A pilot study on serum cutaneous T-cell-attracting chemokine in acne patients: effect of low-fluence long pulsed dye laser therapy

May H. El Samahy[a], Enas A.S. Attia[a], Yasser A. Abd El-Aziz[b], Shereen B. Elsayed[c] and Sameh K.F. Tawfiek[d]

Departments of [a]Dermatology, Venereology and Andrology, [b]Plastic Surgery, [c]Medical Microbiology and Immunology, Faculty of Medicine, Ain Shams University and [d]Department of Dermatology and Venereology, Kobri Al-Kobba Military Hospital, Cairo, Egypt

Correspondence to Enas A.S. Attia, MD, Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Ain Shams University, PO Box 11381, Cairo, Egypt
Tel/fax: +20 2 26830767;
e-mail: annosah1974@yahoo.com

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Background
Recruitment of *Propionibacterium acnes*-specific effector T cells, and hence acne pathogenesis, likely involves the cutaneous T-cell-attracting chemokine (CTACK)/CCL27–CCR10 axis. *P. acnes* is a porphyrin-containing organism, killed by exposure to long pulsed dye laser (PDL).

Objective
To evaluate single-session low fluence long PDL for the treatment of mild to moderate acne, with assessment of serum CTACK before and 8 weeks after treatment.

Patients and methods
Ten patients with mild to moderate acne were administered a single session of low-fluence long nonpurpuric PDL, with clinical evaluation, and assessment of serum CTACK 8 weeks after treatment, compared with controls.

Results
All patients showed improvement, with an excellent response in 20%, good response in 60%, and fair response in 20%, and a 90% satisfaction rate. Improvement was more recognizable with inflammatory than noninflammatory lesions ($P=0.05$). Mild transient hyperpigmentation was reported in two patients. Statistically significant higher CTACK levels were found in patients (whether before or after treatment) than controls ($P<0.001$). Nevertheless, there was a statistically significant reduction in CTACK levels when comparing between pretreatment and post-treatment levels ($P<0.001$).

Conclusion
Low-fluence long PDL seems to be an effective and safe modality for mild to moderate acne, particularly with inflammatory lesions, and tendency toward postinflammatory hyperpigmentation, or acne erythema. Active acne is associated with higher serum CTACK levels compared with controls, which decreased significantly after treatment.

Keywords:
acne, cutaneous T-cell-attracting chemokine, pulsed dye laser

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Introduction

Acne vulgaris is one of the most common skin conditions encountered by physicians, affecting ~85% of individuals between the age of 12 and 24 years. It is one of the chronic inflammatory diseases of the pilosebaceous unit, with the most widely accepted etiologic factors including ductal epidermal hyperproliferation, excess sebum, inflammation, and abnormalities of the microbial flora, *Propionibacterium acnes* proliferation [1,2].

P. acnes release lipases, proteases, and hyaluronidases, which contribute toward tissue injury. In addition, *P. acnes* contribute toward the inflammatory nature of acne by inducing monocytes to secrete proinflammatory cytokines including tumor necrosis factor-α, interleukin (IL)-1β, and IL-8 [3]. Tumor necrosis factor-α, IL-1, and interferon-α are proinflammatory cytokines known to induce cutaneous T-cell-attracting chemokine (CTACK) [4].

CTACK is a small inducible cytokine A27 precursor (CCL27) belonging to the chemokine (β) family (chemokine CC family). CCL27 is a chemokine believed to be involved in the process of establishing the inflammatory infiltrate, characteristic for various inflammatory skin diseases. The skin-specific CCL27 binds the chemokine receptor-10 (CCR10) and selectively chemoattracts skin-homing memory T cells [5]. As early inflammatory acne lesions are characterized by the infiltration of the pilosebaceous duct with CD4+ T-helper 1 cells that are reactive to *P. acnes* [6], the recruitment of *P. acnes*-specific effector T cells and hence acne pathogenesis likely involves the CTACK/CCL27–CCR10 axis.

P. acnes have been a major target of therapy in inflammatory acne [7]. Moreover, the continuous increase in antibiotic-resistant strains reduces the future usefulness of current mainstay therapies, and accordingly, the need for alternative therapies is mandatory.

P. acnes bacterium is a porphyrin-containing organism that is killed by exposure to specific wavelengths of light [8]. Experience in several clinics suggests that a proportion of

patients receiving low-fluence pulsed dye laser (PDL) treatment showed coincidental striking and longstanding improvements in inflammatory acne after a sole treatment of the face [9].

The aim of this study was to evaluate single-session low-fluence long PDL for the treatment of mild to moderate acne, with assessment of serum CTACK before and 8 weeks after treatment, compared with controls. To the best of our knowledge, no previous reports have been published on serum CTACK in acne.

Participants and methods

Participants

Our case–control study included 10 patients with acne vulgaris and 10 age-matched and sex-matched controls ($P = 0.782$ and 0.653, respectively), without any history of acne vulgaris and free from any kind of skin inflammation. Patients were selected from among those attending the Dermatology Outpatient Clinic at Ain Shams University Hospitals. All participants provided an informed written consent before enrollment in the study. The study was carried out according to the Declaration of Helsinki Principles and was approved by the Research Ethical Committee of Faculty of Medicine, Ain Shams University.

Patients were subjected to assessment of history including history of acne: onset, course, duration; history of any current or previous treatments of acne; history of other skin or systemic diseases with a focus on autoimmune diseases; history of medications that could aggravate the inflammatory process of acne (e.g. corticosteroids) and other relevant medications including oral contraceptive pills and isotretinoin, and the date of stopping them; relevant medical conditions (e.g. Herpes simplex infection, photosensitivity, allergy, keloids, hypertrophic scarring, postinflammatory hyperpigmentation); and relevant surgical history including dermabrasion, laser surgery, or fillers injection.

All patients were assessed for severity of acne using the classification of Lehmann *et al.* [10]: grade A: mild acne: <20 comedones, or <15 inflammatory lesions, or total lesion count <30; grade B: moderate acne: 20–100 comedones, or 15–50 inflammatory lesions, or total lesion count 30–125; and grade C: severe acne: >5 cysts or total comedones count >100, or total inflammatory lesion count >50, or total lesion count >125. Patients were also evaluated for skin phototype, the presence of postinflammatory hyperpigmentation, or scars (atrophic or hypertrophic and keloids).

Exclusion criteria included patients with severe acne vulgaris, patients who had received any treatment (systemic or topical) for acne during the last 6 months before laser sessions, patients with a history of isotretinoin therapy within the 2 years before the study, patients on ongoing oral contraceptive pills or anticoagulant therapy, patients with a history of dermabrasion, or filler injections, or laser treatments within 2 years of the study initiation, patients with any dermatological and/or systemic diseases that could affect the outcome of the study such as psoriasis, atopic dermatitis, those taking any medication that affects the immune system, or those with photosensitivity, recurrent herpes simplex infection, allergic reactions, hypertrophic or keloid scars, and patients with diabetes or epilepsy, as well as pregnant or lactating women.

Methods

Full face digital photographs were taken before the laser therapy and 8 weeks after the laser session using a Sony digital camera (Sony CyberShot S2100, Minato-ku, Tokyo, Japan) under identical camera settings and lighting conditions.

All patients included received a single session of low-fluence long nonpurpuric PDL (V-Beam Platinum, 595 nm; Candela Laser Corporation, Wayland, Massachusetts, USA) at the setting of 7 J/cm^2, 10 ms pulse duration, 10 mm spot size, and the dynamic cooling device cryogen spray 30/20. The treatment sessions were carried out after the application of a local anesthetic, a eutectic mixture of local anesthesia for 45–60 min. Patients were instructed to avoid any unnecessary sun exposure and to apply daily sun screen with a high sun-protection factor value after the treatment. No or poor response (score 1) was judged to have occurred if there was less than a 25% decrease in the number of acne lesions. Partial response was estimated as fair, good, or excellent according to the percentage of reduction in the lesions as follows: score of 2 or fair response with a 26–50% reduction in the number of lesions, score of 3 or good response with a 51–75% reduction in the number of lesions, and score of 4 or excellent response with 76% or more improvement. Evaluation of complications included pain, swelling, erythema, pruritus, infection, delayed healing, pigmentary changes, exacerbation of acne, eruption of milia, scarring, and others. Patient satisfaction after the treatment was categorized into very satisfied, satisfied, or not satisfied.

Measurement of serum CTACK using the enzyme immunoassay technique (a type of enzyme-linked immunosorbent assay) was performed for both patients (before and 8 weeks after treatment) and controls using the Quantkine Human CTACK/CCL27 immunoassay kits (R&D Systems Inc., Minneapolis, Minnesota, USA). The minimum detectable dose ranged from 0.58 to 6.05 pg/ml.

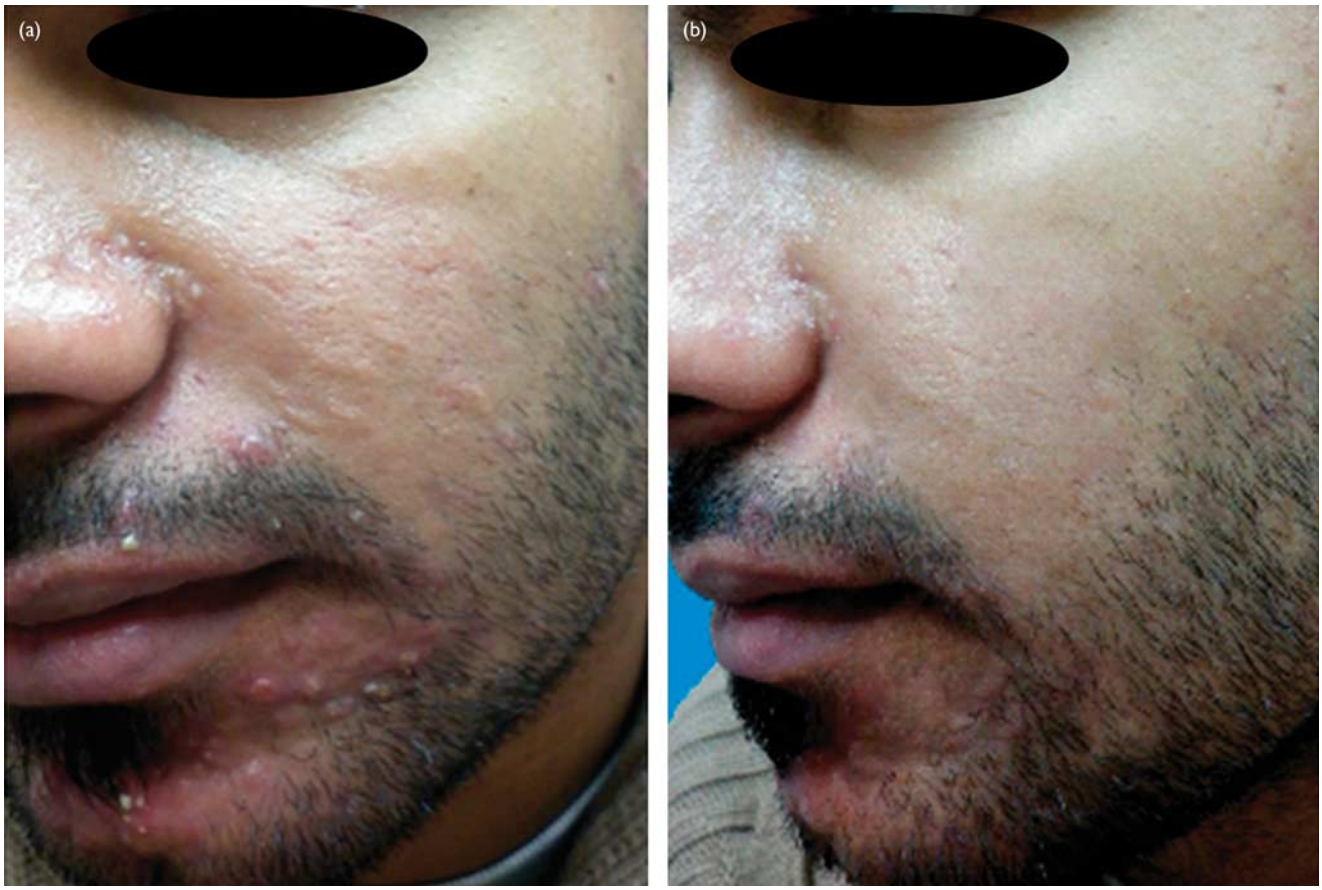
Statistical analysis

Analysis of data was carried out using SPSS 17 (Statistical Package for Scientific Studies, SPSS Inc., Chicago, Illinois, USA) for Windows. Data were explored for normality using the Kolmogorov–Smirnov test of normality. Comparison between quantitative variables was carried out using the Student *t*-test of two independent samples. Comparison of results before and after the treatment was carried out using a paired *t*-test. Comparison between qualitative variables was carried out using the χ^2-test. The Fisher exact test was used instead of the χ^2-test when one expected cell or more were 5 or less. Binary correlation was carried out using the Pearson correlation test. Results were considered significant when the probability (P) value was 0.05 or less.

Results

The patients studied included six men (60%) and four women (40%) (mean age 21.30 ± 2.16 years), whereas

Figure 1.



Patient number 10. Pretreatment photograph (a) with mild acne and post-treatment photograph (b); improvement in acne lesions was excellent (score 4).

among the controls, there were five men (50%) and five women (50%) (mean age 21.60 ± 2.59 years).

The patients' skin phototypes according to Fitzpatrick skin phototyping were as follows: type II for two patients (20%), type III for seven patients (70%), and type IV for one patient (10%). Their grades of acne lesions were mild inflammatory in seven patients (70%), whereas three patients (30%) had moderate inflammatory acne lesions.

Overall, improvement occurred in all patients, more recognizable with inflammatory than noninflammatory lesions ($P = 0.05$) (Table 1), with excellent response in two patients (20%) (Fig. 1), good response in six patients (60%) (Fig. 2), and fair response in two patients (20%). No exacerbation was reported until the end of the study. Ninety percent of our patients were satisfied with the result, with seven patients (70%) very satisfied and two patients (20%) satisfied, whereas only one patient (10%) with a fair response was unsatisfied.

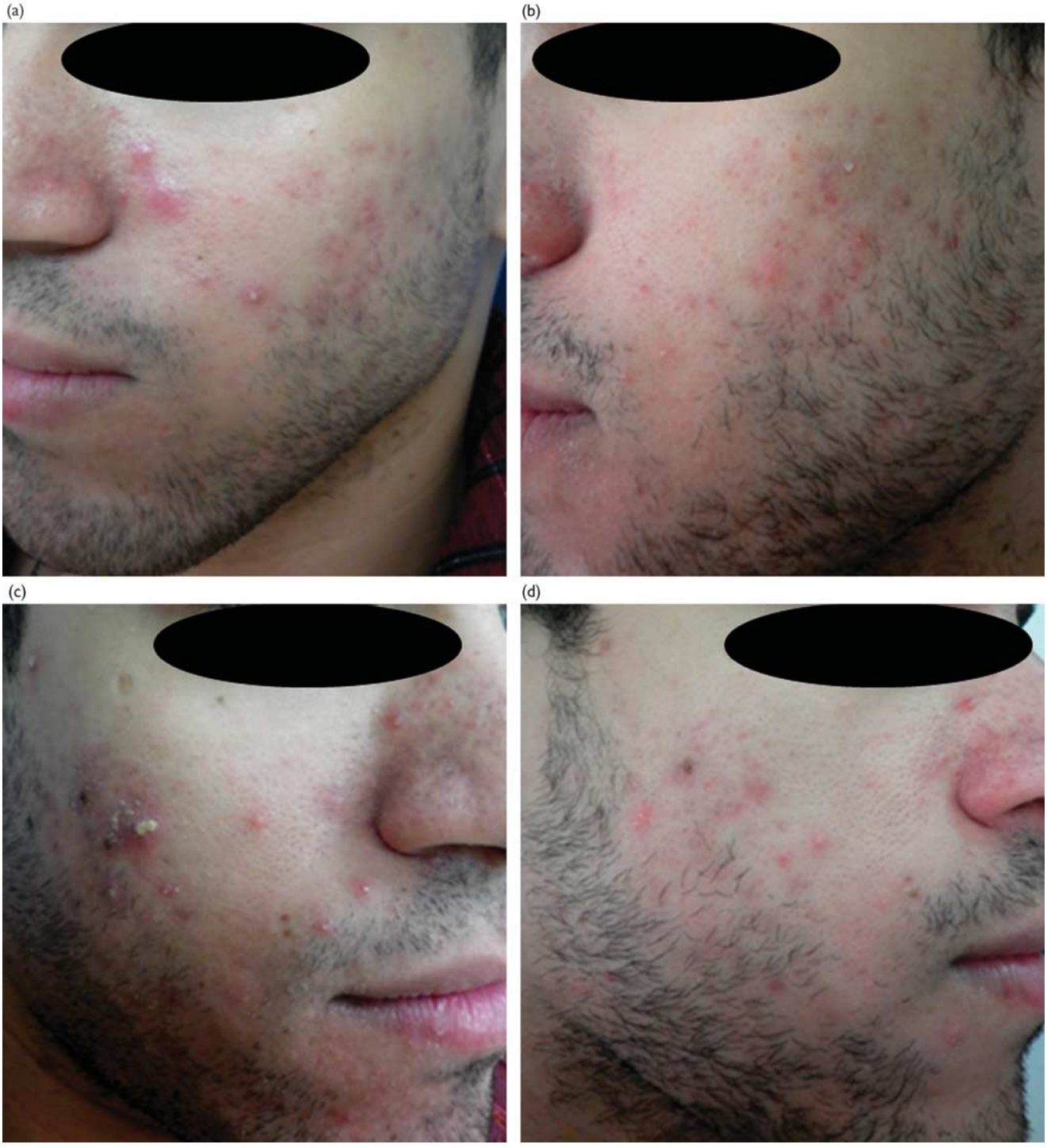
In terms of complications, acute erythema was experienced in all the patients with mild pain and swelling. In four of these patients (40%), the erythema was prolonged (lasted more than 2 weeks). However, an overall improvement in acne erythema was noted at the end of the study. In addition, mild hyperpigmentation occurred in two patients (20%) and resolved spontaneously after 2 months. No other adverse effects were reported.

In terms of CTACK levels, statistically significantly higher levels were found in patients (whether before treatment or 8 weeks after treatment) than controls ($P < 0.001$). Nevertheless, there was a statistically highly significant reduction in CTACK levels when comparing between the pretreatment CTACK levels and the post-treatment levels ($P < 0.001$) (Table 2). None of the pretreatment, post-treatment, or percentage of change in CTACK levels showed a statistically significant difference in male patients compared with female patients ($P = 0.391$, 0.773, and 0.335, respectively) (Table 3), as well as in patients with different skin phototypes ($P = 0.353$, 0.443, and 0.425, respectively) (Table 4), or with different improvement scores (Table 5). No significant correlation was found between the CTACK levels and the age of the patients ($r = -0.342$ and $P = 0.333$, $r = -0.476$ and $P = 0.164$, and $r = 0.244$ and $P = 0.497$, respectively). There was a highly significant positive correlation between pretreatment CTACK levels and post-treatment levels, with an r value of 0.946 and a P-value of less than 0.001.

Discussion

Although acne has been the subject of considerable research, the need for alternative therapies is mandatory

Figure 2.



Patient number 5. Pretreatment photos (a, c) with moderate acne on cheeks and post-treatment photos (b, d); improvement in acne lesions was good (score 3).

because of the continuous increase in antibiotic-resistant *P. acnes*, and the development of side effects to current medications. *P. acnes* produce porphyrins, mainly protoporphyrin and coproporphyrin – photosensitizers, which are molecules that have the trait of absorbing light energy. The long PDL works at 590, 595, and 600 nm and extended pulse durations. This laser can induce relatively deep tissue penetration using large spot sizes and fluencies ranging from 5 to 15 J/cm^2 while maintaining specificity [11].

In our study, single-session low-fluence long PDL led to improvement in all the patients studied (more pronounced with inflammatory lesions) without reported exacerbation. Our reported complications, including delayed erythema and postinflammatory hyperpigmentation, were mild and disappeared spontaneously. In agreement with these results, Seaton *et al.* [12] showed that PDL therapy improved inflammatory facial acne 12 weeks after one treatment with no serious adverse effects in Afro-Caribbean patients. Harto *et al.* [13] also reported more improvement in inflammatory

lesions than that in noninflammatory acne after three sessions of 585-nm PDL (interval every 4 weeks), without reported exacerbations. In addition, Leheta [14] reported that PDL therapy (biweekly sessions for six sessions) mainly led to improvement in the inflammatory lesions of acne with long remission and few adverse effects, with no reported exacerbation. Moreover, Jung *et al.* [15] found that biweekly PDL sessions are effective in improving both inflammatory and noninflammatory acne lesions. Besides, PDL produced gradual and sustained improvements, without reported exacerbation by Choi *et al.* [16].

We found postinflammatory hyperpigmentation in two patients only (20%), which disappeared spontaneously. Ho *et al.* [17] successfully used 595-nm long PDL to treat acne postinflammatory hyperpigmentation in Chinese patients with Fitzpatrick types III and IV skin. Therefore, low-fluence long PDL could be recommended for acne patients, with a tendency toward or coexistent postinflammatory hyperpigmentation. Our results also indicated prolonged erythema only in two patients (20%), which disappeared spontaneously. However, an overall improvement in acne erythema was noted at the end of the study. In agreement, Yoon *et al.* [18] reported significant improvement in erythema and skin elasticity after long 595-nm PDL.

Previous studies have attempted to evaluate light-based therapies in acne by assessment of various inflammatory and remodeling markers. Jung *et al.* [15] reported decreased lesional IL-8 expression and increased transforming growth factor-β expression following PDL for mild to moderate facial acne. Choi *et al.* [16] also showed increased transforming growth factor-β expression after PDL. We report, for the first time, higher serum CTACK levels in acne patients (with no differences on the basis of sex, age, or skin phototype) compared with controls, with a significant reduction in levels after low-fluence long PDL. Yet, post-treatment levels were still higher than control levels and did not correlate with the improvement score. Previous reports have shown enhanced epidermal expression of CCL27/CTACK in some cutaneous conditions including acute graft versus host disease [19], cutaneous lupus erythematosus [20], and drug-induced cutaneous reactions [21].

Table 1. Comparison between inflammatory and noninflammatory acne lesions in terms of the improvement grade

	Improvement				
Types of acne lesions	Poor	Fair	Good	Excellent	Total
Inflammatory [*N* (%)]	0 (0)	0 (0)	6 (60)	4 (40)	10 (100)
Noninflammatory (comedones) [*N* (%)]	4 (40)	2 (20)	2 (20)	2 (20)	10 (100)
χ^2			7.638		
P-value			0.05*		

*$P < 0.05$ = significant.

Table 2. Comparison between pretreatment and post-treatment CTACK among cases as well as in cases versus controls

	Cases		Controls		
	Mean	SD	Mean	SD	*P*-value
Pretreatment CTACK	703.75	192.95	129.27	41.54	<0.001*
Post-treatment CTACK	213.19	26.37			<0.001*
P-value	<0.001*				

CTACK, cutaneous T-cell-attracting chemokine.
*$P < 0.05$ = significant.

Table 3. Comparison of CTACK levels among female versus male patients

	Females (*N*=4)		Males (*N*=6)		
	Mean	SD	Mean	SD	*P*-value
Pretreatment CTACK	641.95	130.45	744.95	227.41	0.391
Post-treatment CTACK	209.98	15.24	215.33	33.14	0.773
CTACK change (%)	−66.57	4.96	−69.85	4.96	0.335

CTACK, cutaneous T-cell-attracting chemokine.

Conclusion

Low-fluence long PDL was found to be an effective and safe modality in the treatment of mild to moderate acne, particularly with inflammatory lesions, and tendency toward postinflammatory hyperpigmentation, acne erythema. Therefore, we consider PDL as a promising

Table 4. Comparison of CTACK levels in patients with different skin phototypes

	Phototype II (*N*=2)		Phototype III (*N*=7)		Phototype IV (*N*=1)		
	Mean	SD	Mean	SD	Mean	SD	*P*-value
Pretreatment CTACK	725.10	210.58	659.41	184.59	971.40	–	0.353
Post-treatment CTACK	220.65	26.38	206.77	26.65	243.20	–	0.443
CTACK change (%)	−68.78	5.43	−67.55	4.91	−74.96	–	0.425

CTACK, cutaneous T-cell-attracting chemokine.

Table 5. Relation between CTACK level and improvement score among the patients studied

	Fair improvement (score 2) (*N*=2)		Good improvement (score 3) (*N*=6)		Excellent improvement (score 4) (*N*=2)		
	Mean	SD	Mean	SD	Mean	SD	*P*-value
Pretreatment CTACK	880.95	127.92	637.57	192.03	725.10	210.58	0.335
Post-treatment CTACK	236.75	9.12	202.85	26.89	220.65	26.38	0.290
CTACK change (%)	−72.92	2.90	−66.99	5.14	−68.78	5.43	0.388

CTACK, cutaneous T-cell-attracting chemokine.

alternative to systemic isotretinoin in scar-prone acne patients, particularly those with contraindication(s) or intolerance to isotretinoin. We reported, for the first time, higher CTACK levels in acne patients compared with controls, with a significant reduction in levels after treatment. Further studies on a larger population of patients are needed to assess both serum and tissue levels of CTACK, and to establish a possible relation to disease severity or activity, if any.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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