ORIGINAL ARTICLE

Effect of antihistamine as an adjuvant treatment of isotretinoin in acne: a randomized, controlled comparative study

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Abstract

Background Isotretinoin has been frequently used for acne therapy. However, it has limitation in acceptance because of its adverse effects. Although antihistamine recently revealed to decrease the lipogenesis, evidence is lacking regarding the clinical relevance of antihistamine in the treatment of acne.

Objectives To evaluate the clinical efficacy and tolerability of antihistamine as an adjuvant treatment of isotretinoin.

Methods Forty patients with moderate acne were included in this randomized, controlled comparative study. Twenty patients were treated with isotretinoin and 20 patients were treated with additional antihistamine, desloratadine. Assessment was made at baseline, after 2, 4, 8 and 12 weeks of treatment.

Results At week 12, compared with isotretinoin only group, isotretinoin with additional antihistamine group showed more statistically significant decrease in acne lesion counts (non-inflammatory lesions: 44.8% vs. 17.8%; inflammatory lesions: 55.8% vs. 22.9%; total lesions: 45.6% vs. 18.7%; all $P < 0.05$). Significant decrease was also observed in the score of global acne grading system and the measured value of sebum and erythema. Moreover, acne flare during the treatment occurred less frequently and adverse events of isotretinoin were more tolerable in additional antihistamine group.

Conclusions This results provide early evidence that antihistamine has a synergic effect with minimizing the side-effect of isotretinoin, and may be used as an adjuvant treatment of moderate acne.

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Conflict of interest

None declared.

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Introduction

Acne is the common skin disease in the general population, highly affected in adolescents with an 85% prevalence rate.[1–3] Due to the chronicity, the disease has a considerable impact on patients' physical and psychological health.[4,5] Multiple factors contribute to the pathogenesis of acne, all of which give rise to the development of antiacne treatments.[6,7] Among these therapeutic agents, isotretinoin is considered the most effective drug available by suppressing sebaceous gland activity.[7] Although approved by the US Food and Drug Administration for the treatment of nodulocystic acne in 1982, isotretinoin is increasingly encouraged for managing patients with moderate to severe acne.[8,9] However, there are many cases of acne that are unresponsive to isotretinoin therapy, and it needs to careful use and monitoring because of unwanted side-effects.[9,10] To overcome these things, not only various dose regimens are being introduced but also an effort to develop new alternatives in reducing sebum is being made.

Histamine has a possible role in acne pathogenesis by working as an inflammatory mediator in the process of immune reaction of inflammatory acne.[11,12] Also, *Propionibacterium acnes* change the pH of the microenvironment of the acne follicle which is an optimal environment for the production of histamine or histamine-like products leading to itching in patients with acne.[13,14] In addition, an *in vitro* study identifying histamine receptors and reduction of squalene levels by an antihistamine in sebocytes proved the role of histamine in sebum production.[12] Putting together, antihistamine not only acts as an effective anti-inflammatory drug but also has shown to decrease the lipogenesis in sebocytes. However, evidence is lacking regarding the clinically relevant action of antihistamine in the treatment of acne, and its potential efficacy also needs to be clarified. Accordingly, the

objective of this study was to evaluate the efficacy and safety of combining isotretinoin and antihistamine compared to conventional single therapy of isotretinoin in acne patients. To our knowledge, this is the first report investigating the role of antihistamine for the treatment of acne in the clinical settings.

Methods

Study design and subjects

This study was designed as a 12-week, randomized, controlled open, with blinded assessment trial. It was not possible to blind either the patient or the therapist, but the examiner was blinded to group assignment during collection of the data. Forty Korean patients with moderate to severe acne were enrolled in this study (Table 1) from March 2013 to June 2013. The patients were classified into two groups: (i) Control group: treated with isotretinoin only (20 mg per day, approximately 0.2–0.4 mg/kg per day); and (ii) Treated group: combination therapy of isotretinoin and antihistamine, desloratadine (5 mg per day). Any other topical or systemic antiacne treatments except for standard washing procedures and moisturizing were not allowed. The patients were assessed at the beginning of treatment and at 2, 4, 8 and 12 weeks after treatment. Exclusion criteria prohibited enrolment of subjects with other systemic diseases, concurrent use of other acne therapies, other dermatological conditions requiring interfering treatment. Women were excluded if they were pregnant, nursing or planning a pregnancy. This study was approved by the Institutional Review Board of Chung-Nam National University Hospital (CNUH 2013-05-008).

Clinical outcome assessments

Before the initiation of the treatment, patients' demographic characteristics including age, gender and duration of acne were recorded. Digital photographs at baseline and at each follow-up visits were used for objective assessments. Measurement of non-inflammatory lesion (comedones) and inflammatory lesion (papules, pustules and nodules) counts was performed at each visit, and dermatological assessments were performed blind by three independent dermatologists.

Table 1 Baseline demographic and clinical characteristics of acne patients

	Isotretinoin (n = 20)	Isotretinoin + Desloratadine (n = 20)
Gender (n)		
Female	12	12
Male	8	8
Age (years, mean ± SD)	21.9 ± 2.1	21 ± 3.7
Duration (years, mean ± SD)	4.8 ± 2.76	4.6 ± 2.99
Dosage of isotretinoin (mg/kg per day, mean ± SD)	0.31 ± 0.05	0.29 ± 0.03
Baseline (n, mean ± SD)		
Non-inflammatory	43.6 ± 19.4	41.5 ± 17.7
Inflammatory	30 ± 15.5	30.6 ± 17
Total	73.7 ± 27.7	72 ± 14.9
GAGS (score, mean ± SD)	27.2 ± 6.09	28.2 ± 6.48

GAGS, global acne grading system.

The global acne grading system (GAGS) score was used for clinical grading of acne lesion.[15] GAGS divides the face, chest and back into six areas (forehead, each cheek, nose, chin and chest and back) and assigns a factor to each area on the basis of the surface area and distribution/density of pilosebaceous units. Each type of lesion is given a value depending on severity: no lesions = 0, comedones = 1, papules = 2, pustules = 3 and nodules = 4. The score for each area (Local score) is calculated using the formula: Local score = Factor × Grade (0–4). The global score is the sum of local scores, and 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.

Facial sebum secretion was measured using a Sebumeter (SM 815®; CL-Electronics, Cologne, Germany) at four different sites on each cheek. To avoid diurnal variation, sebum levels were measured at 10 am. Participants were asked not to put on any cosmetics for 2 h before the measurements. A constant temperature (20°C ± 1°C) and humidity (40% ± 2%) were maintained during sebum measurement. The Minolta CR-400 Chromameter (Minolta Holdings Ltd, Tokyo, Japan) was used to evaluate the erythema that resulted from inflammation of acne lesion by analysing the light source reflected from the flat glass applanation surface. Calibration was performed by using the white plate provided by the manufacturer.

At the end of the study, the participants documented their degree of satisfaction on a 4-point scale (4, very satisfied; 3, satisfied; 2, slightly satisfied; 1, dissatisfied). In both groups, the frequency and severity of acne flares were assessed. Severity of acne flare was ranked by using 4-point scale from none (no new nodule) to severe (>10). In addition, adverse events recorded at each follow-up visits were analysed. Side-effects were recorded at each visit which included incidence and severity of cheilitis, dry skin, mouth, nose and eyes, epistaxis, facial redness, rashes, hair loss, photosensitivity, nail changes and systemic side-effects like fatigue, bone/joint pains, muscular cramps etc.

Statistical analysis

Treatment effects between two groups were compared at each follow-up visits and the data were analysed using the t-test. P-value <0.05 was considered statistically significant.

Results

Demographic and baseline characteristics

Forty patients were included in this study: 20 patients in control group (12 women, 8 men), 20 patients in treated group (12

women, 8 men). The mean age of the patients was 21.9 years in control group and 21 years in treated group. The mean daily dosage of isotretinoin in control group was 0.31 mg/kg and 0.29 mg/kg in treated group. At baseline, the average numbers of non-inflammatory, inflammatory and total lesions were 43.6, 30.1 and 73.7 in control group and 41.5, 30.6 and 72 in treated group respectively. In addition, each group had average acne severity grade of 27.2 and 28.2, respectively, according to GAGS (Table 1). There was no significant difference in the number of acne lesions and GAGS score between the treatment and control groups at baseline.

Acne lesion counts and severity

Both the non-inflammatory lesions and inflammatory lesions decreased significantly during follow-up visits in both groups. In case of non-inflammatory acne lesions in treated group, the mean lesion counts reduced to 17.8% after 12 weeks of treatment, whereas those in control group revealed 44.8%. Similarly, inflammatory acne lesion counts in treated group were reduced to 22.9% and to 55.8% in control group after 12 weeks of treatment.

Accordingly, a significant difference of the mean non-inflammatory and inflammatory acne lesion count between the two groups was found after 12 weeks of treatment ($P < 0.001$), as well as the differences at 2, 4 and 8 weeks after treatment (Fig. 1a,b). This result is also applicable to the total acne lesion count (Fig. 1c).

As shown in fig. 2, acne severity grade improved in both groups according to GAGS during the follow-up visits of the study. Statistically significant differences between the two groups were found at 4, 8 and 12 weeks after treatment ($P < 0.05$). Changes in GAGS success were consistent with percentage change of total lesion counts from baseline. In the treatment group, 40% of the patients showed clearance of acne lesion with only residual hyperpigmentation/erythema, and 50% showed the improvement comparing to before treatment. There was no worsened patient in the treatment group. In the control group, although 20% of the patients showed clearance and 40% showed improvement, 10% of the patients showed worsen state comparing to baseline.

Figure 3 represents clinical photographs that illustrate more rapid improvements in the treatment group than in the control group.

Patient satisfaction

Using 4-point scale, nine patients (45%) in control group were 'slightly satisfied', seven patients (35%) were 'satisfied' and four patients (20%) were 'very satisfied'. In treated group, two patients (10%) were 'slightly satisfied', eight patients (40%) were 'satisfied' and 10 patients (50%) were 'very satisfied' after 8 weeks of combined treatment. Mean ± SD scores were 2.75 ± 0.18 in control group, and 3.4 ± 0.15 in treated group. A significant difference of scores for patient satisfaction was evident between the two groups ($P = 0.008$) (Fig. 4).

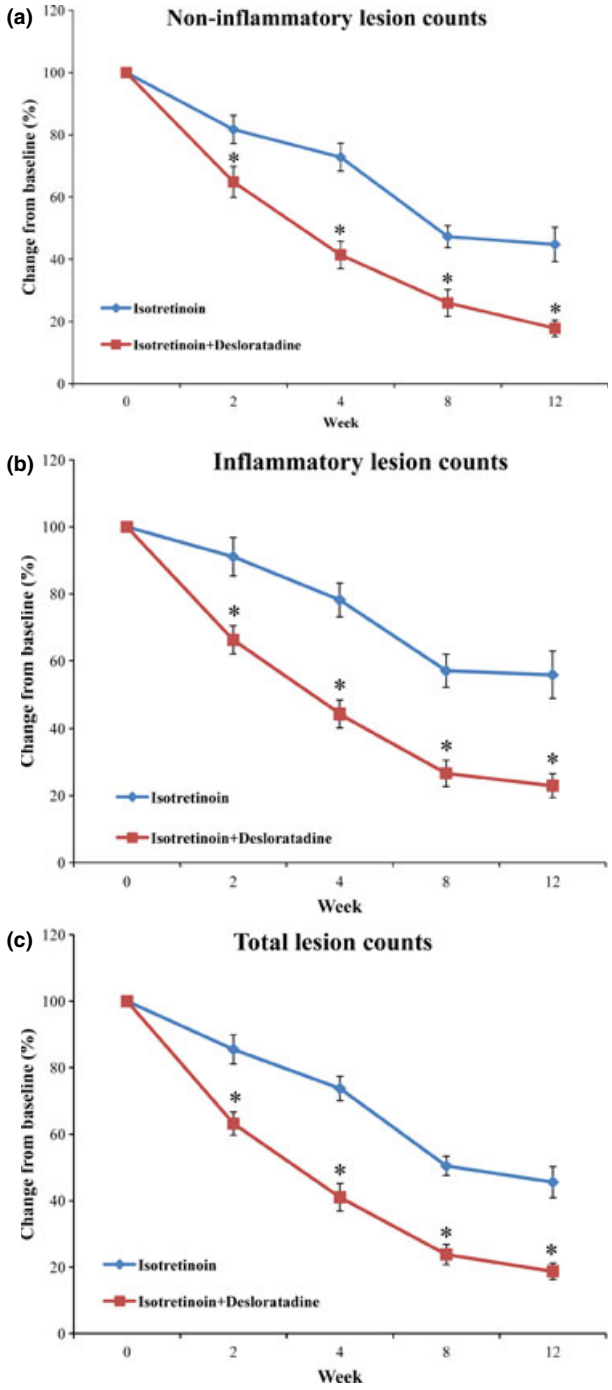

Figure 1 Median percentile changes from baseline in acne lesions. (a) Non-inflammatory. (b) Inflammatory. (c) Total differences between only isotretinoin and isotretinoin with desloratadine were all statistically significant (*$P < 0.05$).

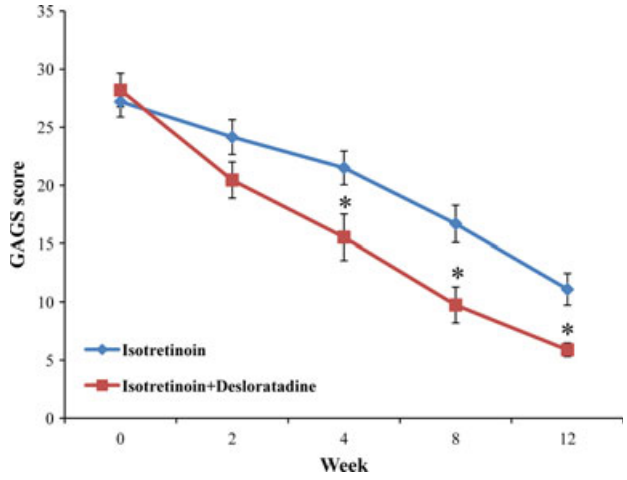

Figure 2 Physician's assessment using global acne grading system global score before treatment and at each visit. Changes in acne severity with time and differences between treated and control groups showed statistical significance at weeks 4, 8 and 12 (*$P < 0.05$).

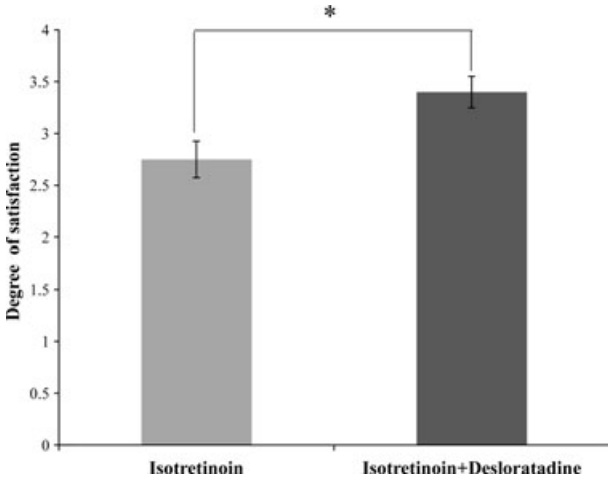

Figure 4 Differences in patients' subjective assessment of satisfaction between treated and control groups (*$P < 0.05$).

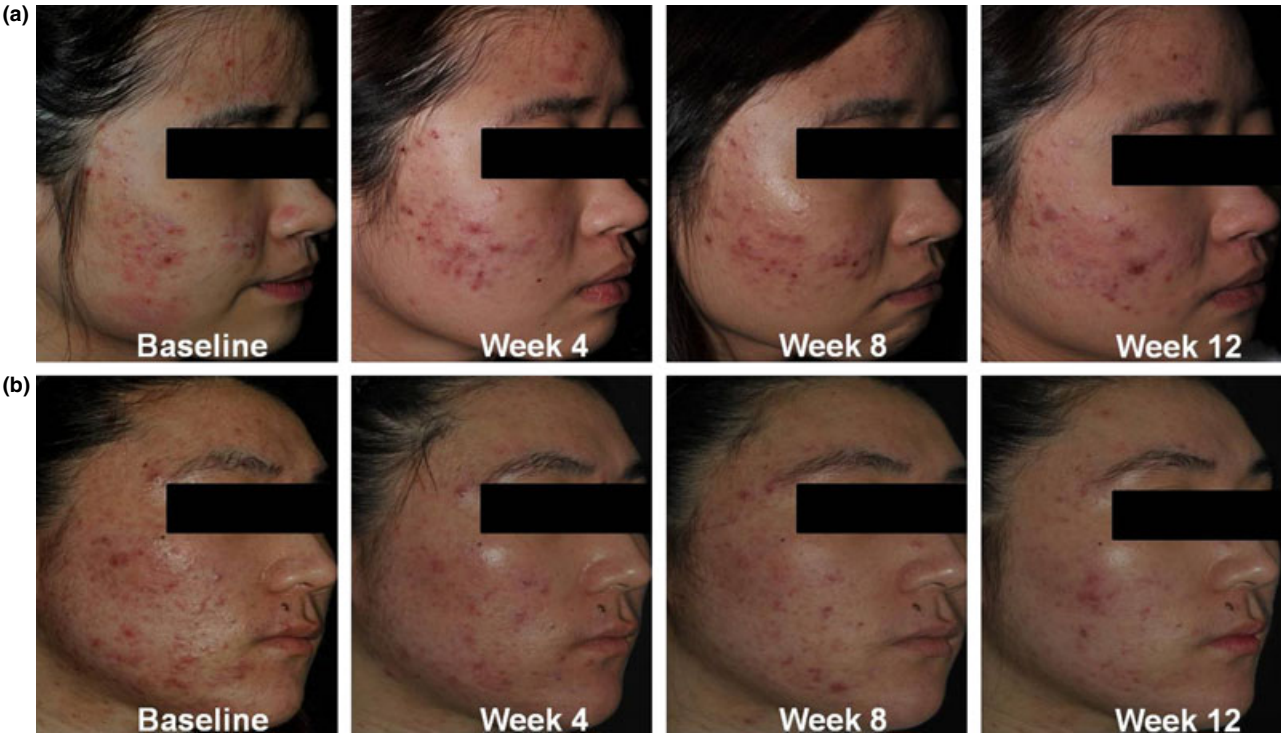

Figure 3 Photographs showing clinical improvement of acne patient; at baseline, after 4, 8 and 12 weeks of only isotretinoin (a) and isotretinoin combined with desloratadine (b).

Skin sebum and erythema measurement

During the follow-up visits after the treatment initiation, the sebum content levels (μg/cm^2) and the erythema scores (arbitrary unit) declined in both groups. In case of sebum levels, a significant difference was found between the two groups after 4, 8 and 12 weeks of treatment ($P < 0.05$). Furthermore, difference in erythema scores reached statistical significance from 2 to 12 weeks of treatment ($P < 0.05$) (Fig. 5).

Acne flare and side-effects

Six patients (34%) in control group experienced acne flares, whereas one patients (5%) in treated group. In addition, experiences of moderate-to-severe acne flares were evident in three patients (15%) in control group, while there was none in the treated group (Fig. 6).

No severe adverse events occurred during the study period. The most common side-effect in both groups was cheilitis characterized as dry lips (90% in control group, and 75% in treated group). Xerosis was the second most common side-effect, occurring in 45% of control group and 40% of treated group. Moreover, patients occasionally complained of pruritus, more frequently occurring in control group (45% in control group, and 15% in treated group). Although both groups were generally well tolerated, treated group relatively showed better tolerability in respect of less frequent experience of side-effects (Fig. 7).

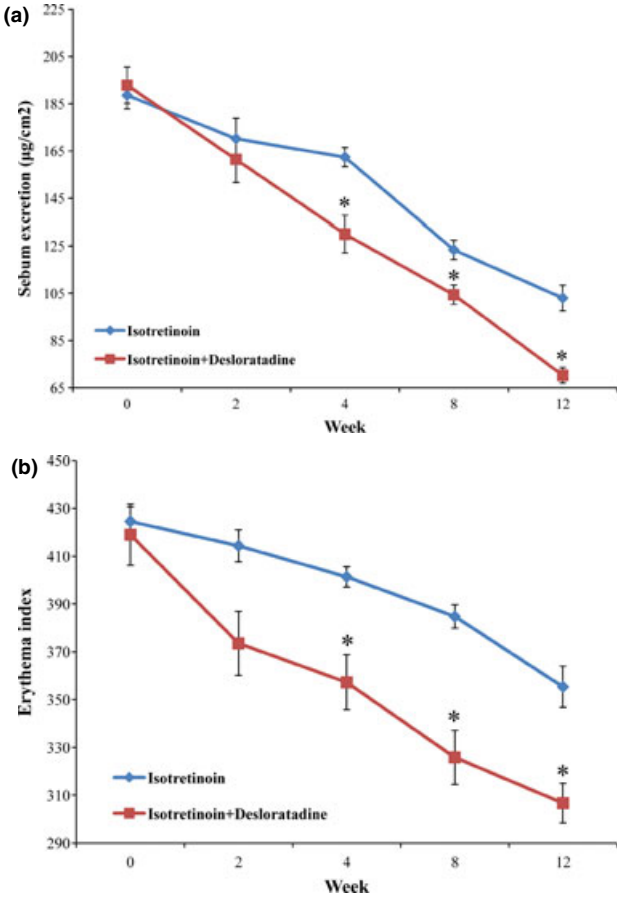

Figure 5 Changes in physical assessment with time and differences between treated and control groups (*$P < 0.05$). (a) Sebum level ($P = 0.005$, at week 4), (b) Erythema score ($P = 0.02$, at week 2).

Discussion

H1-receptor antagonist is an antihistamine, which are among the most widely used medications in the world. To treat inflammatory skin diseases, administration of medications is required such as a therapeutically effective antihistamine, a leukotriene receptor antagonist, or other anti-inflammatory drug alone or in combination. Because the inflammatory response of the acne lesion is mediated by the release of histamines and leukotrienes, the introduction of antihistamine may effectively prevent the formation of new acne lesions and exert a significant impact on the resolution of old lesion. In addition, as it has been discussed in literature, histamine-1 receptor is expressed in sebaceous glands, and a histamine-1 receptor antagonist significantly decreases squalene levels, leading to a new paradigm for antiacne therapy as an inhibitor of sebum production.[12] However, there have been no previous studies evaluating the practical efficacy and safety of antihistamine in the treatment of acne.

Oral isotretinoin is indicated to treat moderate to severe acne unresponsive to other therapies. It is the only drug currently available that affects each of the pathogenic factors involved in acne.[16,17] However, due to dose-dependent side-effects of isotretinoin, caution is required in using the drug. Moreover, severe acne flare at the beginning of isotretinoin therapy leads to discontinuation of this drug. To overcome these concerns, several studies suggested low-dose regimen rather than conventional recommended daily dose of 0.5–1.0 mg/kg.[17] However, effect in severe cases has not been proven with low-dose regimen. To evaluate the capability of antihistamine overcoming limitation of low-dose regimen, moderate to severe acne patients were enrolled in this study. Based on the previously discussed role of histamine in acne pathogenesis, an *in vitro* study demonstrating the possible effect of antihistamine and the results of our study,

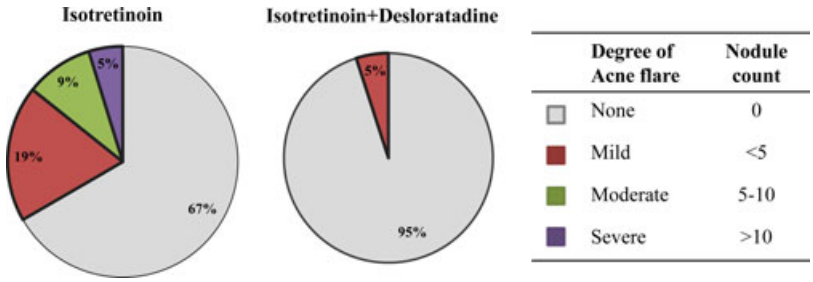

Figure 6 Frequency and severity of acne flare in each group.

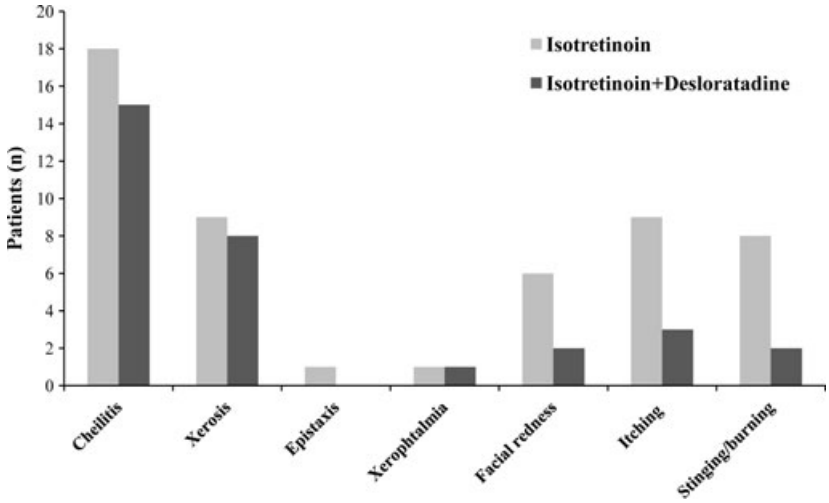

Figure 7 Overall side-effects recorded during follow-up visits in each group.

we could describe several positive aspects of antihistamine as an adjuvant treatment in acne. Through reducing inflammation and sebum, antihistamine could synergize the effects of isotretinoin and thus cutting down the dosage of isotretinoin. This leads to minimizing the adverse effects of isotretinoin. In addition, as it is proved in our study, antihistamine might assist in preventing the occurrence and severity of acne flares. These results suggest that additional administration of antihistamine to isotretinoin is preferable to single regimen of isotretinoin in terms of efficacy, patient satisfaction and tolerability.

Desloratadine is a new, selective, H1-receptor antagonist that also has anti-inflammatory activity. It is the primary active metabolite of loratadine. Early studies demonstrated that desloratadine is approximately 10–20 times more potent in binding to H1-receptor than loratadine, *in vitro* and has 2.5–4 times more antihistaminic potency in animals.[18,19] Desloratadine was also shown to have a significantly longer half-life than loratadine.[20] *In vitro* studies have shown that desloratadine inhibits the release or generation of multiple inflammatory mediators, including IL-4, IL-6, IL-8, IL-13, prostaglandin, leukotriene, tryptase and histamine.[21–23] Furthermore, because of its safety and no drug interaction with isotretinoin, Desloratadine possesses several advantages.

Itching may accompany acne lesions and may have a significant negative influence on patients' well-being.[14] Acne itching should be considered an important target for antipruritic therapy. The use of antihistaminic agents has been sufficiently proved, especially those presenting with symptoms of dermographism.[24] As seen in our study, patients complaining of itching occurred less frequently in treated group. Other considered strengths of antihistamine include antianxiety effect of sedative antihistamine lessening further hormonal derangement in patients with acne.[25] In addition, based on the fact that mast cells might have a central role in skin remodelling and fibrosis, this can complicate acne lesions by scar formation.[25,26] Thus, mast cell stabilizers such as ketotifen, also a histamine H1-receptor antagonist, has a preventive effect in development of this complication.[25,27]

The main limitation of this study is that follow-up evaluation was not performed. Larger studies with longer follow-up period are needed to support this new treatment approach. Even more, we encourage further studies evaluating the efficacy of antihistamine as a single therapeutic method as well as a maintenance therapy after achieving remission of disease using isotretinoin.

In conclusion, the results of this study identified an obvious clinical benefit for antihistamine as an adjuvant treatment of isotretinoin for patients with moderate to severe acne along with well tolerability and higher satisfaction scores. Furthermore, the results suggest that antihistamine may interfere with progression of acne and combination with isotretinoin can be a new candidate for antiacne treatment.

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