ORIGINAL ARTICLE

A new therapeutic option for facial seborrhoeic dermatitis: indole-3-acetic acid photodynamic therapy

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Abstract

Background Indole-3-acetic acid (IAA) is a newly introduced photosensitizer of photodynamic therapy (PDT) for acne, presenting sebum-reducing, anti-inflammatory and antimicrobial activity.

Objective This study was designed to evaluate the efficacy and safety of IAA-PDT in the treatment of facial seborrhoeic dermatitis.

Method In this prospective, single-blinded, 6-week trial, 23 patients with facial seborrhoeic dermatitis were treated with IAA-PDT with green light (520 nm) three times with 1-week intervals. Patients were evaluated at baseline, week 1, 2, 3 and week 6 (3 weeks after last treatment). Efficacy was determined by Seborrhoeic dermatitis Area and Severity Index (SASI), patient's assessment of the symptoms (4-point scale of itchiness, burning, erythema, scale and tightness), sebum secretion rate (measured with Sebumeter®), Erythema Index (EI, measured with Mexameter®) and physician's photographic assessment. Safety was evaluated by questionnaire at each visit.

Result For the 22 subjects completing the trial, SASI and total symptom significantly improved at week 2, which lasted until week 6. Sebum excretion was significantly reduced at week 2 and stayed reduced until week 6. EI presented continuous reduction throughout the study. Photographic assessment showed significant improvement at each visit. The procedure was painless, and no adverse event was observed during and after the treatment.

Conclusion IAA-PDT is a safe and effective therapeutic option for facial seborrhoeic dermatitis.

Received: 9 October 2012; Accepted: 15 November 2012

Conflict of interest

None declared.

Funding sources

Seoul National University Bundang Hospital Research Fund (02-2011-040).

Introduction

Seborrhoeic dermatitis is a chronic, relapsing inflammatory dermatosis with a predilection for areas rich in sebaceous gland.[1] Although data on the exact prevalence are limited, seborrhoeic dermatitis is recognized as one of the most frequent skin disorders, affecting overall 11.6% of the population in the United States.[2] The cause of seborrhoeic dermatitis is poorly understood. Although not all the patients with seborrhoeic dermatitis have excessive secretion of sebum, nor are the sebaceous glands primarily involved, functioning sebaceous glands are probably a permissive factor, as determined from the site of predilection; face, ears and upper part of the trunk.[3] *Malassezia furfur*, lipid-dependent yeast, has been suspected to be potentially pathogenic. Overgrowth of *M. furfur* may induce inflammation through introduction of fungal metabolite, free fatty acids, into the epidermis in susceptible people, and through modulating proinflammatory cytokine production by keratinocytes.[4,5]

The mainstays of the treatment for seborrhoeic dermatitis are topical antifungal agents, topical corticosteroids and topical calcineurin inhibitors.[3] Clinical studies have reported response rate to the topical ketoconazole cream after 4 weeks of up to 90%.[6] However, in the largest double-blind trial involving 1162 patients, the response rates to 2% ketoconazole cream or foam were only 56%, as compared with 42% to placebo.[7] Long-term use of topical corticosteroid leads to side-effects including skin atrophy, steroid rebound phenomenon or steroid-induced rosacea. Such side-effects have lent its use impractical for the treatment of chronic, relapsing seborrhoeic dermatitis. Although topical calcineurin inhibitors may be superior alternatives to corticosteroids without long-term side-effects, adverse effects of burning sensation and irritation have commonly been reported.[8–10]

Indole-3-acetic acid (IAA), also known as auxin, is a phytohormone mediating responses to light. Recently, IAA as a photosensitizer for photodynamic therapy (PDT) in the treatment of acne

has been suggested.[11] With 520-nm green light irradiation, which was the most effective wavelength in activating IAA to produce free radicals among various wavelengths (380–640 nm), IAA-PDT presented sebum-reducing effect without prominent destruction of sebaceous glands, along with antimicrobial activity on *Propionibacterium acnes*. In addition, IAA itself has been reported to have anti-inflammatory effects.[12] This study was designed to evaluate the efficacy and safety of IAA-PDT in the treatment of facial seborrhoeic dermatitis.

Materials and methods

Study design and patients

A total of 23 patients aged older than 20 years with facial seborrhoeic dermatitis were enrolled. The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB approval number: B1109/135-001), and informed consents were obtained from all of the patients. The patients were required to have no history of oral steroid treatment, oral antibiotic treatment and topical agents such as steroid or calcineurin inhibitor within the past 2 weeks. Patients were excluded if they were pregnant or lactating women or had any other facial skin disease. No other treatment for seborrhoeic dermatitis was permitted during the study.

Treatment

After facial skin was gently cleansed, 0.015% IAA (AC gel®; Wellskin, Seoul, Korea) was applied for 15 min under occlusion. A 520-nm green diode light (Nouvo-GB®; M.I tech, Daejeon, Korea) with an intensity of 9 J/cm^2 was illuminated for 15 min. The treatment protocol was repeated three times with 1-week intervals.

Efficacy and safety evaluation

Evaluation was conducted at 0, 1, 2, 3, 6 weeks by two dermatologists. Five symptoms including itchiness, burning sensation, erythema, scale and tightness were self-assessed by the patients using a questionnaire with a grading scale from 0 to 3 at each visit. The parameters were summed up to calculate total symptom score with a range from 0 to 15. Clinical assessment was performed using Seborrhoeic dermatitis Area and Severity Index (SASI). The severity of erythema, scale and greasiness was scored at 0 (none), 1 (mild), 2 (moderate) or 3 (severe). Then, the extent of facial involvement was measured in range of 0–6 (0: 0%, 1: <10%, 2: 10–29%, 3: 30–49%, 4: 50–69%, 5: 70–89%, 6: 90–100%). Involved area was assessed using the rule of fours.[13] A total score ranging from 0 to 54 was calculated as in the same manner in calculating conventional Psoriasis Area and Severity Index (PASI). Sebum secretion rate was measured using Sebumeter SM815® (Courage&Khazaka, Cologne, Germany). The patients were asked not to wash their faces up to 6 h before the measurement, and measurement was performed on the forehead and both cheeks. Erythema Index (EI) was measured at the same seborrhoeic dermatitis lesion using Mexameter® (Courage&Khazaka). If erythema disappeared at the measuring site during the study, the most erythematous lesion at another site was measured. Facial photographs were taken using a standardized camera setting at each visit for photographic assessment where improvement was scored compared with the baseline: 4 (clearance), 3 (excellent), 2 (good), 1 (slight), 0 (no change),−1 (worse). The presence of side-effects such as pain, erythema, desquamation, crust formation, swelling and postinflammatory hyperpigmentation were enquired about at each visit.

Statistical analysis

Each measurement at follow-up visit was compared with baseline score using paired t-tests. SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used to analyse the data with P-values of < 0.05 to be statistically significant.

Results

Study populations

A total of 23 patients were enrolled in the study. The patient age ranged from 26 to 51 years (mean ± SD, 32.05 ± 6.95). All patients were female and had Fitzpatrick skin type III or IV. Of the 23 patients, 22 patients completed the study. One patient was withdrawn due to follow-up loss at week 6.

Efficacy evaluation

For the 22 subjects completing the 6-week study, the total symptom score showed a significant improvement at week 2, week 3 and week 6 compared with baseline (Fig. 1). While itchiness, burning sensation and erythema was significantly reduced after week 2, tightness was relieved 1 week earlier and scale decreased 1 week later.

The mean SASI was significantly decreased at week 2 and week 3 by 15.6% and 27.0%, respectively, compared with baseline (Fig. 2). At week 6, the mean SASI was reduced by 28.9% (from 13.39 to 9.52), 4 weeks after the completion of the three sessions of IAA-PDT.

Compared with baseline, the mean sebum excretion was significantly reduced by 12.2% (from 127.71 to 112.9) at week 2 (Fig. 3). The sebum excretion stayed reduced until the end of the study, with a reduction of 17.2% at week 6. EI presented significant improvement after one session of IAA-PDT and maintained improvement throughout the study. Photographic assessment also showed slight, but significant improvement after one session of IAA-PDT until week 6 (Figs 4 and 5).

Safety evaluation

All the patients tolerated the treatment well. None of the patients complained of immediate side-effects such as erythema, pruritus or pain during and after the IAA-PDT. No serious adverse events including desquamation, swelling, crust formation,

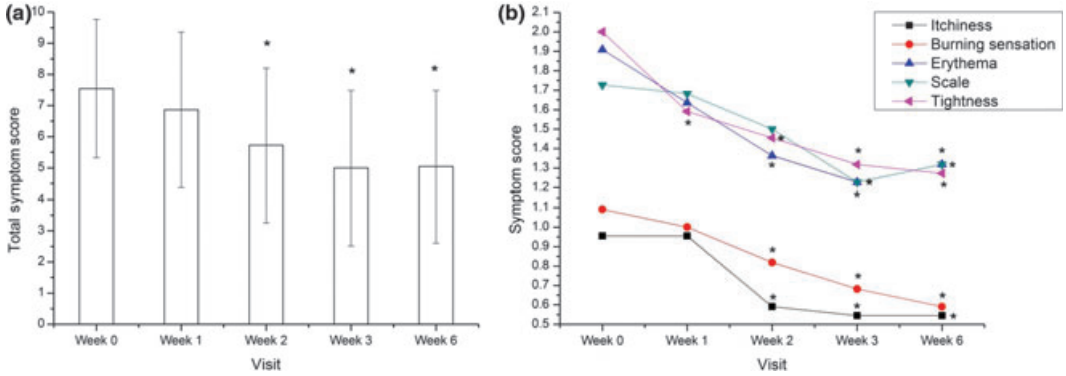

Figure 1 The mean total symptom score (a), and change in the mean scores of the five symptoms (b) of the patients treated with Indole-3-acetic acid-photodynamic therapy. Compared with baseline, mean total symptom score presented significant improvement at week 2 and week 3, and the achievement was maintained until 3 weeks after the end of the treatment. Of the five attributes in the total symptom score, itchiness, burning sensation and erythema significantly reduced since week 2, while tightness and scale relieved since week 1 and week 3 respectively. All of the five symptoms remained improved until week 6. *$P < 0.05$.

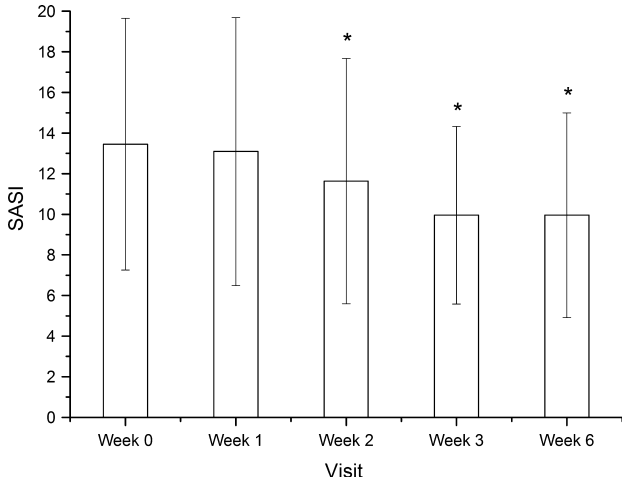

Figure 2 The mean Seborrhoeic dermatitis Area and Severity Index (SASI) score of patients treated with Indole-3-acetic acid-photodynamic therapy (IAA-PDT). Compared with baseline, mean SASI improved significantly at week 2 and week 3, and remained reduced after 3 weeks after three sessions of IAA-PDT. *$P < 0.05$.

postinflammatory hyperpigmentation or scarring were observed during the course of the study.

Discussion

Indole-3-acetic acid itself is non-toxic, but produces reactive oxygen species (ROS) following oxidative decarboxylation by horseradish peroxidase (HRP).[14,15] As the combination of IAA and HRP induces cancer cell apoptosis, its potential role in anticancer therapy has been suggested. Several reports have revealed that IAA is activated not only by HRP but also by UVB or visible light irradiation, which suggests that it has a potential as a photosensitizer.[16,17]

Recently, we reported therapeutic effect of IAA-PDT on acne.[11,18] With 520-nm green light irradiation, IAA-PDT presented sebum-reducing effect, antimicrobial activity on *P. acnes* and *S. aureus* and relief of follicular obstruction via destruction of follicular ostia epithelium. As not all the patients with seborrhoeic dermatitis have excessive secretion of sebum, nor are the sebaceous glands primarily involved, there has been a debate on the association of seborrhoeic dermatitis and excess sebum production. However, functioning sebaceous glands are likely a permissive factor, as seen from the site of predilection.[3] IAA has also been reported to have anti-inflammatory effects.[12] Therefore, it was hypothesized that sebum-reducing and anti-inflammatory effects of IAA-PDT might play a certain role in the treatment of seborrhoeic dermatitis.

Our result demonstrates that all of the five parameters (total symptom score, SASI, sebum excretion, EI and photographic assessment) presented significant improvements after three sessions of IAA-PDT when compared with baseline. Remarkably, EI improved more significantly than the other measurements. Patients also noted significantly less burning sensation and less erythema (statistically insignificant) after one session of treatment. The anti-inflammatory property of IAA may have immediate effects on relieving erythema and burning sensation.

Meanwhile, sebum excretion rate showed delayed reduction, which was significant after the end of the treatment. Although IAA-PDT presented definite sebum-reducing activity, the mechanism is not fully understood as yet. It has been proved that IAA-PDT shows no prominent destruction of sebaceous gland.[11] One explanation is the elimination of *P. acnes*, which has been reported to augment lipogenesis in sebaceous gland.[19] Long time interval in the elimination of *P. acne* and consequent reduced lipogenesis in

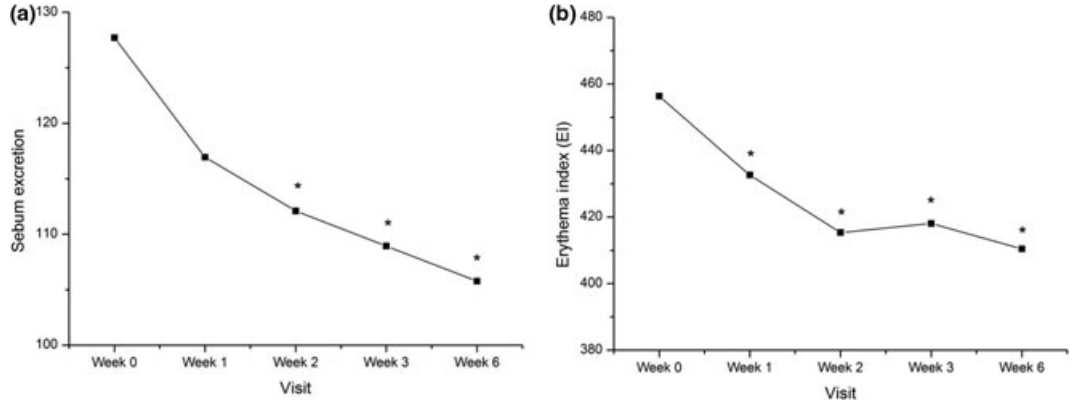

Figure 3 Change in the mean sebum excretion (a) and mean Erythema Index (EI) (b) of the patients treated with Indole-3-acetic acid-photodynamic therapy (IAA-PDT). Compared with baseline, the mean sebum excretion was significantly decreased at week 2, and maintained at the reduced level until the end of the study. EI presented significant improvement after one session of IAA-PDT and remained improved throughout the study. *$P < 0.05$.

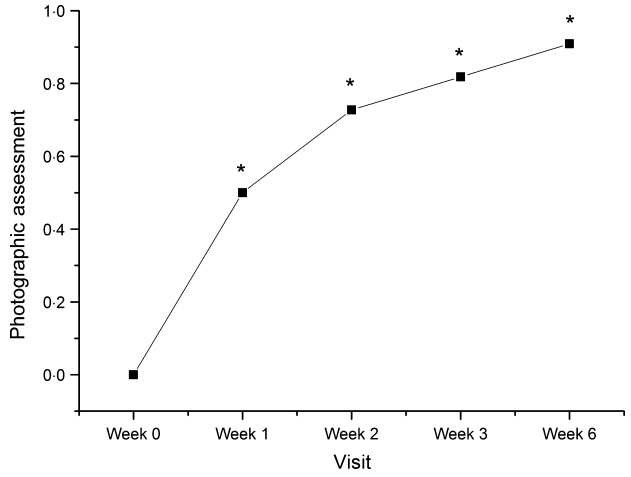

Figure 4 Change in the mean photographic assessment score of the patients treated with Indole-3-acetic acid-photodynamic therapy (IAA-PDT). Photographic assessment showed slight, but significant improvement after one session of IAA-PDT until week 6. *$P < 0.05$.

sebaceous gland may be a clue to the delayed reduction in sebum excretion.

Topical agents in the treatment of seborrhoeic dermatitis including antifungals, corticosteroids and calcineurin inhibitors generally require daily use. It is often impractical for the patients, especially males who are indifferent to daily skin care routine, resulting in poor compliance. In contrast, IAA-PDT requires only three treatments over a 3-week period. One requirement is that the treatment needs to be performed at the clinics, with the duration of approximately 30 min for each visit. Nevertheless, all patients in the study showed excellent compliance with the treatment, with the exception of one patient lost at the follow-up at week 6 (after the end of the treatment). It is noteworthy that the therapeutic effects of IAA-PDT were maintained 4 weeks after the last treatment session (week 6). While recurrence of the disease often occurs after discontinuation of topical agents, it was noteworthy that the therapeutic effects of IAA-PDT continued a minimum of 1 month after the completion of the three sessions.

Although seborrhoeic dermatitis is one of the most common dermatoses, the validated criteria for the grading of its severity are limited. Recently, Seborrhoea Area and Severity Index – Face (SASI-F) was suggested as a grading tool.[20] Two of the index, erythema and scale, are scored on a 5-point scale. The scores are then summed up and multiplied by the relative area of facial involvement ratio. The criteria, however, has limitations in assessing the degree of seborrhoea, a critical feature of seborrhoeic dermatitis both clinically and aetiologically. In our study, we proposed SASI, a modified version of the conventional PASI, which scores three representative features – erythema, scale and greasiness – with a 4-point scale. SASI corresponded closely with objective measurements including not only sebum excretion rate and EI, but also subjective total symptom score by patients.

Compared with the conventional photodynamic therapy using 5-aminolevulinic acid (ALA), IAA-PDT is painless and safe. None of the patients in the study complained of pain or other adverse effects such as erythema, desquamation, swelling, crust formation or postinflammatory hyperpigmentation during or after the treatment. While partial or complete necrosis of sebaceous glands was observed in ALA-PDT, no prominent destruction of sebaceous glands was noted in IAA-PDT.[11,21] It explains the difference in safety profile between the two methods of PDT and the reason why IAA-PDT is not painful. In our institute, over 500 patients have been treated with IAA-PDT without a single case of adverse events observed (personal observations). As topically applied ALA

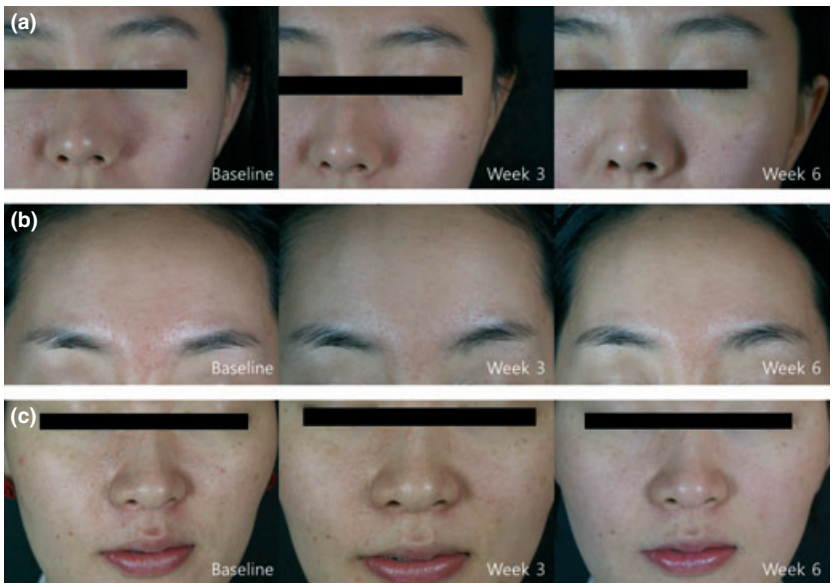

Figure 5 Clinical photographs of the three representative cases with seborrhoeic dermatitis presenting improvement when treated with Indole-3-acetic acid-photodynamic therapy. Compared with baseline, improvements at cheek (a), glabella (b) and perinasal area (c) were observed at week 3, which was maintained until week 6.

becomes photosensitive once metabolized to protoporphyrin IX in epithelial cells, a long incubation time is essential in ALA-PDT. Concentration of protoporphyrin IX increases incubation time dependently, which reaches its highest level in 12 h.[22] IAA-PDT, in contrast, is photosensitive itself, and does not require time for metabolism. In our previous report, IAA-PDT successfully presented its effects with only 15 min of incubation.[11] In addition, no photoprotection is needed in IAA-PDT, while-light avoidance for 48 h is recommended in patients after receiving ALA-PDT to prevent further phototoxicity.[23]

In conclusion, facial seborrhoeic dermatitis improved significantly with three sessions of IAA-PDT via anti-inflammatory and sebum-reducing activities, and the therapeutic effects were sustained for 4 weeks after the end of the treatment. It is painless and safe, requires only a short incubation time without photoprotection after the treatment and shows good compliance of the patients. The results reported here suggest that IAA-PDT is an effective and safe treatment option for facial seborrhoeic dermatitis.

Acknowledgement

This study is supported by grant number 02-2011-040 from the Seoul National University Bundang Hospital Research Fund.

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