed for all patients after 3 months for possible side effect. We didn't select a third group using only clindamycin group because for treatment of moderate acne systemic therapy is essential, and topical therapy is not enough 20 patients were excluded from the study. The analysis was performed among 30 subjects including 15 patients in doxycycline group and 15 subjects in Montelukast group. Data analysis was performed by SPSS (version 20.0) software [Statistical Procedures for Social Sciences; Chicago, Illinois, USA]. Independent-Sample-T, Chi-Square, and Repeated-Measure ANOVA tests were used and were considered statistically significant at $P < 0.05$.

RESULTS

The patients included 24 female (80%) and six male subjects (20%). In Montelukast and doxycycline groups, 13 and 11 female patients were present ($P = 0.651$). The mean age was 26.87 ± 7.10 and 25 ± 4.88 years in Montelukast and doxycycline group, respectively ($P = 0.410$).

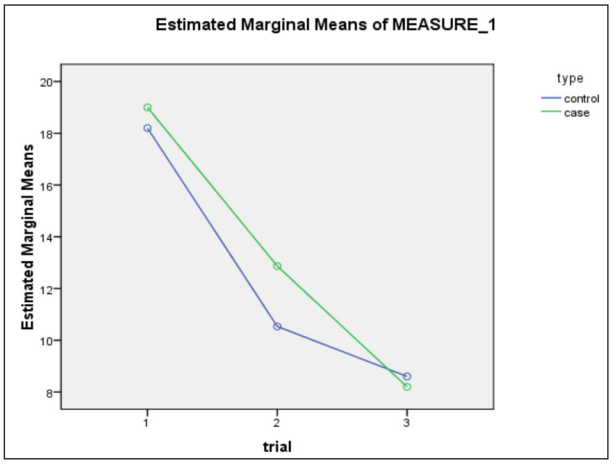

Figure 1: Acne severity index in two groups across the study at baseline (1), after one month (2), and after three months (3). The green line is related to Montelukast group and the blue one is for doxycycline

As shown in Figure 1, the mean acne severity index at baseline was 18.2 ± 6.1 and 19 ± 4.2 in Montelukast and doxycycline group, respectively ($P = 0.679$). The mean acne severity index after 1-month was 10.5 ± 6.2 and 12.9 ± 3.3 in Montelukast and doxycycline group, respectively ($P = 0.001$. Finally, the mean acne severity index after 3 months was 8.6 ± 4.8 and 8.2 ± 1.2 in Montelukast and doxycycline group, respectively. $P = 0.001$, $P = 0.001$). Each groups showed a significant reduction in acne severity index, separately ($P = 0.001$) during follow-up times. None of the patients in Montelukast group had drug adverse effects, but two patients in doxycycline groups developed dyspepsia leading to exclusion from the study. All included patients had normal function test after 3 months

DISCUSSION

This pilot study was performed to determine the efficacy of Montelukast in acne treatment and comparison with doxycycline in a 12-week course of treatment Tissue inflammation has major rolein the acne process. LTB (4) is considered to have major effect on the development of tissue inflammation. Synthesis of LTB (4) is by the enzyme 5-lipoxygenase. Since Zileuton blocks the activity of 5-lipoxygenase, clinical studies have been conducted to test function, as well as efficacy and safety of this compound in the treatment of acne vulgaris, so we decide to do a study with Montelukast that blocks leukotriene receptors with half dose of its use in asthma treatment. However, in both groups, the local Clindamycin was also prescribed for all the patients. The obtained results demonstrate the efficacy of LT-B4 inhibition in the treatment of acne lesions as well as previous studies. In a pilot clinical study with 10 patients with papulopustular acne Zileuton 4 × 600 mg/d p.o. for 3 months decreased the acne severity index in a time-dependent manner being 41% of the initial score at week 12 ($P < 0.05$). This was mostly due to a decrease of the number of inflammatory lesions of 29% ($P < 0.01$). Moreover, total sebum lipids significantly decreased (35%, $P < 0.05$) and the pro-inflammatory free fatty acids (22%) and lipoperoxides (26%) were markedly diminished in patients' sebum under treatment. These data are in agreement with clinical study in 101 patients with mild to moderate inflammatory facial acne conducted in the US, which showed a significant efficacy of Zileuton in patients with moderate acne, whereas those patients treated with Zileuton showed a significant mean decrease in inflammatory lesions compared to the placebo group. In all clinical studies, Zileutonwas found to be safe and well tolerated.[24] In other pilot study, 16 female patients with a diagnosis of sebaceous hyperplasia were compared to a control group of females of a similar age without the disease. Blood tests were performed to measure circulating androgen levels (free and total testosterone and androstenedione levels). These data showed no statistically differences in circulating androgen levels between the patients with sebaceous hyperplasia and the control group; therefore, there is no significant changes in circulating androgen levels (free and total testosterone, androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulfate) in patients with sebaceous hyperplasia.[25]

In our study, since the acne severity index was reduced in both groups, it may be concluded that both medications are effective. However, the efficacy was same across the groups, and there was no significant difference. Also despite the lack of difference in rate of drug adverse effects across the groups, there were no case versus two cases of side effects in doxycycline group. Use of nonantibiotic medications, regarding the increased rate of anti-microbial resistance, is rational especially if there are drugs with good efficacy and high safety such as Montelukast as shown in the current study.

The main limitation in this study was low patients' compliance and also high rate of subjects lost to follow-up. Also, this study was performed as a pilot trial and further studies with larger sample size should be carried out to obtain more definite results. Also, we could not completely evaluate for possible confounding factors, and only the age and gender were studied in currents trial leading to decreased applicability of the obtained results. Also, there was an inevitable limitation in this study; there were no similar reports in this era to be compared.

Finally, according to the obtained results in this study, it may be concluded that Montelukast is an effective and safe medication for acne treatment. Accordingly use of this drug is recommended especially in cases with moderate-level acne. Further studies with longer follow-up sessions would let to decide better about the efficacy of Montelukast and related safety.

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AUTHOR'S CONTRIBUTION

EB contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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SE contributed in the design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

ZA contributed in the conception and design of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

REFERENCES

1. Nast A, Dréno B, Bettoli V, Degitz K, Erdmann R, Finlay AY, *et al.* European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012;26 Suppl 1:1-29.
2. Adityan B, Kumari R, Thappa DM. Scoring systems in acne vulgaris. Indian J Dermatol Venereol Leprol 2009;75:323-6.
3. Zouboulis CC, Jourdan E, Picardo M. Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. J Eur Acad Dermatol Venereol 2014;28:527-32.
4. Jung JY, Kwon HH, Hong JS, Yoon JY, Park MS, Jang MY, *et al.* Effect of dietary supplementation with omega-3 fatty acid and gamma-linolenic acid on acne vulgaris: A randomised, double-blind, controlled trial. Acta Derm Venereol 2014;94:521-5.
5. Zouboulis CC, Baron JM, Böhm M, Kippenberger S, Kurzen H, Reichrath J, *et al.* Frontiers in sebaceous gland biology and pathology. Exp Dermatol 2008;17:542-51.
6. Zouboulis CC, Schagen S, Alestas T. The sebocyte culture: A model to study the pathophysiology of the sebaceous gland in sebostasis, seborrhoea and acne. Arch Dermatol Res 2008;300:397-413.
7. Alestas 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.
8. Guriec N, Le Jossic-Corcos C, Simon B, Ianotto JC, Tempescul A, Dréano Y, *et al.* The arachidonic acid-LTB4-BLT2 pathway enhances human B-CLL aggressiveness. Biochim Biophys Acta 2014;1842:2096-105.
9. Shoeb M, Yadav UC, Srivastava SK, Ramana KV. Inhibition of aldose reductase prevents endotoxin-induced inflammation by regulating the arachidonic acid pathway in murine macrophages. Free Radic Biol Med 2011;51:1686-96.
10. Wróbel A, Seltmann H, Fimmel S, Müller-Decker K, Tsukada M, Bogdanoff B, *et al.* Differentiation and apoptosis in human immortalized sebocytes. J Invest Dermatol 2003;120:175-81.
11. Di Gennaro A, Haeggström JZ. Targeting leukotriene B4 in inflammation. Expert Opin Ther Targets 2014;18:79-93.
12. Narala VR, Adapala RK, Suresh MV, Brock TG, Peters-Golden M, Reddy RC. Leukotriene B4 is a physiologically relevant endogenous peroxisome proliferator-activated receptor-alpha agonist. J Biol Chem 2010;285:22067-74.
13. Zampeli VA, Makrantonaki E, Tzellos T, Zouboulis CC. New pharmaceutical concepts for sebaceous gland diseases: Implementing today's pre-clinical data into tomorrow's daily clinical practice. Curr Pharm Biotechnol 2012;13:1898-913.
14. Grice CA, Tays KL, Savall BM, Wei J, Butler CR, Axe FU, *et al.* Identification of a potent, selective, and orally active leukotriene a4 hydrolase inhibitor with anti-inflammatory activity. J Med Chem 2008;51:4150-69.
15. Keast SL, Thompson D, Farmer K, Smith M, Nesser N, Harrison D. Impact of a prior authorization policy for Montelukast on clinical outcomes for asthma and allergic rhinitis among children and adolescents in a state Medicaid program. J Manag Care Spec Pharm 2014;20:612-21.
16. Lucendo AJ, De Rezende LC, Jiménez-Contreras S, Yagüe-Compadre JL, González-Cervera J, Mota-Huertas T, *et al.* Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. Dig Dis Sci 2011;56:3551-8.
17. Yilmaz O, Altintas D, Rondon C, Cingi C, Oghan F. Effectiveness of Montelukast in pediatric patients with allergic rhinitis. Int J Pediatr Otorhinolaryngol 2013;77:1922-4.
18. Holme H, Winckworth LC. Montelukast can reduce the severity and extent of atopic dermatitis. J Paediatr Child Health 2013;49:412-5.
19. Khan S, Lynch N, Khan S. Allergic diseases of the skin and drug allergies-2021. Efficacy of Montelukast as add-on therapy in patients with chronic idiopathic urticaria. World Allergy Organ J 2013;6 Suppl 1:P108.
20. Shintani T, Ohata C, Koga H, Ohyama B, Hamada T, Nakama T, *et al.* Combination therapy of fexofenadine and Montelukast is effective in prurigo nodularis and pemphigoid nodularis. Dermatol Ther 2014;27:135-9.
21. Tan AW, Tan HH. Acne vulgaris: A review of antibiotic therapy. Expert Opin Pharmacother 2005;6:409-18.
22. Mays RM, Gordon RA, Wilson JM, Silapunt S. New antibiotic therapies for acne and rosacea. Dermatol Ther 2012;25:23-37.
23. Tan HH. Antibacterial therapy for acne: A guide to selection and use of systemic agents. Am J Clin Dermatol 2003;4:307-14.
24. Zouboulis CC. Zileuton, a new efficient and safe systemic anti-acne drug. Dermatoendocrinol 2009;1:188-92.
25. Zouboulis CC, Saborowski A, Boschnakow A. Zileuton, an oral 5-lipoxygenase inhibitor, directly reduces sebum production. Dermatology 2005;210:36-8.

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