

CLINICAL REPORT

Comparison of 5-Aminolevulinic Acid Photodynamic Therapy and Clobetasol Propionate in Treatment of Vulvar Lichen Sclerosus

Lei SHI^{1#}, Fei MIAO^{2#}, Ling-Lin ZHANG¹, Guo-Long ZHANG¹, Pei-Ru WANG¹, Jie JI¹, Xiao-Jie WANG¹, Zheng HUANG^{3,4}, Hong-Wei WANG² and Xiu-Li WANG¹

¹Institute of Photomedicine, Shanghai Skin Disease Hospital, Tongji University School of Medicine, ²Huadong Hospital, Fudan University, Shanghai, China,

³University of Colorado Denver Cancer Center, Aurora, CO, USA, and ⁴College of Photonic & Electronic Engineering, Fujian Normal University, Fuzhou, China

[#]These authors contributed equally and should be considered as first authors.

The aim of this study was to evaluate the effectiveness of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) for the treatment of vulvar lichen sclerosus (VLS) and compare its effectiveness with that of clobetasol propionate. Four sessions of topical photodynamic therapy (PDT) were administered at 2-week intervals ($n=20$). Clobetasol propionate (0.05%) was used daily for 8 weeks ($n=20$). The rate of complete response in the PDT group (14/20) was double that of the clobetasol propionate group (7/20) ($p<0.05$, $\chi^2=4.912$). Horizontal visual analogue scores indicated that PDT was more effective than clobetasol propionate. Pain intensity numeric rating scale values for PDT were between 3.05 and 4.45. One month after the final session of PDT, only one patient relapsed and all 7 patients in clobetasol propionate group relapsed. ALA-PDT is a well-tolerated and effective option for the treatment of VLS. *Key words:* ALA-PDT; lichen sclerosus; pain; PpIX fluorescence; clobetasol propionate.

Accepted Jan 14, 2016; Epub ahead of print Jan 18, 2016

Acta Derm Venereol 2016; 96: 684–688.

Xiu-Li Wang, Institute of Photomedicine, Shanghai Skin Disease Hospital, Tongji University School of Medicine, Shanghai 200443, China. E-mail: xlwang2001@aliyun.com;

Hong-Wei Wang, Huadong Hospital, Fudan University, Shanghai 200040, China. E-mail: hongweiwang2005@aliyun.com

Lichen sclerosus (LS) is a chronic inflammatory skin disease that affects both sexes of all age groups (1). Vulval lichen sclerosus (VLS) can be a serious condition for postmenopausal and perimenopausal women. The most common symptoms of VLS are pruritus, pain, dyspareunia, and postcoital soreness. Hyperkeratosis, atrophy, sclerosis and depigmentation are typical clinical signs of VLS. Purpura or flare, erosions, fissures, and telangiectasia may be present in some cases (2). VLS not only affects quality of life, but is also associated with an increased risk of squamous cell carcinoma (SCC) of the vulva (3).

Topical corticosteroid ointment is the conventional treatment for VLS (4). Clobetasol propionate, an ultra-potent corticosteroid, is a commonly used drug. Other treatments include pharmaceuticals (e.g. testosterone, progesterone, tacrolimus, 5-fluorouracil, and retinoids), surgery, cryosurgery, laser therapy and ultraviolet A1 (UVA1) (5, 6). However, none of these treatments is satisfactory. 5-aminolevulinic acid photodynamic therapy (ALA-PDT) is a relatively new treatment in the case of non-malignant skin diseases (7, 8). The effect of ALA-PDT on VLS was first reported by Hillemanns et al. in 1999 (9). Studies have shown that ALA-PDT can result in partial or even full remission of symptoms and signs (10–16).

The aim of this prospective study on VLS patients was to evaluate the effectiveness and adverse reactions of ALA-PDT in comparison with topical clobetasol propionate.

METHODS (for full details see Appendix S1¹)

In this open-label, randomized controlled prospective study, women of 18 years or older with biopsy-proven active VLS who had the ability to sign written informed consent, willingness to comply with the study requirements, and were not planning to conceive or breastfeed during the study, were recruited. Patients were randomized to either ALA-PDT or clobetasol propionate groups. No other treatments were allowed during the treatment and follow-up.

Photographs of the VLS lesions were used to measure lesion size. A horizontal visual analogue scale was used to evaluate disease extent (including lesion scale and signs) and symptoms.

ALA-PDT. Freshly prepared 10% 5-ALA cream (Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co. Ltd, Shanghai, China) was applied to the lesions with a 1-cm margin and incubated for 3 h. The lesions were irradiated with 100 J/cm² 633 nm red light at 100 mW/cm². The same PDT procedure was repeated 3 times at 2-week intervals.

Clobetasol propionate. A thin layer of 0.05% clobetasol propionate ointment (ShunFeng Pharmaceutical Co. Ltd, China) was applied by the patient herself every night for 8 weeks (17).

Protoporphyrin IX (PpIX) fluorescence image and intensity were examined at different time-points (18).

¹<https://doi.org/10.2340/00015555-2341>

The reduction in lesion size was evaluated at 2, 4, 6 and 8 weeks after the start of treatment. Changes in each horizontal visual analogue score of individual patients were analysed before treatment, at the end of treatment (week 8), and 6 months after the end of treatment. During each session of PDT, the patients were asked to report the severity and duration of treatment-related pain. The maximal painful sensation was evaluated using an 11-point pain intensity numeric rating scale (PI-NRS).

The results were analysed using appropriate statistical methods (see Appendix S1¹).

RESULTS

Patient data

A total of 43 consecutive patients presenting with clinically and histologically verified diffuse VLS were recruited to the study. Twenty-one patients were assigned to the ALA-PDT group and, of these, 20 completed the study. Twenty-two patients were assigned to the clobetasol propionate group and, of these, 20 completed the study. Three patients dropped out of the study due to relocation (Fig. S1¹). The baseline characteristics are listed in Table I. There was no statistical difference between the 2 groups in terms of lesion size ($p=0.809$, $t=0.243$), disease extent ($p=0.931$ for lesion scale, $p>0.39$ for signs) and symptom severity ($p=1.000$).

PpIX production in VLS lesion

Under ultraviolet (UV) irradiation, the VLS lesions showed strong fluorescence, except for some small areas that showed inhomogeneous and weak fluorescence (Fig. S2¹). PpIX production increased with the increase in incubation time. PpIX production in VLS lesions was significantly higher than in perilesional skin ($p<0.05$, $F=50.028$) and adjacent normal skin ($p<0.05$, $F=58.203$). For VLS lesions, under the same dose of 5-ALA the PpIX fluorescence intensity of the first session was higher than that of the second session ($p<0.05$, $F=4.8$), and that of the second session was higher than that of third session ($p<0.05$, $F=10.608$), but there was no statistical difference between the third and fourth sessions ($p>0.05$, $F=0.454$) (Fig. S3¹).

Table I. Baseline characteristics for all participants who completed the study

Baseline characteristics	ALA-PDT	Clobetasol	Total
	group	propionate	
	n=20	n=20	n=40
Age, years, mean \pm SD	50.7 \pm 9.6	52.1 \pm 8.9	51.4 \pm 15.6
Duration, mean \pm SD	58.0 \pm 22.5	52.4 \pm 21.9	55.2 \pm 26.1
Recurrent:newly diagnosed, n	16:4	19:1	35:5
Postmenopausal:perimenopausal, n	13:7	15:5	28:12

ALA-PDT: 5-aminolevulinic acid photodynamic therapy; SD: standard deviation.

Clinical outcomes

In the ALA-PDT group, 14 out of 20 (70%) patients achieved complete response, 4 (20%) partial response, and 2 (10%) minimal response, whereas in the clobetasol propionate group, 7 out of 20 (35%) patients achieved complete response, 6 (30%) partial response, and 7 (35%) minimal response. The rate of complete response in the ALA-PDT group was much higher than that in the clobetasol propionate group ($p<0.05$, $\chi^2=4.912$) (Fig. S4¹). The rates of complete response of different subgroups are shown in Table II. For recurrent cases, although the initial responses were similar between the 2 groups (6.3% vs. 5.3%), the overall response at week 8 after multi-session ALA-PDT was much higher than that after topical corticosteroid treatment (75% vs. 32%). For both groups, the initial response of perimenopausal women was higher than that of postmenopausal women. Interestingly, at week 8 the complete response rate to ALA-PDT of postmenopausal women was much higher than that of perimenopausal women (77% vs. 57%).

Both groups showed a significant reduction in lesion size, although there was no difference between the 2 groups ($p=0.116$, $t=-1.608$)².

ALA-PDT was more effective in reducing the severity of the disease. As shown in Fig. 1, in terms of the ratios of the vulvar surface affected by VLS there was no difference between the 2 groups before treatment. Although there was no difference between the 2 groups at the end of treatment ($p=0.057$, $Z=-1.903$), both groups showed significant improvement (ALA-PDT: $p=0.000$, $Z=-3.993$; clobetasol propionate: $p=0.000$, $Z=-3.974$). The scores of corticosteroid group became much higher than that of ALA-PDT group at 6 months after end of treatment ($p=0.000$, $Z=-5.352$) and essentially returned to a distribution profile similar to that seen before treatment ($p=0.414$, $Z=-8.16$). The scores of the ALA-PDT group at 6 months was similar to those at the end of treatment ($p=0.317$, $Z=-1.000$) and lower than those before treatment ($p=0.000$, $Z=-3.999$).

In terms of clinical signs, there was no difference between the 2 groups before treatment. At the end of treatment, the scores of the topical corticosteroid group were higher than those of the ALA-PDT group (hyperkeratosis: $p=0.018$, $Z=-2.360$; atrophy: $p=0.019$, $Z=-2.342$; sclerosis: $p=0.031$, $Z=-2.163$; depigmenta-

²The mean lesion size of the ALA-PDT group reduced from 35.18 ± 3.51 cm² to 5.38 ± 8.98 cm² ($p=0.000$, $t=11.614$) and that of clobetasol propionate group from 36.29 ± 13.23 cm² to 9.83 ± 8.51 cm² ($p=0.000$, $t=8.119$). At the 6-month follow-up, there was no significant change in the ALA-PDT group ($p=0.523$, $t=-0.651$), but an increase in the clobetasol propionate group ($p=0.000$, $t=-7.245$). The difference between the 2 groups became statistically significant (5.66 ± 8.73 cm² vs. 32.49 ± 12.71 cm²) ($p=0.000$, $t=-7.781$) (see Fig. S3¹ for representative photographs).

Table II. Rates of complete response (CR) of different subgroups after multi-session of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) and clobetasol propionate treatments

Treatment time	ALA-PDT complete response (n=20)			Clobetasol propionate complete response (n=20)		
	Total, %	Recurrent (n=16) vs. newly diagnosed (n=4), %	Postmenopause (n=13) vs. perimenopause (n=7), %	Total, %	Recurrent (n=19) vs. newly diagnosed (n=1), %	Postmenopausal (n=15) vs. perimenopausal (n=5), %
2 weeks	10	6.3 vs. 25.0	7.7 vs. 14.3	10	5.3 vs. 100	6.7 vs. 20.0
4 weeks	40	37.5 vs. 50.0	38.5 vs. 42.9	25	21.1 vs. 100	20.0 vs. 40.0
6 weeks	60	62.5 vs. 50.0	61.5 vs. 57.1	30	26.3 vs. 100	26.6 vs. 40.0
8 weeks	70	75.0 vs. 50.0	76.9 vs. 57.1	35	31.6 vs. 100	33.3 vs. 40.0

tion: $p=0.029$, $Z=-2.188$) although both groups showed improvement. At 6 months of follow-up, the scores of the topical corticosteroid group became much higher than those of the ALA-PDT group. Moreover, clinical signs (except sclerosis) returned to the distribution profile similar to that of before treatment. For the ALA-PDT group, all clinical signs at 6 months' follow-up remained much lower than before treatment (hyperkeratosis: $p=0.000$, $Z=-3.494$; atrophy: $p=0.000$, $Z=-3.923$; sclerosis: $p=0.000$, $Z=-4.028$; depigmentation: $p=0.000$, $Z=-3.938$) (Fig. S5¹).

The symptom scores of the topical corticosteroid group were higher than those of the ALA-PDT group ($p=0.035$, $Z=-2.113$) although both groups showed improvement. At 6 months of follow-up, the scores of the topical corticosteroid group were much higher than those of the ALA-PDT group ($p=0.000$, $Z=-4.934$). Moreover, pruritus, burning or pain feeling reappeared or becoming worse over time in the topical corticosteroid group, since the overall score was even higher than before treatment ($p=0.021$, $Z=-2.309$). However, the scores of the ALA-PDT group remained much lower than before treatment ($p=0.000$, $Z=-3.923$) (Fig. 2).

Adverse reactions

Pain. The mean PI-NRS value of 4 ALA-PDT sessions was 4.45, 3.4, 3.15 and 3.05, respectively. The PI-NRS value of the first session of ALA-PDT was higher than that of the second ALA-PDT ($p<0.05$, $t=3.462$). There was no statistical difference between the PI-NRS values of the second, 3rd and 4th sessions of ALA-PDT ($p>0.05$, $F=3.77$). During the first session of ALA-PDT, 3 of 20 patients had PI-NRS values of 7, 8 and 7, respectively and received a local injection of lidocaine in order to complete the treatment. During the second session of ALA-PDT, their PI-NRS values reduced to 4, 7 and 5, respectively. The patient who had a PI-NRS value of 7 was given another lidocaine injection. During the 3rd and 4th sessions of ALA-PDT, their PI-NRS values were reduced to 4–5 and 3, respectively.

Other. After light irradiation in the first session of ALA-PDT, 6 patients showed redness and swelling, which gradually faded away in 3 days, except for 1 case, which evolved into erosion the following day. The erosion was treated with mupirocin ointment for one week. The same signs were seen during the fol-

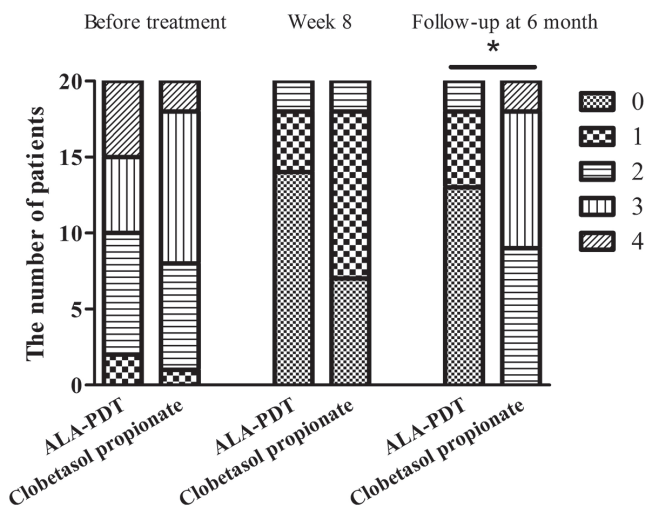


Fig. 1. Distribution of horizontal visual analogue values of lesion scale of the 5-aminolevulinic acid photodynamic therapy (ALA-PDT) group and the clobetasol propionate group before treatment, at the end of treatment (week 8), and 6 months after the end of treatment. The lesion scale was graded as: 0=none, 1=less than 25%, 2=25–50%, 3=51–75%, 4=more than 75% of the vulvar surface affected. * $p<0.05$.

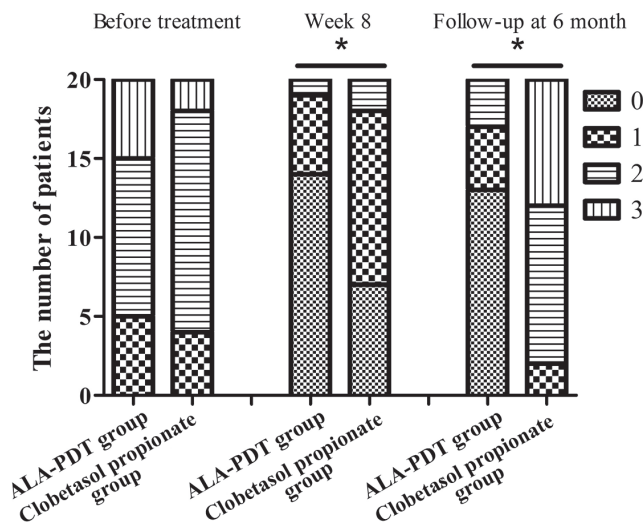


Fig. 2. Horizontal visual analogue value of subjective symptoms in the 5-aminolevulinic acid photodynamic therapy (ALA-PDT) group and the clobetasol propionate group before treatment, at the end of treatment (week 8), and 6 months after the end of treatment. The severity of symptoms (pruritus, burning and pain feeling) were graded as: 0=absent, 1=mild, 2=moderate, 3=severe. * $p<0.05$.

lowing sessions, but were less severe than during the first session.

Neither corticosteroid-dependent dermatitis nor secondary infection was observed in the clobetasol propionate group during the course of treatment.

Relapse

All patients finished the 6-month follow-up. In the ALA-PDT group 1 out of 14 (7.1%) patients relapsed one month after completion of treatment. The remaining 13 patients showed no signs of recurrence during follow-up. In the clobetasol propionate group, 7 out of 7 (100%) patients relapsed one month after treatment.

DISCUSSION

PpIX production and accumulation in VLS is a key step in ensuring the effectiveness of ALA-PDT. *In situ* observation of PpIX fluorescence showed that the distribution of PpIX matched the location of the VLS lesions (see Fig. S2¹). Less severe lesions occasionally presented weak PpIX accumulation or inhomogeneous distribution, whereas peripheral areas showed a lack of PpIX fluorescence. Possible explanations were that some of these areas absorbed less 5-ALA or there was a lack of infiltration of inflammatory cells. Nevertheless, this study showed that the fluorescence intensity of lesional skin was significantly higher than that of perilesional skin and adjacent normal skin (see Figs S3 and S4¹). The PpIX fluorescence intensity of the first session of ALA-PDT was higher than that of the second session, and that of the second session of ALA-PDT was higher than that of the third session, possibly due to the improvement in lesion severity.

Pain is the main adverse reaction in ALA-PDT and the precise mechanisms remain unknown (19). Cytotoxic substances or inflammation created by the photodynamic reaction, and several other parameters (i.e. lesion location, treatment times, PpIX accumulation, light intensity) are thought to play a role in the pathogenesis of the pain (20). PI-NRS values in this study suggest that patients felt the worst pain during the first session of ALA-PDT. During subsequent treatments the pain subsided, possibly due to the improvement in lesion severity, reduction in PpIX accumulation, and less inflammatory reactions. Patients with PI-NRS ≥ 7 were given lidocaine, which becomes active 5 min after injection. The application of local lidocaine injection might interrupt PDT for a few minutes, but it has no influence on PpIX photobleaching and ALA-PDT outcome (21).

Guidelines suggest using a topical corticosteroid for 12 weeks; once at night for the first 4 weeks, then on alternate nights for 4 weeks, and then twice weekly for another 4 weeks (4). In order to ensure patient compliance, topical corticosteroid was applied daily at night

for 8 weeks. To observe the effectiveness and duration of clobetasol propionate, after stopping the medication at week 8 no corticosteroid maintenance treatment was used. At the end of treatment, both groups showed improvement in terms of clinical signs and subjective symptoms (see Figs 1 and 2). Signs and symptoms returned during follow-up in some patients who received topical corticosteroid treatment. The complete response rate in the ALA-PDT group was much higher than that of the topical corticosteroid group ($p < 0.05$). Patients with lower scores showed better response. Although it was difficult to draw conclusions about whether newly diagnosed cases had a better or worse response to PDT due to the small sample size, it seemed that the recurrent cases showed better overall response to multi-session PDT than to topical corticosteroid treatment (see Table II). Perimenopausal women showed a better overall response to PDT than to topical corticosteroid treatment. Interestingly, the complete response rate of postmenopausal women to ALA-PDT was much higher than that of perimenopausal women. This may be due to a reduced level of reproductive hormones in postmenopausal women (22).

The signs and subjective symptoms in the ALA-PDT group improved more significantly than in the clobetasol propionate group, especially for sclerosis and atrophy, which are usually less treatable. In this study, the ALA-PDT group showed a significantly low recurrence rate (7.1%)³.

This study has several limitations; first, the sample size is small; and secondly, the follow-up time was only 6 months. More work and longer observation is needed to verify whether ALA-PDT could prevent subsequent vulvar SCC and scar formation. Finally, the lack of universal parameters to assess disease severity and treatment response might influence the efficacy comparison of different treatments.

In conclusion, this study demonstrates that ALA-PDT is a safe and effective therapeutic option for VLS of various severities. ALA-PDT shows a longer remission duration and a higher complete response rate than clobetasol propionate. For patients who relapse after ALA-PDT, steroids can be used as a palliative treatment for those whose symptoms are less severe. If symptoms worsen, ALA-PDT can be administered repeatedly to control recurrent and remaining lesions. Since steroids can alleviate some post-PDT transitory symptoms, a combination of ALA-PDT and corticosteroids might be considered in order to reduce treatment cost.

³The review of the recurrent case showed that the patient was 61 years old, had a 7-year history, and had received irregular corticosteroid treatments in the past. Her lesion scale score was 3 and the scores for hyperkeratosis, atrophy, sclerosis, and depigmentation were 1, 1, 2, and 2, respectively. The severity might be a key factor in her recurrence. After a further 5 sessions of ALA-PDT, the patient was disease-free for 6 months of follow-up.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Natural Science Foundation (81272990, 81472538) and the Key Project of Shanghai Municipal Commission of Health and Family Planning (20124034).

The authors declare no conflicts of interest.

REFERENCES

- Kantere D, Lowhagen GB, Alvingren G, Maneskold A, Gillstedt M, Tunback P. The clinical spectrum of lichen sclerosis in male patients – a retrospective study. *Acta Derm Venereol* 2014; 94: 542–546.
- Virgili A, Borghi A, Toni G, Minghetti S, Corazza M. Prospective clinical and epidemiologic study of vulvar lichen sclerosis: analysis of prevalence and severity of clinical features, together with historical and demographic associations. *Dermatology* 2014; 228: 145–151.
- Carlson BC, Hofer MD, Ballek N, Yang XJ, Meeks JJ, Gonzalez CM. Protein markers of malignant potential in penile and vulvar lichen sclerosis. *J Urol* 2013; 190: 399–406.
- Neill SM, Lewis FM, Tatnall FM, Cox NH. British Association of Dermatologists' guidelines for the management of lichen sclerosis 2010. *Br J Dermatol* 2010; 163: 672–682.
- Beattie PE, Dawe RS, Ferguson J, Ibbotson SH. UVA1 phototherapy for genital lichen sclerosis. *Clin Exp Dermatol* 2006; 31: 343–347.
- Virgili A, Lauriola MM, Mantovani L, Corazza M. Vulvar lichen sclerosis: 11 women treated with tacrolimus 0.1% ointment. *Acta Derm Venereol* 2007; 87: 69–72.
- Wang X-L, Wang H-W, Guo M-X, Huang Z. Combination of immunotherapy and photodynamic therapy in the treatment of Bowenoid papulosis. *Photodiagnosis Photodyn Ther* 2007; 4: 88–93.
- Fan Z-X, Zhang L-L, Wang H-W, Wang P-R, Huang Z, Wang X-L. Treatment of cutaneous lichen planus with ALA-mediated topical photodynamic therapy. *J Innov Opt Health Sci* 2015; 8: 1540004.
- Hillemanns P, Untch M, Pröve F, Baumgartner R, Hillemanns M, Korell M. Photodynamic therapy of vulvar lichen sclerosis with 5-aminolevulinic acid. *Obstet Gynecol* 1999; 93: 71–74.
- Biniszkiwicz T, Olejek A, Kozak-Darmas I, Sieroń A. Therapeutic effects of 5-ALA-induced photodynamic therapy in vulvar lichen sclerosis. *Photodiagnosis Photodyn Ther* 2005; 2: 157–160.
- Olejek A, Kozak-Darmas I, Kellas-Slecza S, Steplewska K, Biniszkiwicz T, Birkner B, et al. Effectiveness of photodynamic therapy in the treatment of lichen sclerosis: cell changes in immunohistochemistry. *Neuro Endocrinol Lett* 2009; 30: 547–551.
- Osiecka BJ, Nockowski P, Jurczyszyn K, Ziolkowski P. Photodynamic therapy of vulvar lichen sclerosis et atrophicus in a woman with hypothyreosis – case report. *Photodiagnosis Photodyn Ther* 2012; 9: 186–188.
- Romero A, Hernandez-Nunez A, Cordoba-Guijarro S, Arias-Palomo D, Borbujo-Martinez J. Treatment of recalcitrant erosive vulvar lichen sclerosis with photodynamic therapy. *J Am Acad Dermatol* 2007; 57: S46–47.
- Sotiriou E, Apalla Z, Patsatsi A, Panagiotidou D. Recalcitrant vulvar lichen sclerosis treated with aminolevulinic acid-photodynamic therapy: a report of five cases. *J Eur Acad Dermatol Venereol* 2008; 22: 1398–1399.
- Sotiriou E, Panagiotidou D, Ioannidis D. An open trial of 5-aminolevulinic acid photodynamic therapy for vulvar lichen sclerosis. *Eur J Obstet Gynecol Reprod Biol* 2008; 141: 187–188.
- Zawislak AA, McCluggage WG, Donnelly RF, Maxwell P, Price JH, Dobbs SP, et al. Response of vulvar lichen sclerosis and squamous hyperplasia to photodynamic treatment using sustained topical delivery of aminolevulinic acid from a novel bioadhesive patch system. *Photodermatol Photoimmunol Photomed* 2009; 25: 111–113.
- Neill SM, Tatnall FM, Cox NH. Guidelines for the management of lichen sclerosis. *Br J Dermatol* 2002; 147: 640–649.
- Wang HW, Wang XL, Zhang LL, Guo MX, Huang Z. Aminolevulinic acid (ALA)-assisted photodynamic diagnosis of subclinical and latent HPV infection of external genital region. *Photodiagnosis Photodyn Ther* 2008; 5: 251–255.
- Barge J, Glanzmann T, Zellweger M, Salomon D, van den Bergh H, Wagnieres G. Correlations between photoactivable porphyrins' fluorescence, erythema and the pain induced by PDT on normal skin using ALA-derivatives. *Photodiagnosis Photodyn Ther* 2013; 10: 683–693.
- Miller IM, Nielsen JS, Lophaven S, Jemec GB. Factors related to pain during routine photodynamic therapy: a descriptive study of 301 patients. *J Eur Acad Dermatol Venereol* 2011; 25: 1275–1281.
- Mikolajewska P, Juzeniene A, Moan J. The effect of lidocaine on PpIX photobleaching and outcome of ALA-PDT in vitro. *Photodiagnosis Photodyn Ther* 2007; 4: 249–253.
- Fistarol SK, Itin PH. Diagnosis and treatment of lichen sclerosis: an update. *Am J Clin Dermatol* 2013; 14: 27–47.