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Efficacy of 3.6% topical ALA-PDT for the treatment of severe acne vulgaris

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Abstract. – OBJECTIVE: To evaluate the efficacy and safety of topical 5-aminolevulinic acid (ALA) mediated photodynamic therapy (PDT) for the treatment of severe acne vulgaris.

PATIENTS AND METHODS: A total of 125 patients with Pillsbury III-IV severe facial acne were treated with 3 courses of ALA-PDT with an interval of 2 weeks. ALA gel (3.6%) was applied topically to acne lesions for 1.5 h. The lesions were irradiated by a LED light of 633 nm with a light intensity of 66 mW/cm^2 and a light dose of 126 J/cm^2. Patients were evaluated for efficacy and safety at weeks 2, 4, 6, 8, 12 after the initial treatment.

RESULTS: The total effective rates were 1.6%, 24.8%, 68.8%, 89.6% and 88.8% at the 2- 4- 6- 8- and 12-week after the initial treatment respectively. The clinical outcomes were the best at 4 weeks after the final treatment. The best effective rate and cure rate were 89.6% and 44% respectively. 26 patients and 16 patients showed apparent exacerbation of acne lesions before the 2nd and 3rd treatment respectively, but all of them showed good or excellent improvement after 3-course treatment. Adverse reactions were mild and transient.

CONCLUSIONS: 3.6% ALA-PDT is a simple, safe and effective therapeutic option for the treatment of severe acne vulgaris.

Key Words:
Severe acne vulgaris, Aminolevulinic acid, Photodynamic therapy.

Introduction

Acne is the most common skin disease seen in dermatological practices worldwide. It affects many teenagers and may continue into adulthood. It is a follicular disorder that affects susceptible *pilosebaceous follicles* and is characterized by both non-inflammatory and inflammatory lesions[1]. Although acne does not cause direct physical impairment, it can produce a significant psychosocial burden[2]. The current skin lesions of acne can lead to social phobia, lowered self-image, anxiety, and even depression. Suicidal ideation is more common in those with severe acne compared with mild acne[3].

The pathophysiology of acne is multifactorial, involving 4 causative factors, including inflammation, hyperkeratinization, *Propionibacterium acnes* proliferation, and excess sebum production[4]. The severity of acne in adolescence is associated with several factors, including a positive history of severe acne in first-grade relatives, especially them other[5]; occurrence in boys in early puberty[6]; and occurrence in girls with notably elevated dehydroepiandrosterone sulfate serum levels during the adrenarche[7].

All forms of severe acne require systemic treatment[8]. The available options include oral antibiotics, hormonal antiandrogens for female patients and oral isotretinoin, as well as other combination treatments. Widespread use of antibiotics in acne has led to significant problems with antimicrobial resistance, which have begun to compromise the usefulness of antibiotics[9]. Oral isotretinoin is the only drug available that affects all four pathogenic factors of acne. However, oral isotretinoin is a pregnancy category × teratogen and is associated with significant side effects[10]. The reported side effects associated with the use of oral isotretinoin include depression, attempted suicide, cheilitis, dermatitis, myalgia, dry eyes, nonspecific gastrointestinal symptoms, and arthralgia. A European directive states that oral isotretinoin should be used only as a second-line therapy in cases of severe, nodular and conglobate acne[11].

Therefore, the development of new alternative treatment is desirable. With or without a photosensitizer, light based treatments present an alternative or adjuvant to traditional pharmacologic therapy[12]. Photodynamic therapy (PDT) with topical aminolevulinic acid (ALA) is an emerging modality for the treatment of acne vulgaris.

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In this study, we further examined the effectiveness of Low-dose topical 5-aminolevulinic acid photodynamic therapies and the red light emitting diode (LED) in the treatment of severe facial acne vulgaris in chinese patients.

Patients and Methods

Patients

Patients of both sexes who presented with Pillsbury III-IV severe facial acne vulgaris and Fitzpatrick skin type III-IV were enrolled. Severe acne lesions were characterized predominantly as including inflammatory papules, pustules, nodules, scars and cysts. Some lesions were accompanied with large pus-filled cysts, substantial swelling and exfoliation around the infections[13]. Patients who were exposed to systemic retinoids during the 6 months prior to the study; systemic antibiotics, contraceptive or photosensitive drugs 1 month prior to the study; or topical acne drug treatments 2 weeks before the study; patients with severe heart, liver or renal diseases or dysfunction of immune system or, with a history of photosensitive diseases, porphyria, porphyrin sensitivity or intake of photosensitive drugs, and pregnant or lactating women were excluded. No patient with large cysts had received surgical excision and drainage or intralesional corticosteroid injection. Before starting treatment, all patients were provided with an informed written consent form.

Methods

A 3.6% ALA lotion was freshly prepared with ALA powder (Shanghai Fudan-Zhangjiang Bio-Pharmaceutical, Shanghai, China) 150 mg joined in 4 ml gel in a dark room before application. Fresh ALA gel was applied evenly to acne lesions plus 1cm margin. Before using ALA, each subject's face was cleaned with foam wash, and the oily crusts were removed. The contents of the cysts, which were fluctuant when palpating the lesions, were taken out with a syringe before each treatment. Comedos were extruded with comedo extractor after disinfecting the treatment site before the 2nd and 3rd treatment session. The ALA applied area was occluded with a cling film and covered with a black sheet for light protection. After 1.5 h of incubation, lesion surface was cleaned with a wet cotton gauze to remove the excess ALA. The lesions were then exposed to a LED light panel (Omnilux Revive, Photo Therapeutics Ltd., Altrincham, Manchester, UK) with peak wavelength at 633 ± 3 nm and the dose level of 126 J/cm^2 and a fixed power density of 66 mw/cm^2 for 20 min, and the distance between the light panel and patient's apex nasi was set at 10 cm. Patient's eyes were protected during the light irradiation of the whole face. Immediately after light irradiation, spritzing cold water was applied for 30 min to minimize redness and pain. The treatment was repeated twice for all patients at two-week intervals.

Clinical Evaluations

The patients were examined and digital photographs were obtained. The number of acne lesions (including papules, pustules, nodules and cysts) was recorded by the same dermatologist for all patients. The study protocol included three treatment sessions and three follow-up visits. The evaluation of clinical improvement was carried out before the 2nd (2 weeks) and 3rd (4 weeks) treatment session. After completion of treatment, follow-up assessment was carried out at the 2nd (6 weeks), 4th (8 weeks) and 8th weeks (12 weeks) after the final treatment for all patients.

Clinical evaluation was conducted based on the following formula: The clearance rate of skin lesions (%) = (the total number of skin lesions before treatment – the total number of skin lesions after treatment)/the total number of skin lesions before treatment × 100%. Clinical assessment was performed using the following criteria: Cure ≥ 90% clearance; Excellent response -60-89% clearance; Good response -20-59% clearance; Poor response ≤ 19% clearance or no significant response; worsened < 0% exacerbation of acne lesions.

The effective rate (%) = (the cases of cure + the cases of the excellent response)/total cases × 100%

The cure rate (%) = the cases of cure/total cases × 100%

All adverse events including pain, erythema, edema, pustules, vesicles, exudation, desquamation, and hyperpigmentation were recorded in detail in each treatment and follow-up visit. Adverse events were recorded according to severity (ranked on a scale from 0 to 3, 0 = absent; 1 = mild; 2 = moderate; and 3 = severe), persistence, time to resolve, treatment measure and outcome[14].

Statistical Analysis

All data were analyzed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). Comparison of categorical variables amongst groups was performed using chi-square. Comparison of numerical variables amongst groups was performed using repeated measure.

p-values of less than 0.05 were considered statistically significant.

Results

The study was conducted from February 2011 to January 2015. All patients came from our dermatology clinic. A total of 125 (males = 87, females = 38, ratio = 2.29:1) patients with Pillsbury III-IV severe facial acne vulgaris was selected for the ALA-PDT study. The distribution of acne severity is 35 cases grade III and 90 cases grade IV. The ages ranged from 14 to 35 years old (mean = 21.36 years old). The length of history ranged from 6 months to 5 years (mean = 30.58 months). All lesions were confined to the face, mainly on the forehead, cheek, and chin areas. Amongst them, 125 (100%) patients had used prescribed antibiotics systemically or topically, 26 (20.8%) used oral retinoids and 3 (2.4%) used systemic steroids in the past. Others had tried over the counter products. 15 (12%) patients have positive history of severe acne in first-grade relatives.

Table I summarizes the clinical outcomes.

All patients had finished the three sessions of treatment. Most patients showed apparent clearance of acne lesions and improved cutaneous appearance at the treated site after three sessions. These improvements include the marked clearance of inflammatory papules and pustules, reduction in the number and size of nodules and cysts, reduction in acne activity, decrease in the production of sebum, and softening of scars as shown in the representative photographs (Figure 1). The effective and cure rates were increased after the multiple therapies and a few patients got the excellent or good effects after 1-2 courses treatments. The statistical significant differences are found in the different observe time points. The maximum effects of clinical outcomes were at four weeks after the final treatment. The best effective rate and cure rate of the 3.6% ALA-PDT procedure are 89.6% and 44% respectively. White and black comedos did not have obvious reactions after one-course therapy. A few comedos had been changed into inflammatory papules. So we routinely extruded them with comedo extractors before the 2nd and 3rd treatment session. We had observed that only a few new comedos developed at the follow-up visits after the final treatment. It was noticeable that 26 patients and 16 patients showed apparent exacerbation of acne lesions before the 2nd and 3rd treatment respectively, but all of them showed good or excellent improvement after three-course treatment. These aggravations include increases in the number and size of papules, pustules, nodules, and cysts as shown in the representative photographs (Figure 1).

Figure 2 shows the mean inflammatory lesion (papules, pustules and nodules/cysts) counts at each treatment session and at each follow-up visit. The mean counts of each type of inflammatory acne lesion were reduced at each treatment session as compared with that at the previous visit. All inflammatory lesion counts continued to decrease significantly during the 4-week follow-up period. No significant differences of effective rate and cure rate were observed among papules, pustules and nodules/cysts at the follow-up session. A few patients showed mild relapse including papules and comedos at eight weeks after the final treatment.

Table I. The clinical outcomes of 2, 4, 6, 8, 12 weeks after the initial treatment.

Treatment schedule	No.	Cure	Excellent	Good	Poor	Worsen	Effective rate (%)	Cure rate (%)
2 weeks	125	0	2	64	33	26	1.6%	0
4 weeks	125	0	31	48	30	16	24.8%	0
6 weeks	125	40	46	24	15	00	68.8%	32%
8 weeks	125	55	57	8	5	0	89.6%	44%
12 weeks	125	53	58	9	5	0	88.8%	42.4%
χ^2							253.98	107.552
p							0.000	0.000

Multiple group comparison amongst different treatment points. $p < 0.05$ means that the difference was statically significant.

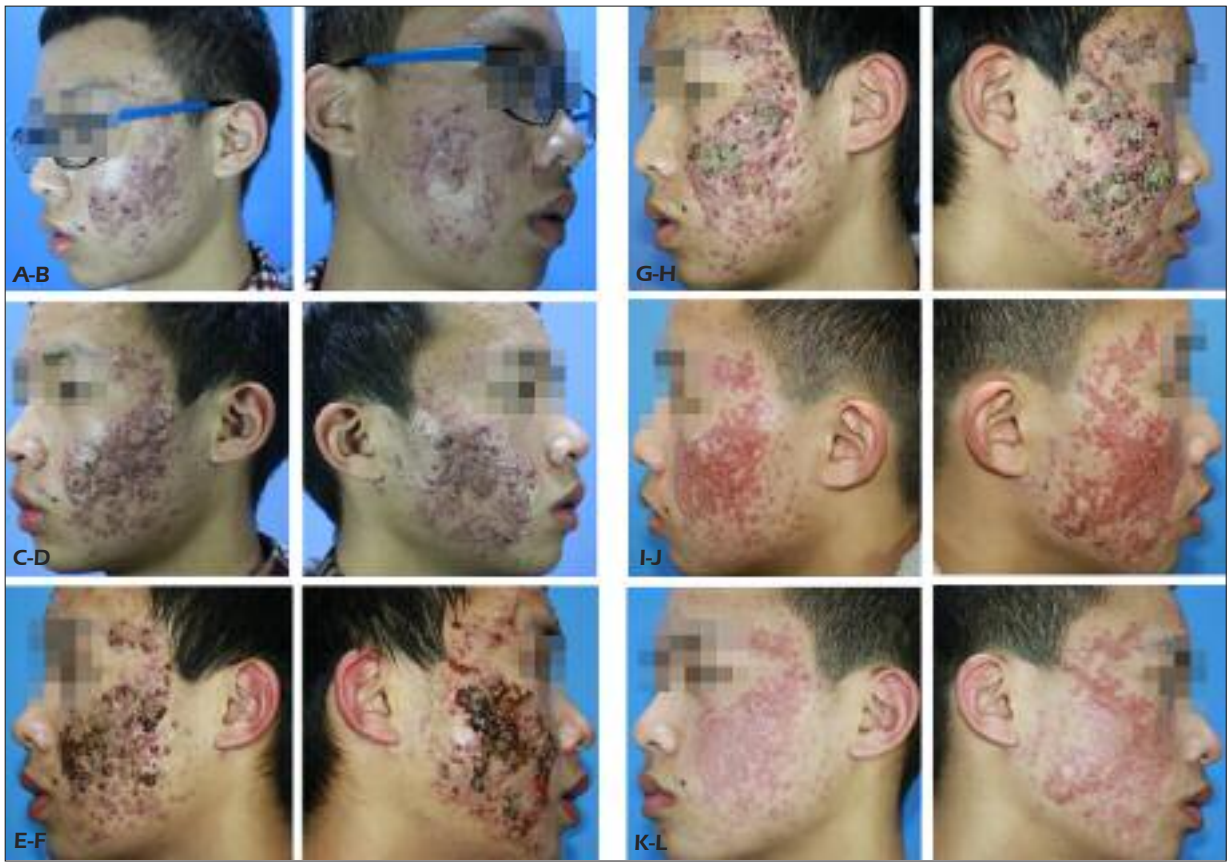

Figure 1. Clinical photographs from an adolescent patient with severe acne (Pillsbury grade IV) treated with 3.6% topical 5-aminolevulinicacid photodynamic therapy at the baseline visit. ***A-B,*** 2 weeks. ***C-D,*** 4 weeks. ***E-F,*** 6 weeks. ***G-H,*** 8 weeks. ***I-J,*** 12 weeks. ***K-L,*** Respectively.

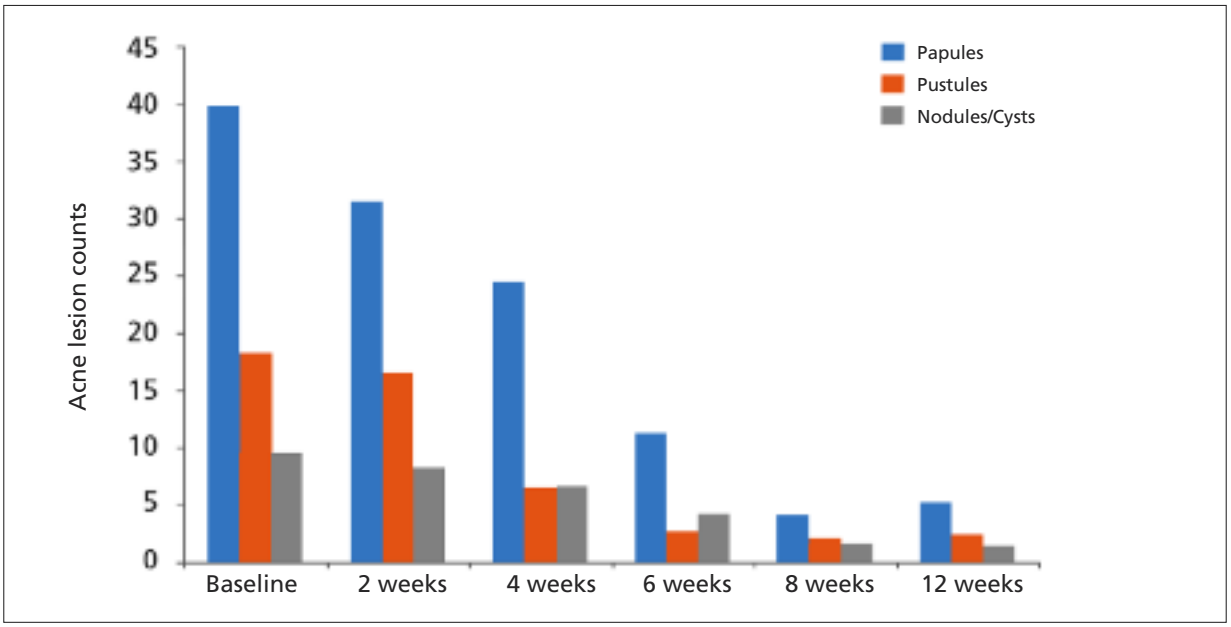

Figure 2. Mean lesion counts at each time point. $p < 0.05$ showed statistical significance as compared with the previous visit. No significant differences of effective rate and cure rate were observed among papules, pustules and nodules/cysts at the follow-up session compared with those of the previous visit ($p > 0.05$).

Adverse Events

Mild painful feelings were obtained in 66 (52.8%) patients at the beginning of irradiation, which subsided after a few minutes. Immediately after exposure to light, the treated sites showed mild to moderate edematous erythema (82/125, 65.6%). The edematous erythema could subside within one to three days in most patients. An ice bag or cold spray could help to alleviate the erythema and edema. 12 patients (9.6%) had mild to moderate desquamation at the treated site, which resolved gradually within two weeks. 26 patients (20.8%) presented with temporary hyperpigmentation after PDT, which disappeared in all the patients within 1-2 months after treatment without any further intervention. None of the patients developed ulcers, infection, purpura, scarring or other substantial adverse effects.

Discussion

Topical photodynamic therapy has been widely used in dermatology for the treatment of oncologic conditions, as well as for non-oncologic dermatological diseases[15]. The rationale for the use of AlA-PDT in the treatment of acne vulgaris was first investigated by Hongcharu et al[14] in the United States and Itoh et al[16] in Japan by coupling red light and ALA to treat mild to moderate acne.

Several relevant studies regarding the use of PDT for adult acne treatment have been published since then[17].

Different photosensitizers and drug delivery methods have been reported for acne treatment. ALA and methyl-ester of ALA (MAL) are available for possible off-label treatment of acne vulgaris. ALA is the natural biosynthetic precursor of heme. After topical application of ALA, it penetrates the stratum corneum and accumulates in the abnormal tissues of the epidermis and dermis and then is converted to protoporphyrin IX (PpIX).

Following exposure to intense visible light, PpIX is excited into a triplet state, which reacts with oxygen to produce single oxygen and reactive radicals, causing membrane damage and cell destruction. As a result, the ALA-mediated photodynamic reaction directly kills the pathogenic P. acnes and specifically damages the pilosebaceous glands, thus leads to clinical improvement of acne lesions[18,19]. Several laser- or LED-based light sources of various wavelengths have been used in topical PDT for the treatment of moderate to severe acne. The combination of topical ALA and red LED light has been successfully used to treat several skin conditions[20]. LED offers several advantages including large uniform beam profile, reduced procedural pain and reduced cost. Longer wavelength (630 nm) can reach the deep sebaceous glands[21].

In China, ALA's first approved indication is condylomata acuminate[16], but topical ALA-PDT has been practiced for off-label acne treatment since 2007, and papers have been published since 2009[22,23]. A consensus on ALA-PDT for treatment of acne vulgaris was primarily reached in 2011 by Chinese Dermatologist Association (CDA) based on those pilot studies[24]. The recommended scheme was described as low ALA concentration, short incubation time and red light PDT protocol with an ALA concentration of 2.5-10%, an occlusion time of 0.5-2 h, a dosimetry of red light with of 72-126 J/cm^2, and a treatment course of 3-4 consecutive cycles performed every 7-14 days.

In our work, ALA gel (3.6%) was applied topically to acne lesions for 1.5 h. The lesions were irradiated by a LED light of 633 nm with a light intensity of 66 mW/cm^2 and a light dose of 126 J/cm^2. It was found to be highly effective for inflammatory acne lesions, as demonstrated by the statistically significant reduction in the different types of lesions, including papules, pustules and nodules/cysts. Furthermore, the observed reduction continued during the 4-week follow-up after the final treatment. Optimal effectiveness appears to be obtained at, or after, 4 weeks following the final treatment session. Although a few patients obtained good to excellent results after one to two treatments, most patient needed three-courses to reach a favorable result. It was noticeable that a few patients showed apparent exacerbation of acne lesions before the 2nd and 3rd treatment respectively. Thus, up to three-course multiple sessions are necessary for the patients with severe acne. Compared this study with the other study[25], which used 5% topical ALT with 1h incubation time and every 7-10 days for consecutive 3or 4 sessions for the treatment of moderate and severe acne, statistical analysis showed no significant differences in the effective rate of Pillsbury III-IV severe acne (Table II).

Skin preparation affects the uptake of topical drugs[26]. We took out the contents of the cysts before each treatment, which might help drug penetration and increase the concentration of ALA in

Table II. Effective rate and cure rate in the two treatment groups.

Group	No. of patients	Cure	Excellent	Effective rate	Cure rate
This study	125	55	57	89.6%	44%
The other study in China[25]	323	108	165	84.52%	33.44%
				$\chi^2 = 1.924$	$\chi^2 = 4.345$
				$p = 0.165$,	$p = 0.37$

the cysts with low dose and short time incubation. In addition, we extruded all the comedos before 2nd and 3rd session treatment because they did not have visible reaction after 1st session. We also observed that PDT could prevent the development of new comedos at the three follow-up visits.

Adverse effects of topical ALA-PDT for acne treatment are apparently related to the accumulation of porphyrins in the epidermis and light source and light dosimetry. Inflammatory and pigmentary side effects are common, while permanent injuries such as ulceration and scarring are very rare[26]. In the present report, the side-effects were all transient from mild to moderate degree. Erythema and edema of the treated site immediately after irradiation occurred most frequently, meanwhile painful feelings, desquamation, hyperpigmentation, transient exacerbation of acne lesions and exudation were also seen in our study. However, the prevalence of side effects, especially painful feeling and hyperpigmentation, is really lower compared to the other two ALA-PDT studies conducted in severe acne patients using higher concentration (5-10%) of topical ALA[27,28].

Conclusions

We observed that 3.6% ALA-PDT can improve severe acne in an effective and safe manner in adolescents, and is associated with mild and temporary side effects. The drawback of high cost associated with ALA PDT is still a challenge to overcome in China. The further studies must be performed to reduce the cost of the ALA and develop a good and well-tolerated clinical technique regarding the number of PDT sessions and optimal drug and light doses.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. J Am Acad Dermatol 1998; 39: 34-37.
2) Koo J. The psychosocial impact of acne: patients' perceptions. J Am Acad Dermatol 1995; 32: 26-S30.
3) Tan JK, Bhate K. A global perspective on the epidemiology of acne. Br J Dermatol 2015; 172 (Suppl 1): 3-12
4) Zaidi Z. Acne vulgaris-an update on pathophysiology and treatment. J Pak Med Assoc 2009; 59: 635-637.
5) Ghodsi SZ, Orawa H, Zouboulis CC. Prevalence, severity and severity risk factors of acne in high school pupils: a community-based study. J Invest Dermatol 2009; 129: 2136-2141.
6) Lucky AW, Biro FM, Huster GA, Morrison JA, Elder N. Acne vulgaris in early adolescent boys: correlations with pubertal maturation and age. Arch Dermatol 1991; 127: 210-216.
7) Lucky AW, Biro FM, Simbart LA, Morrison JA, Sorg NW. Predictors of severity of acne vulgaris in young adolescent girls: results of a five-year longitudinal study. J Pediatr 1997; 130: 30-39.
8) Nast A, Dréno B, Bettoli V, Degitz K, Erdmann R, Finlay AY, Gancevicience R, Haedersdal M, Layton A, López-Estebaranz JL, Ochsendorf F, Oprica C, Rosumeck S, Rzany B, Sammain A, Simonart T, Veien NK, Zivkovi MV, Zouboulis CC, Gollnick H. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol Venereol 2012; 26 (Suppl. 1): 1-29.
9) Dreno B, Thiboutot D, Gollnick H, Bettoli V, Kang S, Leyden JJ, Shalita A, Torres V; Global Alliance to Improve Outcomes in Acne. Antibiotic stewardship in dermatology: limiting antibiotic use in acne. Eur J Dermatol 2014; 24: 330-334.
10) Charakida A, Mouser PE, Chu AC. Safety and side effects of the acne drug, oral isotretinoin. Expert Opin Drug Saf 2004; 3: 119-129.
11) Zouboulis CC, Bettoli V. Management of severe acne. Br J Dermatol 2015; 172 (Suppl 1): 27-36.
12) Bowe W, Kober M. Therapeutic update: acne J Drugs Dermatol 2014; 13: 235-238.

13) Pillsbury DM, Shelley WB, Kligman AM. A manual of cutaneous medicine. Philadelphia: W.B. Saunders, 1961.

14) Hongcharu W, Taylor CR, Chang Y, Aghassi D, Suthamjariya K, Anderson RR. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol 2000; 115: 183-192.

15) Torezan L, Niwa AB, Neto CF. Photodynamic therapy in dermatology: basic principles. An Bras Dermatol 2009; 84: 445-459.

16) Itoh Y, Ninomiya Y, Tajima S, Ishibashi A. Photodynamic therapy of acne vulgaris with topical delta-aminolaevulinic acid and incoherent light in Japanese patients. Br J Dermatol 2001; 144: 575-579.

17) Pollock B, Turner D, Stringer MR, Bojar RA, Goulden V, Stables GI, Cunliffe WJ. Topical aminolaevulinic acid photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action. Br J Dermatol 2004; 151: 616-622.

18) Iinuma S, Farshi SS, Ortel B, Hasan T. A mechanistic study of cellular photo destruction with 5-aminolevulinic acid-induced porphyrin. Br J Cancer 1994; 79: 21-28.

19) Divaris DX, Kennedy JC, Poittier RH. Phototoxic damage to sebaceous glands and hair follicles of mice after systemic administration of 5-aminolevulinic acid correlates with localized proto porphyrin IX fluorescence. Am J Pathol 1990; 136: 891-897.

20) Szeimies RM, Matheson RT, Davis SA, Bhatia AC, Frambach Y, Klövekorn W, Fesq H, Berking C, Reifenberger J, Thaçi D. Topical methylaminolevulinate photodynamic therapy using red light-emitting diode light for multiple actinic keratoses: a randomized study. Dermatol Surg 2009; 35: 586-592.

21) Barolet D. Light-emitting diodes (LEDs) in dermatology. Semin Cutan Med Surg 2008; 27: 227-238.

22) Lin MY, Ding HL, Xiang LH. Photodynamic therapy with 5% 5-aminolevulinic acid in the treatment of acne: a randomized, controlled trial. Chinese Journal of Dermatology 2009; 42: 81-83.

23) Zhang L, Wang X, Wang H, Su L, Guo M. Topical aminolevulinic acid-photodynamic therapy in acne. Chinese Journal of Dermatology 2009; 42: 78-80.

24) Task Group of laser treatment, Chinese Dermatological Doctor Branch of Chinese Medical Doctor Association. A consensus on 5-aminolevulinic acid-medicated photodynamic therapy for treatment of acne vulgaris. Chinese Journal of Dermatology 2011; 44: 75-76.

25) Ma L, Xiang LH, Yu B, Yin R, Chen L, Wu Y, Tan ZJ, Liu YB, Tian HQ, Li HZ, Lin T, Wang XL, Li YH, Wang WZ, Yang HL, Lai W. Low-dose topical 5-aminolevulinic acid photodynamic therapy in the treatment of different severity of acne vulgaris. Photodiagnosis Photodyn Ther 2013; 10: 583-590.

26) Sakamoto FH, Torezan L, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part II. Understanding parameters for acne treatment with photodynamic therapy. J Am Acad Dermatol 2010; 63: 195-211.

27) Ma Y, Liu Y, Wang Q, Ren J, Xiang L. Prospective study of topical 5-aminolevulinic acid photodynamic therapy for the treatment of severe adolescent acne in Chinese patients. J Dermatol 2015; 42: 504-507.

28) Wang XL, Wang HW, Zhang LL, Guo MX, Huang Z. Topical ALA PDT for the treatment of severe acne vulgaris. Photodiagnosis Photodyn Ther 2010; 7: 33-38.