

CASE SERIES

Rosacea in Adolescents and Young Adults: High Prevalence Concurrent with Acne Vulgaris Treated with Benzoyl Peroxide and/or Adapalene

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ABSTRACT

BACKGROUND

The incidence of rosacea in adolescents and young adults with acne vulgaris has been increasing; however, the underlying factors and clinical symptoms have not been clearly described.

AIM

To investigate the factors underlying the recent increase in the prevalence of rosacea with acne vulgaris, with a focus on changes in social and medical factors over the past decade.

METHODS

A case series of rosacea conducted from April 2022 to May 2023. Characteristics and clinical symptoms of rosacea with acne vulgaris in adolescents and young adults were investigated. As a countermeasure against rosacea, two-color (blue and red) light-emitting diodes (LED) were irradiated.

RESULTS

Of the total 84 patients with rosacea, 34 (40.8%) had rosacea with acne vulgaris. All patients had onset before the age of 30 years, particularly in the teenage years (25 cases). All patients with rosacea and acne vulgaris developed rosacea during benzoyl peroxide and/or adapalene (BPO/adapalene) therapy, with a higher incidence in females than in males. During the study period, 863 patients with acne vulgaris were identified in the author's clinic, and 34 (3.9%) had rosacea and acne vulgaris. Among the 863 patients with acne vulgaris, 437 (50.6%) were using BPO/adapalene, whereas all (100%) patients with rosacea and acne vulgaris were using BPO/adapalene ($p = 0.0083$). Among the female patients with acne vulgaris, 265 used BPO/adapalene, and 29 (10.9%) developed rosacea. Contrastingly, 172 males used BPO/adapalene, and 5 (2.9%) developed rosacea, which was a lower rate than that in females ($p = 0.0051$).

CONCLUSION

In the present study, all patients with rosacea and acne vulgaris had an age of onset of less than 30 years, and most were teenage females. All patients developed rosacea during BPO/adapalene therapy for acne vulgaris and wore masks for at least 6 hours per day. Rosacea in patients with acne vulgaris may be induced by BPO/adapalene and prolonged mask-wearing. Preventing rosacea development during acne vulgaris treatment is important, especially in female adolescents; mask-wearing should be avoided as much as possible, and additional LED therapy may help prevent rosacea during BPO/adapalene therapy.

KEYWORDS

Acne vulgaris; Adapalene; Adolescent; Benzoyl peroxide; Light-emitting diodes; Rosacea

INTRODUCTION

Rosacea is a chronic inflammatory skin disease characterized by transient or persistent erythema, telangiectasia, papules, and pustules which are predominantly distributed in the centropalpebral region [1-5]. The estimated global prevalence of rosacea is 5.46% in the adult population. Regarding sex and age, rosacea affects both females (5.41%) and males (3.90%) and is mainly present among individuals aged 45 years - 60 years [6]. Rosacea usually begins between the ages of 30 years and 50 years but can occur at any age [2,4].

Previously, rosacea was classified into four subtypes; [1,7,8] however, current guidelines recommend a phenotypic approach that fully considers patient characteristics and facilitates personalized treatment. Specific diagnostic features include persistent centropalpebral erythema with periodic intensification by potential trigger factors, along with phymatous changes [3,9]. In the absence of these features, a diagnosis of rosacea can be established by the presence of at least two of the following major features: flushing (transient central facial erythema), inflammatory papules and pustules, telangiectasia, and/or eye symptoms (e.g., lid margin telangiectasia, blepharitis, keratitis, conjunctivitis, or sclerokeratitis) [3,9].

Although the pathophysiology of rosacea has not been fully elucidated, inflammatory pathways involved in rosacea pathogenesis include immune dysregulation and neurocutaneous mechanisms [10,11]. Clinical observations and the results of histopathologic studies suggest that pilosebaceous follicle inflammation is central to rosacea pathogenesis [12,13], and microorganisms may contribute to rosacea development [14,15]. Disruption of the epidermal barrier in rosacea is associated with altered microbial flora, [14-18] and both can induce the activation of innate and adaptive immunity [15]. In rosacea, activation of innate immunity leads to the upregulation of keratinocyte-derived Toll-like receptor 2 (TLR-2) and proteinase-activated receptor 2 [19]. These proteins promote expression of the antimicrobial peptide cathelicidin, which is then converted to bioactive LL-37 by kallikrein-5 (KLK-5) protease; LL-37 is associated with increased innate cutaneous inflammation, vasodilation, and vascular proliferation, all of which are characteristic features of rosacea [19-24].

Acne vulgaris is a common chronic inflammatory skin disease that occurs in approximately 80% of young adults and adolescents. This disease affects pilosebaceous units in the skin and can cause inflammatory or non-inflammatory lesions [25-27]. The four main pathological factors involved in acne development are increased sebum production, irregular follicular desquamation, *Propionibacterium acnes* (*P. acnes*) proliferation, and regional inflammation [28,29]. Cutaneous microbiome dysregulation and altered epidermal barrier function are

suspected to have important roles in acne vulgaris and rosacea [16,30]. In the protracted inflammation stage of acne vulgaris, *P. acnes* induces inflammatory cytokine responses via TLR-2 activation [31]. TLR-2 expression is increased in the sebaceous glands of adult women with acne lesions; its expression was significantly reduced after treatment with a topical azelaic acid gel, which results in clinical improvement [32] Azelaic acid also inhibits skin proteases and Toll-like receptor expression in rosacea [33].

As noted above, rosacea and acne vulgaris share a common etiology; however, few studies have reported on patients with concurrent acne vulgaris and rosacea. In 2020, Chen et al. [34] reported an increase in the incidence of rosacea in young people; they described 563 patients (mean age, 23.2 years) with rosacea and acne vulgaris using the phrase “rosacea in acne vulgaris.” In that study, the authors comprehensively examined factors associated with rosacea development; frequent makeup use, family history, and age at acne onset were mentioned as contributing factors. However, the reason for the increased incidence of rosacea with acne vulgaris in young people is still unclear.

The author’s clinic is also seeing an increase in cases of rosacea with acne vulgaris. In April 2022, the author began documenting patients with rosacea and analyzed the characteristics, clinical manifestations, and dermoscopy findings of patients with rosacea and acne vulgaris.

CASE SERIES

Diagnosis

This series included patients with rosacea and excluded those with skin lesions of atopic dermatitis or seborrheic dermatitis on the face, who had received topical steroids or tacrolimus on the face, and with collagen diseases. Consent for the publication of treatment-related photographs was provided by all patients.

The diagnosis and severity of rosacea and acne vulgaris were determined based on clinical features [8,35] and dermoscopy findings [8,35]. Although dermoscopy is not essential for the diagnosis of rosacea, it is particularly useful in confirming telangiectasia.

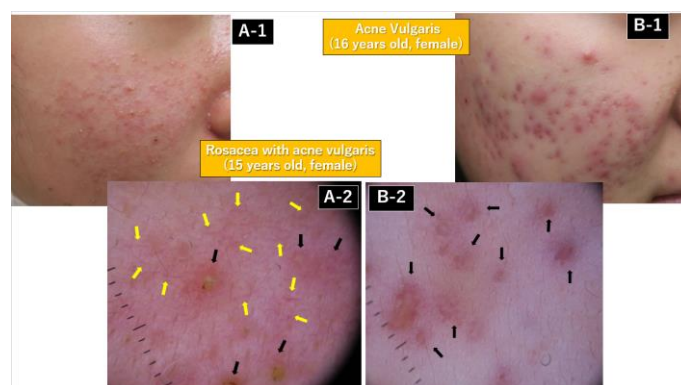


Figure 1: Comparison of clinical and dermoscopy findings in rosacea and acne vulgaris vs acne vulgaris alone. In rosacea with acne vulgaris, erythema of the face (A-1) with dermal telangiectasia (A-2, yellow arrows) are observed. The patient with acne vulgaris also exhibits a follicular reddish halo and/or perifollicular telangiectasia, regardless of rosacea status (A-2, B-2, black arrows).

Figure 1 compares the clinical and dermoscopy findings between a case of rosacea with acne vulgaris and that with acne vulgaris alone. There are facial erythema and dermal telangiectasia in case of rosacea with acne (Figures

A-1, B-1, A-2; yellow arrows), whereas follicular reddish halos or perifollicular telangiectasia was seen in both cases (Figures A-2, B-2; black arrows).

When skin lesions associated with acne vulgaris and rosacea are both present, it is sometimes difficult to clearly distinguish these lesions (e.g., acne papules vs. rosacea papules) and evaluate the severity of each disease. Therefore, when the concurrent presence of these diseases hindered detailed analysis, emphasis was placed on the coexistence of both diseases rather than the severity of each disease.

Characteristics of Patients with Rosacea and Acne Vulgaris

A total of 84 patients with rosacea were identified at the author’s clinic. Rosacea with acne vulgaris was observed in 34 patients (40.8% of the total rosacea cases). Until the development of rosacea, all patients with rosacea and acne vulgaris used topical benzoyl peroxide (BPO) and/or adapalene (BPO/adapalene), whereas those with conventional rosacea used no treatments or treatments other than BPO/adapalene such as ketoconazole, emollients, and other over-the-counter products (Figure 2). Therefore, all patients with rosacea and acne vulgaris developed rosacea during BPO/adapalene therapy.

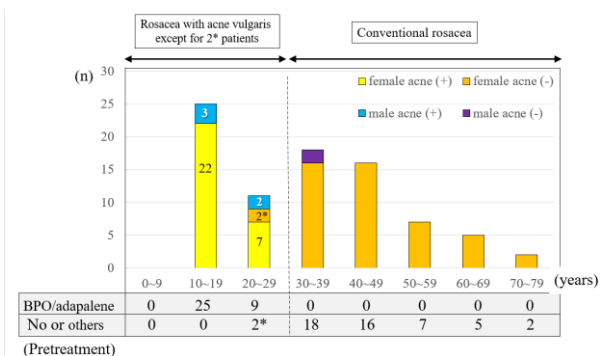


Figure 2: Characteristics of patients with rosacea and acne vulgaris. A total of 84 patients with rosacea were identified. Rosacea with acne vulgaris was seen in 34 patients (40.8%). Among them, 25 were teenage patients with predominance of females. All patients with rosacea and acne vulgaris used topical BPO and/or adapalene (BPO/adapalene) before the onset of rosacea, whereas patients with conventional rosacea used no treatments or received treatment other than BPO/adapalene.

During the study period, the author’s clinic provided treatment for 863 patients with acne and 84 patients with rosacea. Thirty-four patients with rosacea and acne vulgaris constituted 3.9% of all cases with acne vulgaris. Among the 863 patients with acne vulgaris treated in the authors’ clinic, 437 (50.6%) were treated with BPO/adapalene, and BPO/adapalene was used in 100% of patients with rosacea and acne vulgaris (p = 0.0083, two-tailed Fisher’s exact test).

Patients Examined in the Author's Clinic		n	%	p*
1	Acne vulgaris	863		
	Rosacea with acne vulgaris	34	3.90%	
2	Acne vulgaris	863		0.0083
	Acne vulgaris using BPO/adapalene	437	50.60%	
3	Rosacea with acne vulgaris	34		
	Rosacea with acne vulgaris using BPO/adapalene	34	100.00%	
4	Females with acne vulgaris using BPO/adapalene	265		0.0051
	Females with rosacea and acne vulgaris using BPO/adapalene	29	10.90%	
5	Males with acne vulgaris using BPO/adapalene	172		
	Males with rosacea and acne vulgaris using BPO/adapalene	5	2.90%	

Table 1: Characteristics of patients with rosacea and acne vulgaris.
*Two-tailed Fisher’s exact test
BPO: Benzoyl Peroxide

Among patients with acne vulgaris treated in the author's clinic, 265 females used BPO/adapalene, and 29 of them (10.9%) developed rosacea. Although 172 males used BPO/adapalene, only 5 of them (2.9%) developed rosacea, which was lower than that in females ($p = 0.0051$, two-tailed Fisher's exact test) (Table 1).

Light-Emitting Diode (LED) Therapy

Methods

In the author's clinic, irradiation using two LED colors (blue and red) was used to treat rosacea. This LED therapy approach was previously reported by the author, [36] based on its inhibitory effects on TLR-2, KLK-5, and cathelicidin (LL-37). Once-weekly simultaneous irradiation with blue (405 nm - 415 nm; integrated illuminance, 2.36 J/cm²) and red (620 nm - 630 nm; integrated illuminance, 1.32 J/cm²) LEDs for 10 minutes was conducted using an N-LED 5000DK (Aderans Medical Research Co., Ltd., Tokyo, Japan). The effects of LED irradiation were evaluated after 4 weeks - 12 weeks of treatment. Upon improvement, the patients were switched to maintenance treatment comprising once-monthly irradiation.

Results

LED therapy was initiated in 34 patients with rosacea and acne vulgaris, and 23 patients received the full course of treatment (mean number of irradiation treatments, 7.7). Among the 23 patients, 22 (87.0%) showed improvement in the rosacea symptoms. The mean erythema scores (0 [absent] to 3 [severe]) of rosacea before and after irradiation were 1.83 ± 0.64 and 0.61 ± 0.64 , respectively ($p < 0.01$, Wilcoxon signed-rank test) [8]. The remaining 11 patients did not complete LED therapy for the following reasons: Irregular irradiation interval ($n = 8$), change in topical treatment during LED therapy ($n = 1$), and dropout ($n = 2$).

Representative Patients with Rosacea and Acne Vulgaris

Figure 3 shows the first patient with rosacea and acne vulgaris. A 15-years-old girl presented to the author's clinic with mild acne vulgaris; she began treatment with topical BPO (Figure 3A). Nine months after the initiation of BPO therapy, the patient exhibited slight erythema on the cheeks and temples; this erythema was regarded as a reaction to topical BPO (Figure 3B). Sixteen months after the initiation of BPO therapy, the erythema became more pronounced (Figure 3C). Dermoscopy was performed at that time, and rosacea was diagnosed based on the presence of telangiectasia.

Figure 4 shows a patient with rosacea and acne vulgaris who was treated with LED therapy. A 15-years-old girl presented to the author's clinic with moderate acne vulgaris. Topical BPO with clindamycin was initiated, and the patient continued to visit the author's clinic six times per year for BPO treatment. At age 18, she presented to the author's clinic with complaints of facial erythema (erythema scores of 3 on the cheeks and 1 on the temples and forehead) (Figure 4A-1). A dermoscopy of the right cheek showed keratotic plugs with perifollicular telangiectasia (black arrows) and dermal telangiectasia (blue arrows) (Figure 4A-2). LED therapy was initiated along with topical BPO. The acne vulgaris lesions improved to mild severity, and the rosacea lesions on the cheeks improved to an erythema score of 1. Erythema on the patient's temples and forehead disappeared after 2 months of LED therapy (Figure 3B-1). A dermoscopy of the cheek during LED therapy showed that the follicular reddish halo remained (yellow arrows); however, the dermal telangiectasia was improved (Figure 3B-2). Since then, the frequency of LED therapy was switched to once-monthly maintenance treatment; over approximately 6 months, no signs of recurrence was observed.



Figure 3: The first patient with rosacea and acne vulgaris diagnosed at the author's clinic; (A) Before initiation of topical BPO. (B) Nine months after initiation of BPO therapy, slight erythema was detected on the cheeks and temples. (C) Sixteen months after initiation of BPO therapy, the erythema had become more pronounced.

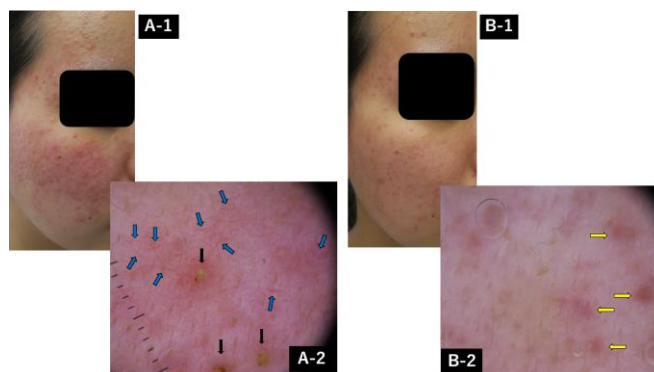


Figure 4: A patient with rosacea and acne vulgaris before and after LED therapy. (A-1) Moderate acne vulgaris and rosacea (erythema scores of 3 on the cheeks and 1 on the temples and forehead) during topical BPO therapy. (A-2) Dermoscopy findings of keratotic plugs with perifollicular telangiectasia (black arrows) and dermal telangiectasia (blue arrows). (B-1) Two months after LED therapy, the acne lesions improved to mild severity; the erythema also improved. (B-2) Although dermoscopy findings revealed a follicular reddish halo (yellow arrows) at 2 months after initiation of LED therapy, improvement of dermal telangiectasia was observed.

DISCUSSION

This study investigated the factors underlying the recent increase in the prevalence of rosacea with acne vulgaris, focusing on changes in social and medical factors over the past decade. A key factor to consider in this context is the prevalence of face mask-wearing. Currently, masks are worn both indoors and outdoors in Japan. Since the coronavirus disease (COVID-19) pandemic began, the concepts of “maskne” and “mask rosacea” have been described [37-41]. In the present study, all patients with rosacea and acne vulgaris reported wearing a mask for at least 6 hours per day.

Another important factor is the emergence of topical treatment with BPO and retinoids. In Japan, topical acne treatment has dramatically changed over the past 10 years, from antibiotics to adapalene and then to BPO. In the present study, the BPO/adapalene usage rate among rosacea patients aged under 30 years who had acne vulgaris (100%) was considerably higher than the rate in all patients with acne vulgaris (50.6%) ($p = 0.009$, Table 1).

Erythema was initially regarded as a reaction to BPO/adapalene. However, the erythema gradually worsened and persisted for several years, and telangiectasia was revealed by dermoscopy. Furthermore, the erythema improved after additional rosacea treatment with LED irradiation, despite the continued use of BPO/adapalene (Figure 3). This finding suggests that the erythema was a symptom of rosacea rather than a reaction to BPO/adapalene. Additionally, erythema tended to be more intense on the cheeks, nose, and chin than on the temples and forehead (i.e., areas not covered by a face mask), suggesting that rosacea on the temples and forehead is caused by topical

BPO/adapalene, whereas rosacea on the cheeks, nose, and chin may be caused by the combination of topical BPO/adapalene and face-mask wearing.

Current treatments for acne vulgaris have keratolytic properties, which enable the degradation of desmosomes and hemidesmosomes to reverse abnormal keratinization [16]. The gold standard for topical treatment of acne is BPO, which was introduced in 1930 [17]. It controls oxidation and free radical formation by reducing *Cutibacterium acnes* colonization [42]. Topical treatments also include retinoids (e.g., adapalene, azelaic acid, salicylic acid, and tazarotene), which have effects similar to BPO [17]. Although current treatment regimens may reduce inflammation, they can indiscriminately damage the cutaneous microbiome and epidermal barrier function [16,43,44].

Additionally, face-mask wearing impairs skin barrier function; [45] the Koebner phenomenon associated with mask-wearing induces the activation of keratinocytes and mast cells [46]. Mast cells are key mediators of LL-37 (cathelicidin)-induced skin inflammation in rosacea [47].

In both rosacea and acne vulgaris, skin barrier dysfunction is observed in association with the skin microflora [14,18,30]; however, the impairment of the skin barrier may be more severe in rosacea than in acne vulgaris [48]. Acne vulgaris symptoms are improved by BPO/adapalene treatment, but microbial diversity is reduced, and the epidermal barrier is damaged. These changes may lead to the enhancement of innate immunity, activation of TLR-2 expression, and induction of rosacea development in some patients with acne vulgaris receiving topical BPO/adapalene. The activation of mast cells and keratinocytes via mask-wearing may further stimulate innate immunity, resulting in greater TLR-2 expression in keratinocytes and the onset of rosacea. These findings and potential mechanisms support the notion that both long-term mask-wearing and topical BPO/adapalene are risk factors for the development of rosacea in patients with acne vulgaris, especially in female adolescents.

Chen et al. [34] analyzed 563 patients with rosacea who had acne vulgaris; they were included based on the following criteria: female sex, age 15 years - 50 years, concurrent presence of facial acne vulgaris, and no history of topical or systemic treatment for acne vulgaris and/or rosacea. Detailed statistical analysis suggested that frequent makeup use, frequent use of skin care products, family history of rosacea, and age at acne onset were the main factors contributing to rosacea onset. However, that study did not specifically address mask-wearing. Yang et al. [49] examined 840 female patients with rosacea and reported that patients aged ≤ 30 years constituted 31.8% of the overall cohort. They also found that the clinical characteristics were significantly different among the age groups. Middle-aged and older patients (>45 years) were more likely to have severe persistent erythema and telangiectasia; however, the authors did not specifically address the coexistence of acne vulgaris. In Korea, Lee et al. [50] examined 580 patients with rosacea; 13.3% of these patients were aged <30 years. The authors found that the cutaneous complications of rosacea were seborrheic dermatitis (8.5%), acne (24.4%), and atopic dermatitis (15.1%); however, they did not specifically address the relationship between rosacea and topical agents for acne treatment.

In Japan, Wada-Irimada et al. [51] observed 340 patients with rosacea (mean age at the first visit, 51.5 years [range: 11 years - 88 years]). They reported that the cutaneous complications of rosacea were contact dermatitis (19.4%), seborrheic dermatitis (8.5%), and atopic dermatitis (4.7%); however, they did not specifically address

the coexistence of acne vulgaris. Among these four reports on rosacea in East Asian countries, Chen et al. [34] and Lee et al. [50] recognized that rosacea accompanies acne vulgaris, but the other two reports did not mention the relationship between rosacea and acne vulgaris. The lack of focus on concurrent acne vulgaris may be related to either the absence of cases actually complicated by acne vulgaris or the assumption that acne vulgaris in adolescents and young adults is a universal skin symptom rather than a skin disease complicated by rosacea.

LED irradiation is a well-established treatment option for acne vulgaris. LEDs have antibacterial effects (blue LED), [52,53] sebocyte inhibitory effects (blue and red LEDs), [54] and suppressive effects on the expression of TLR-2, kallikrein, and LL-37 in the skin of mice with rosacea-like symptoms (red and infrared LEDs) [55]. Furthermore, low levels of red LED inhibit hyperkeratinization and inflammation effects in an experimental model of acne [56]. These effects suggest that LED therapy is useful for both acne vulgaris and rosacea [57], which are inflammatory diseases centered on the pilosebaceous system [12,13,25-27].

Combining the blue and red LED therapy for acne vulgaris, 20 minutes of twice-weekly irradiation with blue illuminance (accumulated illuminance) of $6 \text{ mW/cm}^2 - 40 \text{ mW/cm}^2$ (equivalent to $7.2 \text{ J/cm}^2 - 48.0 \text{ J/cm}^2$) and red illuminance of $8 \text{ mW/cm}^2 - 100 \text{ mW/cm}^2$ ($9.6 \text{ J/cm}^2 - 120.0 \text{ J/cm}^2$) is recommended [58]. Although infrared LED may suppress the expression of TLR-2, kallikrein, and LL-37, it can also stimulate mast cells, [59,60] which are key mediators of LL-37-induced skin inflammation in rosacea; [47] thus, infrared LED may be avoided for rosacea. Furthermore, rosacea is exacerbated through the production of reactive oxygen species by exposure to ultraviolet rays and infrared rays [7,61]. Red LEDs cause human umbilical vein endothelial cells to proliferate in a dose-dependent manner at doses between 2.5 J/cm^2 and 10.0 J/cm^2 *in vitro* [62]. Although this effect is beneficial for wound healing applications, angiogenesis stimulation in rosacea may cause symptom exacerbation. Therefore, a low integrated illuminance was chosen to avoid overexposure to rosacea, although the setting of LED therapy for rosacea is probably insufficient for acne vulgaris. In this study, complete LED therapy was administered to 23 patients, and 20 showed improvements (efficacy rate: 87.0%) even after continuing BPO/adapalene treatment.

Among patients with acne vulgaris who used BPO/adapalene in the author's clinic, rosacea occurred in a higher percentage of female patients (10.9%) than that in male patients (2.9%, $p = 0.0051$) (Table 1). Although the reasons for the higher incidence in female patients are unknown, it cannot be ignored as the adverse effects of BPO/adapalene.

To prevent rosacea development during acne vulgaris treatment, mask-wearing should be avoided as much as possible within socially acceptable limits. Furthermore, topical BPO/adapalene combined with LED irradiation may be a more tolerable treatment regimen than BPO/adapalene alone for preventing rosacea development in patients with acne vulgaris, especially in female adolescents.

Appropriately developed prescriptions and over-the-counter preparations may selectively influence the microbiome and promote the maintenance/restoration of epidermal barrier function. By understanding this relationship, dermatologists can provide better education to patients concerning the importance of appropriate skin care [16].

More information regarding rosacea with acne vulgaris is needed, and the causes, countermeasures, and treatments should be clarified.

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CONFLICT OF INTEREST

No conflict of interest found.

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