Journal of Innovative Optical Health Sciences
Vol. 8, No. 1 (2015) 1540004 (7 pages)

DOI: 10.1142/S1793545815400040





# Treatment of cutaneous lichen planus with ALA-mediated topical photodynamic therapy

Zhi-Xia Fan[*,†,‖], Ling-Lin Zhang[*,†,‖], Hong-Wei Wang[‡], Pei-Ru Wang[*], Zheng Huang[§] and Xiu-Li Wang[*,¶]

[*]*Shanghai Skin Diseases Hospital*
*Shanghai 200050, P. R. China*

[†]*Shanghai Skin Diseases Clinical*
*College of Anhui Medical University*
*Shanghai 200050, P. R. China*

[‡]*Department of Dermatology*
*Huadong Hospital, Shanghai 200040, P. R. China*

[§]*University of Colorado Denver Cancer Center*
*and CAPT Lab, CO, USA*
[¶]*xlwang2001@aliyun.com*

Received 12 October 2013
Accepted 12 January 2014
Published 20 February 2014

**Purpose:** To evaluate the effectiveness of topical 5-aminolevulinic acid (ALA)-mediated photodynamic therapy (PDT) for the treatment of cutaneous lichen planus (LP). **Methods:** A total of 17 symptomatic LP lesions in 7 Chinese patients were assessed. ALA cream (10%) was applied topically to LP lesions for 3 h. The lesions were irradiated with a 635 nm diode laser at the dose level of 100 J/cm$^2$. The treatment was repeated at two-week intervals. Clinical assessment was conducted before each treatment. Follow-up was performed once a month for up to six months. **Results:** Lesions showed significant improvement after one to four courses of treatments. Complete response was achieved in 13 lesions (five patients) and partial remission in four lesions (two patients). The complete response rate was 71%. There was no significant side effects except the feeling of pain that most patients could tolerate. Follow-up of five patients who achieved complete response showed no signs of recurrence. **Conclusion:** Topical ALA PDT is effective in the treatment of cutaneous LP.

*Keywords*: 5-aminolevulinic acid; photodynamic therapy; lichen planus.

[‖]These two authors contributed equally to this study.

## 1. Introduction

Lichen planus (LP) is a chronic inflammatory disease that often affects human skin and mucous membranes. It may also involve the nails, scalp, esophagus and anogenital regions.[1] Both sexes are equally affected by LP and half of them have classical lesions. Mucosal involvement along with cutaneous lesions are observed in 16.8% and genital involvement in 5.2% of patients. Nail changes are observed in 15.1% of patients. Recurrence might occur in 10% of patients.[2]

Although the exact cause of LP is unknown, T-cell mediated immunology has been indicated.[3] Among various recommended treatment options, topical corticosteroid is still the mainstay of therapy. However, the treatment outcome is often disappointing. It is difficult to remove LP lesions on the sensitive regions such as the face and genitalia. Moreover, adverse effects associated with laser and surgery, such as erosions, ulcers and scars, could seriously affect the quality of life.

Photodynamic therapy (PDT) is an effective therapy for premalignant and malignant cutaneous lesions, condyloma acuminate and inflammatory acne lesions.[4–7] It has also been reported that PDT is effective for the treatment of psoriasis.[8] Several case reports suggest that topical PDT mediated with prodrug 5-aminolevulinic acid (ALA) might be a useful modality in the treatment of LP. Here, we report the clinical results of topical ALA PDT of seven cutaneous LP cases of Chinese patients.

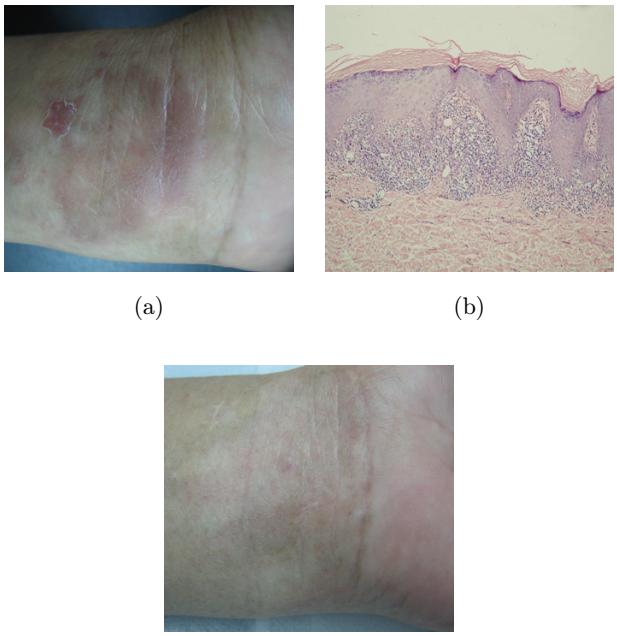
## 2. Subjects and Methods

### 2.1. *Patient data*

A total of 7 patients (male = 5, female = 2) with clinical and histopathological diagnosis of LP were selected in this study (Table 1). The ages ranged from 33 to 70 years old (mean = 45.7 ± 12.5 years old). The length of history ranged from 1 month to 12 months (mean = 6.9 months). A total of 13 lesions localized on the penis were identified on 5 male patients and one of them had 6 lesions. One female patient had a total of three lesions localized on the forehead, nose and around the mouth and another female patient had one lesion confined to the wrist [Fig. 1(a)]. The size of lesions ranged from 0.77 to 9 $cm^2$. Cases 5 and 6 were recurrent after topical corticosteroid therapy. Case 4 failed to respond to 5% imiquimod cream. None of them had systemic diseases such as diabetes mellitus or hypertension.

Table 1. Patient demographical data.

| No. | Sex/Age (years) | Duration (months) | Location genital/skin | Previous treatments | Primary/Relapse |
|---|---|---|---|---|---|
| 1 | M/33 | 12 | +/− | — | +/− |
| 2 | F/56 | 12 | −/+ | — | +/− |
| 3 | F/70 | 3 | −/+ | — | +/− |
| 4 | M/37 | 1 | +/− | 5% imiquimod cream | +/− |
| 5 | M/45 | 12 | +/− | Steroid cream | −/+ |
| 6 | M/41 | 4 | +/− | Steroid cream | −/+ |
| 7 | M/38 | 4 | +/− | — | +/− |



(a) (b) (c)

Fig. 1. LP located on the wrist (Case 2). (a) gross view before PDT, (b) histopathological view before PDT (×400) and (c) CR at six months after four courses of PDT treatments.

### 2.2. *Histopathological examination*

Before PDT treatment, all patients were subjected to routine biopsy and H&E staining for histopathological assessment.

### 2.3. *PDT procedure*

Fresh ALA cream (10%, w/w) was prepared using ALA powder (Shanghai Fudan-Zhangjiang

Bio-Pharmaceutical Co., Ltd. Shanghai, China). LP lesions were cleaned with 0.9% saline solution. ALA cream was then applied evenly to lesions plus a 0.5 cm margin. ALA-applied area was occluded with a cling film and covered with a black sheet for light protection. After 3 h of incubation, excess ALA was removed from the lesions and light irradiation was carried out using a 635 nm diode laser (XD-635AB, Guilin Xingda Photoelectric Medical Devices Co., Ltd.) at a fluence rate of 100 mW/cm$^2$ and light dose of 100 J/cm$^2$. The treatment was repeated at two-week intervals for three times or until complete remission was achieved. Lincomycin Hydrochloride Gel or Lidocaine Hydrochloride Gel was used in these cases requested for the intervention of pain and discomfort during light irradiation. The evaluation of clinical improvement and adverse effects was carried out before and after each treatment.

### 2.4. *Fluorescence examination*

Before light irradiation, fluorescence images were acquired by a digital camera under UV illumination (410 nm) to confirm the production of protoporphyrin IX (PpIX) in LP lesion.[6]

### 2.5. *Clinical observation and assessment*

Clinical responses were classified as:

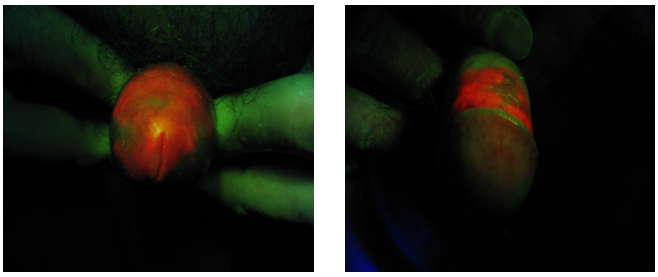
- Complete response: complete disappearance of lesions (CR).
- Partial response: more than 50% clearance of residual lesions (PR).
- No response: $<$ 50% clearance of lesions or no significant response (NR).[9]

All patients received not more than four courses of treatment. Follow up assessment was carried out at one-month intervals for up to six months after the last treatment.

## 3. Results

### 3.1. *Histopathological characteristics*

The routine H&E staining showed that LP lesions were characterized as epidermal hyperplasia, thickening of the granular cell layer, "saw-tooth" pattern of Rete ridges, vacuolar alteration of the basal layer of the epidermis and T cells infiltration at the dermal-epidermal junction [Fig. 1(b)].



(a) (b)

Fig. 2. PpIX fluorescence images after topical application of ALA. (a) case 6 and (b) case 7.

### 3.2. *PpIX production*

After the topical application of 10% ALA cream for 3 h, noticeable red fluorescence could be seen on the ALA-applied areas. The intense PpIX fluorescence was primarily located at inflammatory LP lesions, whereas the noninflammatory lesions showed weak or no fluorescence (Fig. 2).

### 3.3. *Clinical outcomes*

As shown in Table 2, 5 out of 7 patients (71.43%) achieved CR after 1 to 4 courses of ALA PDT and 2 out of 7 patients (28.57%) PR after 4 courses of ALA PDT. Amongst them, 2 patients (Cases 5 and 6) showed CR after one course of PDT, 1 patient (Case 7) after two courses, 1 patient (Case 2) after three courses and 1 patient (Case 4) after four courses [Figs. 1(c) and 3]. CR in the relapse lesions (Cases 5 and 6) after a single session of PDT suggested that there was no difference between the response of primary lesion and relapse lesion to ALA PDT.

During the six-month follow-up, none of the CR patients showed signs of recurrence.

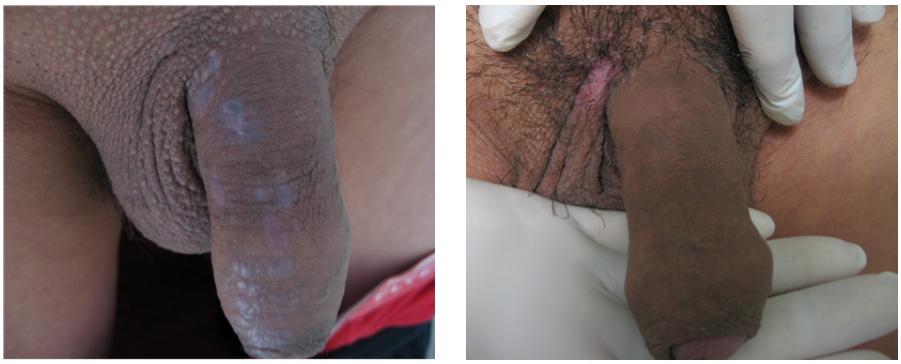
### 3.4. *Adverse effects*

All the patients experienced various degrees of pain and burning feeling during light treatment. Acute pain following treatment occurred in three male patients who required topical Lidocaine spray for pain relief. Immediately after treatment, the treated

Table 2. Treatment outcomes.

| Case No. | Number of lesions | Mean lesion size ($cm^2$) | Courses of treatments | Response | Side effects | Recurrence |
|---|---|---|---|---|---|---|
| 1 | 1 | 6.4 | 4 | PR | Pain, burning, Erythema, | Yes |
| 2 | 1 | 9 | 3 | CR | Pain, burning, Erythema,swelling, itching | No |
| 3 | 3 | 2.1 | 4 | PR | Pain, swelling, burning | Yes |
| 4 | 6 | 3.4 | 4 | CR | Pain, burning, Erythema erosion | No |
| 5 | 1 | 0.77 | 1 | CR | Pain, burning, Erythema erosion | No |
| 6 | 2 | 2 | 1 | CR | Pain, burning, erosion | No |
| 7 | 3 | 4 | 2 | CR | Pain, burning, erosion | No |

*Note*: N.B.: CR — complete remission, PR — partial remission.



(a) (b)

Fig. 3. LP located on the penis (Case 4). (a) before PDT and (b) CR at six months after four courses of PDT treatments.



site showed mild or moderate erythema, which disappeared within 5–10 days without a need for treatment. Among them, one female patient felt itching on the wrist lesion and had mild swelling. Four male patients with lesions located at the genital areas had mild erosion which crusted after 7–10 days. No patients had severe adverse effects such as ulcer or scarring.

## 4. Discussion

LP is a relatively common chronic mucocutaneous disease and is characterized as pruritic, erythematous, flat-topped and polygonal papules [Fig. 1(a)].[1] Its diagnosis is based on both clinical and histological examination. Typical pathologic features include a dense lymphohistiocytic infiltrate in the inflamed lesion [Fig. 1(b)].

Currently, there is no effective treatment to cure LP and the main purpose of treatment is to reduce the length and severity of symptomatic outbreaks.[10] On the other hand, the lesions affecting mucous membranes may be more persistent and resistant to treatment. Recurrence of LP is common even after multiple treatments. High-potency topical corticosteroids are the first-line therapy for mild cutaneous LP and oral antihistamines may be used to control pruritus.[11,12] Therapeutic options for severe lesions include systemic corticosteroids, retinoids, cyclosporine, photochemotherapy, hydroxychloroquine, azathioprine, and other immunosuppressants.[13,14] These treatments often require a long term of use. Many patients relapse when treatment is discontinued. LP lesions can also become resistant after a long term of treatment. Phototherapy is another commonly utilized treatment for severe and generalized LP. Topical photochemotherapy with psoralens and ultraviolet A (PUVA) is effective but can cause many side-effects and has the potential of carcinogenicity.[15] Despite many treatment options, since there exist high rates of treatment failure, there is still a need of searching for effective treatment modalities.

PDT is a minimally invasive treatment that uses photosensitizers, such as ALA, methyl ester of ALA (MAL) or methylene blue (MB), activated by light at a specific wavelength to destroy the targeted cells and tissue. Compared with the conventional treatment for LP, PDT has been considered as having a noninvasive nature, negligible risk of accumulative toxicity and being relatively selective. It can be used alone or together with chemotherapy, radiotherapy or surgery. Since the early 1990's, ALA PDT has been used to treat skin tumors.[16] Recently, topical PDT has been successfully used for the treatment of condyloma acuminatum, acne and photoaging in China.

The rationale for the use of ALA PDT for treating LP was first investigated by Kirby *et al.* in 1999.[17] They assessed the usefulness of 20% ALA mediated PDT for the treatment of hypertrophic LP located in the penis of an elderly patient. After two treatments, the lesion was cleared without recurrence during six-month follow up. ALA, a commonly used prodrug, is a hydrophilic, low molecular weight molecule, and precursor of PpIX in the heme pathway. In China, a topical formulation of ALA (Aila®) has been approved for treating condyloma acuminatum in 2007.[18] Current clinical research of ALA is focused on its application in the treatment of genital warts, inflammatory acne vulgaris and actinic keratosis in China.[19–22] The hyperproliferating or inflammatory cells, often present in malignancies and LP lesions, can selectively uptake ALA and convert them to PpIX, which shows red fluorescence under UV irradiation. The normal tissue and noninflammatory cells uptake little to no ALA and show weak or no red fluorescence.[23,24] This study demonstrated that LP lesions could generate strong PpIX signals (Fig. 2).

In this study, the combination of 10% ALA and 635 nm diode laser (100 J/cm$^2$ at 100 mW/cm$^2$) was used based on our previous experience.[25] After 1–4 courses of ALA PDT, 75% of CR was achieved without recurrence [Figs. 1(c) and 3]. PDT was effective in treating both primary and relapse lesion and might delay the relapse as well. Similar results were reported by Sadaksharam *et al.* in 2012.[26] Due to the saturation process of PpIX formation and rapid photobleaching during irradiation, the risk of overtreatment is relatively low and ALA PDT can be repeated without serious side effects.[27] However, previous studies also showed that various degrees of erythema, swelling, itching, erosion and pain could be associated with topical PDT.[16] Although to a certain extent such local reactions are unavoidable, they can disappear within 5–10 days without a need for treatment. Aghahosseini *et al.* suggest that MB-mediated PDT might be useful for treating oral LP.[10,28]

The exact mechanism of ALA PDT in the treatment of LP is still unclear. Research show that PDT might act on hyperproliferating cells, which selectively uptake ALA and undergo apoptosis and necrosis following PDT.[29] It also has been suggested that PDT may have immunomodulatory effect based on the fact that there is an increase in the CD8+ reaction in the damaged tissue following PDT. The initial pain and soreness indicate that there may be an influx of new T cells, followed by an overall reduction in the number of inflammatory cells and tissue healing.[30] It is believed that PDT is effective in the management of inflammatory cells as well as neoplastic conditions.[17]

In conclusion, ALA PDT may be an effective alternative for treating LP without causing major side effects and recurrence. It also can be used for patients resistant to steroids or when steroids are contraindicated. However, there are some limitations from this clinical study due to its small number of cases. More studies are needed to confirm the efficacy of PDT in the treatment of LP and to understand its mechanisms.

## Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (81272990), the Natural Science Foundation of Shanghai (11ZR1432800) and the Key Project of Shanghai Health Bureau (A 20124034).

## References

1. L. Le Cleach, O. Chosidow, "Clinical practice. Lichen planus," *N. Engl. J. Med.* **366**(8), 723–732 (2012).
2. M. Bhattacharya, I. Kaur, B. Kumar, "Lichen planus: A clinical and epidemiological study," *J. Dermatol.* **27**(9), 576–582 (2000).
3. S. Arias-Santiago, A. Buendia-Eisman, J. Aneiros-Fernandez, M. S. Girón-Prieto, M. T. Gutiérrez-Salmerón, V. G. Mellado, R. Naranjo-Sintes, "Cardiovascular risk factors in patients with lichen planus," *Am. J. Med.* **124**(6), 543–548 (2011).

4. X. L. Wang, H. W. Wang, M. X. Guo, S. Z. Xu, "Treatment of skin cancer and pre-cancer using topical ALA-PDT — a single hospital experience," *Photodiagn. Photodyn. Ther.* **5**(2), 127–133 (2008).
5. X. L. Wang, H. W. Wang, H. S. Wang, "Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminate," *Br. J. Dermatol.* **151**(4), 880–885 (2004).
6. X. L. Wang, H. W. Wang, L. L. Zhang, "Topical ALA PDT for the treatment of severe acne vulgaris," *Photodiagn. Photodyn. Ther.* **7**(1), 33–38 (2010).
7. G. Liu, C. Pan, K. Li, Y. Tan, X. Wei. "Phototherapy for mild to moderate acne vulgaris with portable blue and red LED," *J. Innov. Opt. Health Sci.* **4**(1), 45–52 (2011).
8. Y. K. Tandon, M. F. Yang, E. D. Baron, "Role of photodynamic therapy in psoriasis: A brief review," *Photodermatol. Photoimmunol. Photomed.* **24**(5), 222–230 (2008).
9. F. Pavlotsky, N. Nathansohn, G. Kriger, D. Shpiro, H. Trau, "Ultraviolet-B treatment for cutaneous lichen planus: Our experience with 50 patients," *Photodermatol. Photoimmunol. Photomed.* **24**(2), 83–86 (2008).
10. F. Aghahosseini, F. Arbabi-Kalati, L. A. Fashtami, M. Fateh, G. E. Djavid, "Treatment of oral lichen planus with photodynamic therapy mediated methylene blue: A case report," *Med. Oral. Patol. Oral. Cir. Bucal.* **11**(2), E126–E129 (2006).
11. B. Cribier, C. Frances, O. Chosidow, "Treatment of lichen planus. An evidence-based medicine analysis of efficacy," *Arch. Dermatol.* **134**(12), 1521–1530 (1998).
12. G. Corrocher, G. Di Lorenzo, N. Martinelli, "Comparative effect of tacrolimus 0.1% ointment and clobetasol 0.05% ointment in patients with oral lichen planus," *J. Clin. Periodontol.* **35**(3), 244–249 (2008).
13. K. P. Kyriakis, S. Terzoudi, I. Palamaras, "Sex and age distribution of patients with lichen planus," *J. Eur. Acad. Dermatol. Venereol.* **20**(5), 625–626 (2006).
14. S. Handa, B. Sahoo, "Childhood lichen planus: A study of 87 cases," *Int. J. Dermatol.* **41**(7), 423–427 (2002).
15. A. Kuusilehto, R. Lehtinen, R. P. Happonen, "An open clinical trial of a new mouth-PUVA variant in the treatment of oral lichenoid lesions," *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.* **84** (5), 502–505 (1997).
16. J. C. Kennedy, R. H. Pottier, D. C. Pross, "Photodynamic therapy with endogenous protoporphyrin IX: Basic principles and present clinical experience," *J. Photochem. Photobiol. B* **6**(1–2), 143–148 (1990).
17. B. Kirby, C. Whitehurst, J. V. Moore, V. M. Yates, "Treatment of lichen planus of the penis with photodynamic therapy," *Br. J. Dermatol.* **141**(4), 765–766 (1999).
18. Z. Huang, "An update on the regulatory status of PDT photosensitizers in China," *Photodiagn. Photodyn. Ther.* **5**(4), 285–287 (2008).
19. H. Liu, P. Zhang, X. An *et al.* "$CO_2$ laser plus photodynamic therapy versus $CO_2$ laser in the treatment of condyloma acuminatum: A randomized comparative study," *J. Innov. Opt. Health Sci.* **5**(1), 1150008-1–1150008-7 (2012).
20. J. Xu, L. Xiang, J. Chen, Q. He, Q. Li, J. Li, J. Wang, "The combination treatment using $CO_2$ laser and photodynamic therapy for HIV seropositive men with intraanal warts," *Photodiagn. Photodyn. Ther.* **10**(2), 186–193 (2013).
21. L. Ma, L. H. Xiang, B. Yu, "Low-dose topical 5-aminolevulinic acid photodynamic therapy in the treatment of different severity of acne vulgaris," *Photodiagn. Photodyn. Ther.* **10**(4), 583–590 (2013).
22. H. Cai, Y. X. Wang, P. Sun, Z. Y. Yang, R. Tian, X. Y. Liu, Q. Li, L. Qiao, W. Liu, "Photodynamic therapy for facial actinic keratosis: A clinical and histological study in Chinese patients," *Photodiagn. Photodyn. Ther.* **10**(3), 260–265 (2013).
23. X. L. Wang, H. W. Wang, Z. Huang, "Study of protoporphyrin IX (PpIX) pharmacokinetics after topical application of 5-aminolevulinic acid in urethral condylomata acuminate," *Photochem. Photobiol.* **83**(5), 1069–1073 (2007).
24. J. Kennedy, R. Pottier, "Endogenous protoporphyrin IX, a clinically useful photosensitizer for photodynamic therapy," *J. Photochem. Photobiol. B: Biol.* **14**(4), 275–292 (1992).
25. H. W. Wang, T. Lv, L. L. Zhang *et al.*, "Prospective study of topical 5-aminolevulinic acid photodynamic therapy for the treatment of moderate to severe acne vulgaris in Chinese patients," *J. Cutan. Med. Surg.* **16**(5), 324–333 (2012).
26. J. Sadaksharam, K. P. Nayaki, N. P. Selvam, "Treatment of oral lichen planus with methylene blue mediated photodynamic therapy — a clinical study," *Photodermatol. Photoimmunol. Photomed.* **28**(2), 97–101 (2012).
27. B. Krammer, K. Plaetzer, "ALA and its clinical impact, from bench to bedside," *Photochem. Photobiol. Sci.* **7**(3), 283–289 (2008).
28. F. Aghahosseini, F. Arbabi-Kalati, L. A. Fashtami, "Methylene blue-mediated photodynamic therapy: A possible alternative treatment for oral lichen planus," *Lasers Surg. Med.* **38**(1), 33–38 (2006).

29. T. Amo, N. Kawanishi, M. Uchida, "Mechanism of cell death by 5-aminolevulinic acid-based photodynamic action and its enhancement by ferrochelatase inhibitors in human histiocytic lymphoma cell line U937," *Cell Biochem. Funct.* **27**(8), 503–515 (2009).

30. D. W. Edström, A. Porwit, A. M. Ros, "Photodynamic therapy with topical 5-aminolevulinic acid for mycosis fungoides: Clinical and histological response," *Acta Derm. Venereol.* **81**(3), 184–188 (2001).