Original Article

The Adjunctive Effect of Desloratadine on the Combined Azithromycin and Isotretinoin in the Treatment of Severe Acne: Randomized Clinical Trial

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Abstract

Background: Desloratadine, when combined with isotretinoin, had a favorable effect in the treatment of moderate acne; however, its effect in severe nodulocystic acne remained to be elucidated. **Aim of the Study:** The aim of the study was to evaluate the effect of adding oral desloratadine to the combined azithromycin and isotretinoin regimen for severe acne. **Patients and Methods:** Patients were randomly classified into two groups: 1st (control) included 38 patients and received alternating isotretinoin and azithromycin orally and 2nd (intervention) group included 38 patients and received same regimen plus desloratadine 5 mg/day. Assessment was made at baseline, 4, 8, and 12 weeks of the trial. **Results:** In both groups, there was statistically significant reduction in count of inflammatory lesions at 12 weeks compared to baseline (59 ± 19–9 ± 7 for 2nd group and from 57 ± 18 to 21 ± 8 for control) ($P < 0.05$) and it was significantly higher in 2nd than in 1st control ($P < 0.05$). Significant reduction in non-inflammatory lesions count (from 18 ± 3 to 8 ± 2 and 18 ± 4 to11 ± 2 for 2nd and 1st group, respectively). At 12th week, 19 (50%) patients in the intervention and 12 (31.6%) of control groups were achieved excellent improvement (>80%). **Conclusion:** Oral desloratadine had antiacne properties, and when combined with azithromycin plus isotretinoin protocol, it significantly improves severe acne lesions and minimizes the adverse drug reactions.

Keywords: Acne, desloratadine, nodulocystic, severe

Introduction

Acne is a chronic inflammatory disease of the pilosebaceous units. It is characterized by open and closed comedones, erythematous papules, and pustules, and in more severe cases, nodules, deep pustules, and pseudocysts. In some cases, it is accompanied by scarring. The condition usually starts at adolescence and resolved by mid-20s.[1] The pathogenesis of acne is multifactorial; basic steps have been identified: seborrhea, comedone formation, overgrowth of microorganisms, particularly *Propionibacterium acne,* and inflammation.[2] The presence of histamine-1 receptor (H-1 receptor) in the sebocytes was revealed by reverse transcriptase-polymerase chain reaction analysis and immunofluorescence of an immortalized sebocyte cell line (SZ95) and thus indicated that histamines, and conversely, antihistamines could potentially modulate sebocyte function directly.[3] When sebocytes were incubated with an H-1 receptor antagonist, diphenhydramine, a significant decrease in squalene levels, a biomarker for sebum, was observed.[3]

The combination of a squalene-reducing agent with retinoid is, particularly, interesting because retinoids reduce sebum in general, but they have little effect on squalene.[4] Therefore, antihistamine activity in sebocytes might represent an alternative or, perhaps, an adjunctive treatment to retinoid therapy for acne. Desloratadine, the active metabolite of loratadine, is a second-generation nonsedating oral antihistamine with proven efficacy in randomized, controlled clinical trials and a safety and tolerability profile similar to placebo.[5,6] It is along acting tricyclic antihistamine, anti-inflammatory, mast cell degranulation inhibitor,[7,8] and has antichemotactic activities against many inflammatory cells,[9,10] in addition to its sebum regulatory effect.[3] Accordingly, we hypothesized that desloratadine may

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have an antiacne potential and it may mitigate the adverse effects of systemic medications used in severe acne, to test this theory, we sought to evaluate the effect of adding desloratadine to the combined azithromycin and isotretinoin alternating day protocol for treatment of severe nodulocystic acne in terms of efficacy, adverse events, and patients' satisfaction.

Patients and Methods

The study was a prospective, randomized, comparative, open-label clinical trial conducted on ninety patients at Basra General Hospital Outpatient Clinic at the period from October 1, 2015, to October 1, 2016. During this period, 560 acne patients were screened and only 90 patients with severe and nodulocystic acne (Grade 4 and 5 according to the US FDA global score[11]) were enrolled in the study, 76 of them were completed the study period. The main exclusion criteria were pregnant women or planning to have pregnancy, history of macrolide allergy, patients with any biochemical abnormalities at baseline investigations, and patients with previous topical or systemic retinoids therapy. Participants who already on anti-acne medications, a washout period for 2 weeks for topical and 4 weeks for oral medication was carried out. Patients who met the inclusion and exclusion criteria were carefully interrogated and a full detailed history was obtained. They were informed about the nature of the study and written informed consents were obtained from them.

Patients were randomly (1:1) allocated into two groups: 1st control group (38 patients) and received oral isotretinoin 20 mg 3 times per week on Sunday, Tuesday, and Thursday plus azithromycin 500 mg on Saturday, Monday, and Wednesday after meal for a total period of 12 weeks and 2nd intervention group (38 patients) received the same regimen above plus oral desloratadine 5 mg at morning daily for 12 weeks. A follow-up every 4 weeks for 12 weeks was performed to assess the clinical response and to report any drug adverse effects. Patients' satisfaction was recorded at the end of the trial [Flow Diagram 1].

Baseline investigations were done including complete and differential blood count, lipid profile, renal function, liver function, and pregnancy test. Patients were informed not to use any topical or systemic antiacne therapy except topical rinse off cleanser.

The efficacy of therapy was assessed in both groups by numerical counting of each inflammatory lesion (papules, pustules, nodules, and cysts) and noninflammatory lesion (comedones) at the affected areas (face, upper chest, upper back, and shoulders) at baseline, 4th, 8th, and 12th week of the trial using the following parameters:

1. Calculating and comparing the mean number of each acne lesion (comedone, papule, pustule, nodule, and cyst)
2. Calculating the percentage of total reduction of acne lesions at 12th week and compared to baseline
3. Grading the response according to the percentage of total reduction in acne lesions as follows: >80% reduction = excellent, 60%–79% reduction = good, 40%–59% reduction = moderate, and <40% reduction = poor response
4. Recording the adverse effects in both groups at each visit.

At the end of the study, the degree of patients' satisfaction was assessed in each group using 4-point satisfaction scale as follows: 3 = very satisfied, 2 = satisfied, 1 = slightly satisfied, and 0 = unsatisfied.

Statistical analyses of changes from baseline to 12th week in both inflammatory and noninflammatory acne lesion counts were analyzed using statistical package SPSS version 20, IBM Corporation. The quantitative data were recorded using range, means, standard deviation, and percentage. Comparison between two groups was done using *t*-test analysis, $P \leq 0.05$ was considered statistically significant.

Results

Seventy-six patients were completed the study period [Table 1]. The duration of their acne was ranged from 10 to 60 months (mean = 25 ± 12).

In both groups, there was a significant reduction of the inflammatory lesions count at the end of the trial compared to baseline (the mean was reduced from 59 ± 19 to 9 ± 7 for intervention and from 57 ± 18 to 21 ± 8 for control) ($P < 0.05$). In comparison, the number of inflammatory lesions was more significantly reduced in the intervention than in control group [Table 2 and Figure 1].

For both groups, the onset of response to treatment among different types of acne lesions was variable, the pustules were responded earlier than other types (within 1st month), and significant reduction in the intervention group when compared to control (18 ± 4–6 ± 1 versus 19 ± 2–14 ± 3), $P < 0.05$ [Table 3].

Table 1: Demographic criteria and baseline characteristics of participants

	Cases group	Control group
Sex	38	38
Male	17	15
Female	21	23
Mean age (year)±SD	19±2	19±2
Duration (months)±SD	25±12	26±13
Inflammatory lesion count (mean±SD)	59±19	57±18
Noninflammatory lesion count (mean±SD)	18±3	18±4

SD: Standard deviation

Table 2: Mean±standard deviation of inflammatory lesions before and after treatment in both groups

	Cases	Control	*P*
Baseline	59±19.37	57.6±18.1	0.77
12th week	9.4±7	21±8.5	<0.05*
P	<0.05*	<0.05*	

Data presented as (mean±SD), **P*-value significant ≤0.05. SD: Standard deviation

Table 3: Mean number of acne lesions in intervention (n=38) and controls (n=38) at baseline and during course treatment

	Lesions									
	Papules		Pustules		Nodules		Cysts		Comedones	
	Groups intervention	Groups control	Groups intervention	Groups control	Groups intervention	Groups control	Groups intervention	Groups control	Intervention	Control
Time										
Baseline	33±9	31±7	18±4	19±2	5±1	5±1	1±0	1±0	18±3	18±4
P	0.55		0.78		0.64		0.65		0.9	
4 weeks	21±5	25±4	6±1	14±3	3±0	3±1	0.8±0	1±0	14±3	16±3
P	0.08		<0.05*		0.48		0.26		0.32	
8 Weeks	13±3	17±3	2±0	8±1	2±0	2±0	0.4±0	0.8±0	11±2	12±3
P	0.05*		<0.05*		0.32		0.01*		0.59	
12 weeks	7±2	12±2	1±0	6±2	0.8±0	1±0	0.2±0	0.5±0	8±2	11±2
P	<0.05*		0.00*		0.008*		0.02*		0.1	

Data presented as (mean±SD), **P*-value significant ≤0.05. SD: Standard deviation

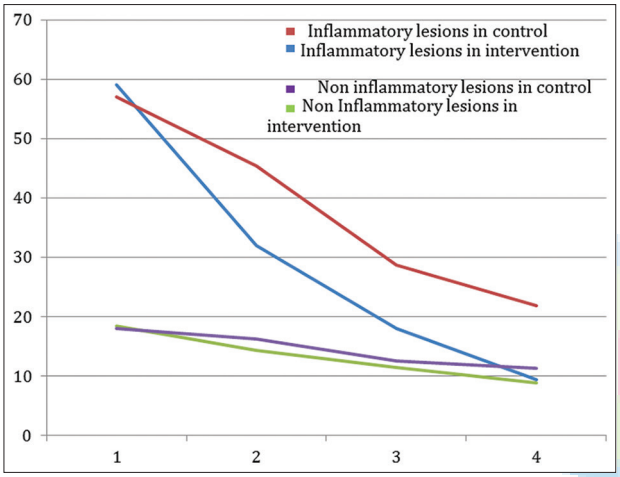


Figure 1: Mean number of acne lesions count at baseline and during follow-up 4 weeks intervals

Furthermore, at the end of the trial, the pustules showed the highest percentage of reduction (95% for intervention and 69% for control), whereas the papules showed 78% reduction for intervention and 58% for control, 86% for nodules in intervention, and 65% in control, the difference was statistically significant ($P < 0.05$) [Table 4 and Figures 2,3].

Although there was no statistical difference between both groups regarding the noninflammatory lesions count [Table 3 and Figure 1], there was a significant reduction of comedones counts at the end of the trial compared to baseline (18 ± 3–8 ± 2 and 18.1 ± 4.3–11 ± 2 for intervention and control, respectively) [Table 3].

Nineteen (50%) patients in the intervention group were achieved excellent response, whereas 12 (31.6%) of control group showed similar improvement, none of the intervention group, and 3 (7.9%) of control showed poor response [Table 5].

Twenty-nine (73.7%) patients of intervention and 20 (52.6%) of control groups were very satisfied with the improvement they achieved, while none of intervention and two (5.3%) of controls were unsatisfied with the results.

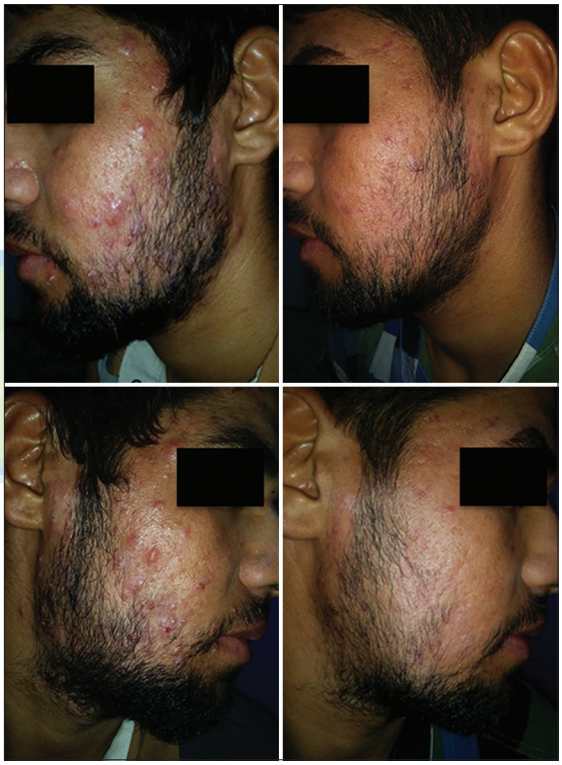


Figure 2: A 22-year-old adult male in intervention group with severe acne vulgaris before and 12 weeks after treatment showed dramatic improvement of the inflammatory lesions

The most common side effects of both treatment regimens were mucocutaneous and gastrointestinal. Dryness of the face being the most frequent in both groups and gastrointestinal symptoms were less frequent in intervention than in control group ($P < 0.05$) [Table 6].

Discussion

Acne vulgaris is a very common skin disease with high prevalence rate among adolescent. In Iraq, acne vulgaris is prevalent in 73% of males and 62% of females in the adolescent population.[12]

Table 4: Percentage of reduction of the acne lesions count from the baseline to the end of the treatment for intervention (*n*=38) and controls (*n*=38)

	Lesion									
	Papule		Pustule		Nodule		Cyst		Comedon	
	Case (%)	Control (%)	Case (%)	Control (%)	Case (%)	Control (%)	Case (%)	Control (%)	Case (%)	Control (%)
Time										
4 weeks	38	17.5	66	22.4	31	25	49	14.5	20.7	11
P	<0.05*		<0.05*		0.44		<0.05*		0.06	
8 weeks	62	43.8	86	55	60	50	80	31	40	30
P	<0.05*		<0.05*		0.17		<0.05*		0.06	
12 weeks	78	58	95	69	86	65	91	60	52	37
P	<0.05*		<0.05*		0.001*		<0.05*		0.002*	

Data presented as (mean, percentage of reduction), (**P* value significant ≤0.05)

Table 5: Scoring the response for intervention (*n*=38) and controls (*n*=38) according to the percentage of total reduction in acne lesions

Percentage of reduction	*n* (%) of patients	
	Intervention group	Control group
≥80% reduction (excellent)	19 (50)	12 (31.6)
60-79% reduction (good)	15 (39.5)	13 (34.2)
40-59% reduction (moderate)	4 (10.6)	10 (26.3)
<40% reduction (poor)	0	3 (7.9)

Table 6: Adverse reactions to the treatment regimens in intervention (*n*=38) and controls (*n*=38)

Adverse reaction	Intervention group	Control group
Dryness of face	30 (78.9)	28 (73)
P	0.078	
Cheilitis sicca	22 (57.9)	34 (89)
P		<0.05*
Erythema	8 (21)	8 (21)
P	1	
Peeling	4 (10)	7 (18)
P	0.335	
Mild abdominal pain	12 (32)	18 (47)
P	0.163	
Diarrhea	4 (10)	6 (16)
P	0.504	

*Significant *P*≤0.05

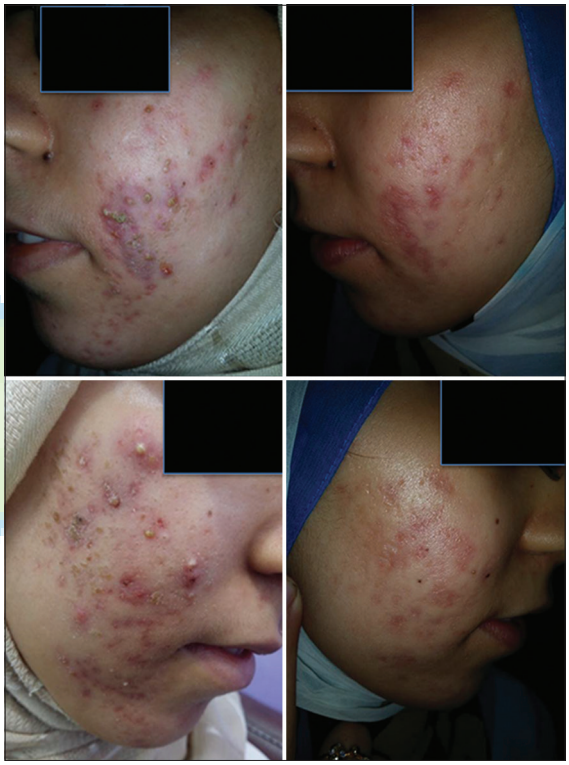
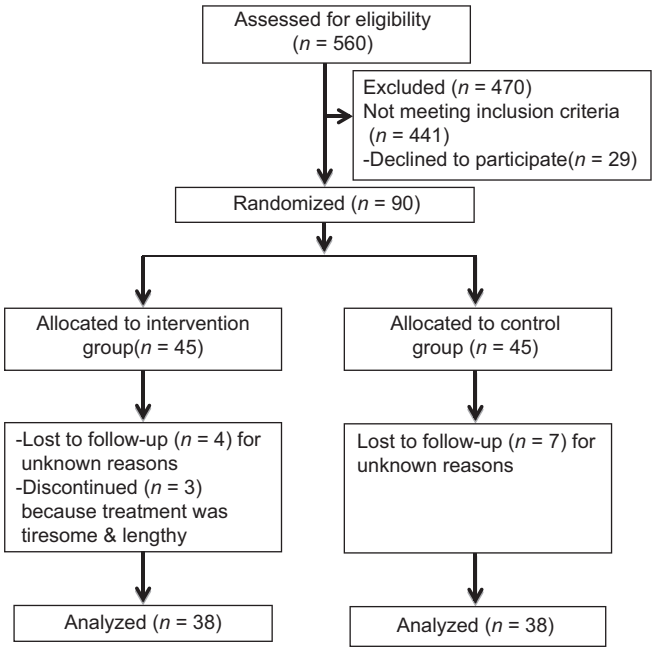


Figure 3: A 17-year-old adolescent female in intervention group with severe acne at baseline and 12 weeks after treatment showed remarkable improvement of inflammatory lesions leaving minimal scar and erythema

A recently published study demonstrated the effectiveness and safety of combined oral azithromycin and isotretinoin on alternative daily regimen in the treatment of severe and nodulocystic acne.[13] However, such treatment was frequently accompanied by intolerable adverse reactions including mucocutaneous and gastrointestinal manifestations; therefore, to optimize the efficacy and to minimize the unwanted side effects of such combination, we attempted to evaluate if there is any beneficial effect from adding oral antihistamine (desloratadine 5 mg/day) as adjuvant therapy to the combined azithromycin and isotretinoin in a randomized clinical trial for the treatment of severe and nodulocystic acne.

In the present study, we demonstrated that adding oral desloratadine to the combined treatment regimen provide a better outcome and advantage in terms of efficacy and tolerability than combined treatment alone. In general, antihistamines had a sebum regulating effect; notably, they reduce squalene release, a biomarker of sebum,[3] from sebaceous glands by blocking the overexpressed histamine receptors in sebocytes, resulting in low squalene level and this phenomenal effect will not be influenced by concomitant isotretinoin therapy because retinoids were lacking the squalene-reducing property[4]. Furthermore, low release of sebum will, in turn, minimize microcomedone formation and subsequent inflammation.[3] Furthermore, antihistamines had



Flow diagram 1: Flow chart of the trial show the progress of participants during the study period

a remarkable anti-inflammatory and antipruritic effects,[14] thereby minimizing the inflammation and scar formation.[15]

Lee *et al*., in 2014, published a comparative study addressing the effect of adding antihistamine on the outcome of acne treatment.[16] The authors pointed out that patients with a moderate type of acne were treated with isotretinoin on daily regimen basis in addition to oral desloratadine and they achieved 77.1% reduction in the inflammatory lesions at the end of the trial. Comparatively, our patients showed a higher reduction (87.5%) of their inflammatory lesions despite that they had severe nodulocystic type and this may be partly explained by the therapeutic effect of oral azithromycin in our regimen.

Different types of inflammatory lesions responded variably to treatment; the pustules in those who received additional desloratadine demonstrated earlier reduction (within first 4 weeks of treatment) compared to the control group; this finding is difficult to explain, however, it may be related to the synergistic effect of desloratadine in ameliorating the inflammatory acne lesions and to its indirect antichemotactic effect by reducing the release of leukotrienes and chemotactic substances from mast cells.[7,8] An evidence for the involvement of inflammatory events in the very earliest stages of acne lesion development was shown by Jeremy *et al*.[17] Moreover, his observation suggests that the favorable effect of desloratadine may not only involve the already formed lesions but also in prevent new lesion development.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Layton AM. Disorder of the sebaceous glands. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's Textbook of Dermatology. 8th ed., Vol. 42. London: Blackwell Publishing Company; 2010. p. 1-89.
2. Habif TP. Acne, rosacea and related disorder. In: Clinical Dermatology: A Color Guide to Diagnosis and Therapy. 4th ed., Vol. 7. China: Mosby; 2004. p. 162-262.
3. Pelle E, McCarthy J, Seltmann H, Huang X, Mammone T, Zouboulis CC, *et al.* Identification of histamine receptors and reduction of squalene levels by an antihistamine in sebocytes. J Invest Dermatol 2008;128:1280-5.
4. Zouboulis CC, Korge B, Akamatsu H, Xia LQ, Schiller S, Gollnick H, *et al.* Effects of 13-cis-retinoic acid, all-trans-retinoic acid, and acitretin on the proliferation, lipid synthesis and keratin expression of cultured human sebocytes *in vitro*. J Invest Dermatol 1991;96:792-7.
5. Breathnach SM, Smith CH, Chalmers RJ, Hay RJ. Systemic therapy. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's Text Book of Dermatology. 8th ed., Vol. 74. Singapore: Blackwell Scientific Publication; 2010. p. 3926.
6. Bousquet J, Bachert C, Canonica GW, Mullol J, Van Cauwenberge P, Bindslev Jensen C, *et al.* Efficacy of desloratadine in intermittent allergic rhinitis: A GA(2) LEN study. Allergy 2009;64:1516-23.
7. Lippert U, Möller A, Welker P, Artuc M, Henz BM. Inhibition of cytokine secretion from human leukemic mast cells and basophils by H1- and H2-receptor antagonists. Exp Dermatol 2000;9:118-24.
8. Weller K, Maurer M. Desloratadine inhibits human skin mast cell activation and histamine release. J Invest Dermatol 2009;129:2723-6.
9. Vignola AM, Crampette L, Mondain M, Sauvère G, Czarlewski W, Bousquet J, *et al.* Inhibitory activity of loratadine and descarboethoxyloratadine on expression of ICAM-1 and HLA-DR by nasal epithelial cells. Allergy 1995;50:200-3.
10. Agrawal DK, Berro A, Townley RG. Desloratadine attenuation of eosinophil chemotaxis, adhesion, and superoxide generation. Allergy 2000;55 Suppl 63:S276.
11. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Acne Vulgaris: Developing Drugs for Treatment; 2005.
12. Sharquie KE, Al-Hamdi KI, Noaimi AA, Al-Battat RA. Scarring and none scarring facial acne vulgaris and the frequency of associated skin diseases. Iraqi Postgrad Med J 2009;8:11.
13. Dhaher SA, Luaibi MR. Efficacy & safety of combined isotretinoin & azithromycin for treatment of severe nodulocystic acne. Med J Basra Univ 2016;34:68-76.
14. Zouboulis CC, Nestoris S, Adler YD, Orth M, Orfanos CE, Picardo M, *et al.* A new concept for acne therapy: A pilot study with zileuton, an oral 5-lipoxygenase inhibitor. Arch Dermatol 2003;139:668-70.
15. Wilgus TA, Wulff BC. The importance of mast cells in dermal scarring. Adv Wound Care (New Rochelle) 2014;3:356-65.
16. Lee HE, Chang IK, Lee Y, Kim CD, Seo YJ, Lee JH, *et al.* Effect of antihistamine as an adjuvant treatment of isotretinoin in acne: A randomized, controlled comparative study. J Eur Acad Dermatol Venereol 2014;28:1654-60.
17. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol 2003;121:20-7.