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A clinical evaluation of efficacy of photodynamic therapy in treatment of reticular oral lichen planus: A case series

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ABSTRACT

Background The aim of the study was to clinically evaluate the efficacy of photodynamic therapy in treatment of reticular oral lichen planus (OLP).

Methods Fifty patients aged 26–84, with 124 OLP lesions in total, underwent photodynamic therapy (PDT) mediated with topically applied 5% 5-aminolevulinic acid. ALA was activated by a custom-made diode lamp with a high-power LED emitting light at 630 nm and 300 mW delivered through an optical fiber probe. A light exposure dose was 150 J/cm^2. The therapy comprised of 10 weekly illumination sessions. The lesions' response was macroscopically measured in millimeters with a periodontal probe and clinically evaluated at each session, then on completion of the series and throughout the 12-month follow-up.

Results The baseline mean size of lesions was 3.99 cm^2 ± 3.73. The lesions on the buccal mucosa and lips (lining mucosa) were larger than those on the gingiva and tongue (masticatory mucosa) – 4.58 cm^2 ± 4.01 and 2.93 cm^2 ± 2.91 respectively. On completion of the therapy 109 sites improved, including 46 in complete remission. The mean reduction in size was 62.91% ($p = 0.000000$). 12-month after therapy mean reduction of the lesions was 78.7% ($p = 0.000000$), specifically 79.48% ($p = 0.000000$) within the lining mucosa and 76.11% on the masticatory mucosa.

Conclusions The results proved that ALA-mediated photodynamic therapy with a 630 nm light was effective and as such it can be used as an optional treatment for symptomatic OLP.

1. Introduction

Lichen planus is a chronic immune-mediated disorder that affects skin and mucosa and is estimated to touch 0.5–2% of the population, particularly middle-aged women [1]. Oral lichen planus (OLP) is a subtype that occurs in oral mucosa and is usually harder to treat than cutaneous lichen planus, which can be self-limited while the former is usually persistent and generally requires long-term treatment and follow-up [2,3].

The reticular form of oral lichen planus (OLP) is the most frequent variant of the disease [4]. Its typical manifestation are symmetrically arranged, white keratotic strips called Wickham's striae, most often found bilaterally on the buccal mucosa, less frequently on the lateral parts of the tongue, lips and gingiva [5]. Taste may become disrupted when the superior surface of the tongue is affected. Typically, however, the reticular form of OLP is asymptomatic and remains undetected until a coincidental self-examination or routine clinical test reveals its presence [6]. Since the etiology of the disease has not yet been fully explained, treatment is difficult, merely symptomatic and prone to failure [7–18].

Topical corticosteroids dominate among the drugs in treatment of symptomatic OLP, but their use commonly brings about candidiasis, dysgeusia, nausea, dry mouth, swollen lips or sore throat [19]. Systemic application of corticosteroids carries an even greater risk of potentially dangerous adverse side effects such as severe candidiasis, hypothalamic-pituitary-adrenal (HPA) axis suppression, diabetes, digestive disorders, telangiectasia or relapses due to discontinuation of treatment, thus it is reserved only for treatment of exceptionally resistant,

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generalized lesions and/or erosive-ulcerative OLP [11,20–23]. When lesions resist most potent steroids, immunomodulatory drugs (azathiopryne, calcineurin inhibitors, ciclosporin, takrolimus, sirolimus, pimekrolimus) and retinoids are recommended. These, however, are in limited use due to high toxicity and multiple side effects [7,12,17,20].

The implementation and effectiveness of invasive therapies, namely surgery, cryotherapy and laser treatment, have also their limits, since they depend largely on the extent of lesions. Topically used PUVA therapy, however effective in treatment of various OLP forms, is potentially carcinogenic, hepatotoxic and causes nausea, vomiting and vertigo [15,24]. Alternatively, PUVASOL (Psolaren Ultra-Violet A and Solar Radiation) and Narrow Band UVB- 311 nm are comparable to PUVA outcome-wise, but less carcinogenic [15,16,25]. A notable current method of OLP treatment is Photodynamic Therapy (PDT), whose major advantages are insignificant invasiveness and minor side effects. The concept of PDT is deceptively simple in that it requires only three components, i.e. a photosensitizer, light source, and oxygen. A therapeutic effect is achieved activation of a photosensitizing agent with light, hence in the presence of oxygen, reactive oxygen intermediates are formed. These intermediates irreversibly oxidize essential cellular components, causing apoptosis and necrosis [26,27]. PDT's efficacy seems promising, albeit it is scarcely documented in the literature reflecting a variety of protocols [20,28–34]. With a view to further developing the method, the aim of this study was to clinically evaluate the efficacy of the authors' own protocol of ALA-mediated photodynamic therapy in treatment of reticular form of OLP.

2. Materials and methods

The study encompassed a group of 50 patients, comprising 36 females and 14 males, with a total number of 124 OLP lesions. Eighty of them were on the buccal and labial mucosa (lining, non-keratinized) and the other 44 on the gingiva and tongue (masticatory mucosa). Five patients (3 women and 2 men) actively smoked up to 10 cigarettes a day at the time of the study and 8 persons (5 women, 3 men) were smokers in the past.

The therapy and its follow-up stage took place at the Department of Periodontal and Oral Mucosa Diseases, Medical University of Białystok and lasted three years, from 2013 to 2015. The study was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2008, and was reviewed and approved by the local ethical committee (Ethics Committee No.: R-I-002/263/2012). Each patient gave an informed written consent and was instructed about the nature of PDT. Participation in the project was voluntary with a clause entitling to withdraw from the study at any stage.

Each patient's course of the disease, past treatment, if any, and the current signs and symptoms, particularly the character and extent of lesions, were looked at. The primary criterion inclusion for treatment was a histopathologically confirmed clinical diagnosis. The patients who declared or confirmed any of the following facts or states were excluded from the study: age under 18, pregnancy, breast feeding, systemic diseases, allergy, drug consumption, photosensitivity, previous treatment for OLP at least 6 month prior to the beginning of the study, schedules conflicting with the regular weekly and monthly appointments, physical or mental disability that prevented keeping the occlusive dressing in place, suffering from oral conditions other than OLP.

All the patients were given reassurance and counselling regarding the disease and underwent complete oral prophylaxis.

3. Therapeutic procedure

The authors' own protocol incorporated 5-aminolevulinic acid (ALA) as a topical photosensitizer in a form of 5% gel solution (Ala-Plus, Farmapol, Polska). An innitial 2 mm layer of the gel was applied directly onto the saliva-free lesion and surrounding mucosa 2 h before light activation. The site was protected with a non-woven occlusive dressing overlapping the lesion and stabilized with a few extra layers of sterile gauze. Three subsequent applications of the photosensitizer followed, each every 30 min within 2 h. To activate ALA the authors used a custom-designed diode lamp providing light at 630 nm and 300 mW. The study used a lamp in which the light source was a high-power LED, (Seoul Semiconductor R11292, 2.5 W) and the delivery system – an optical fiber probe (Dentsply, 10 mm diameter). The emitted light had a peak power density of 150 J/cm^2 at spot area and peak power density 150 J/cm^2 at tissue, while the beam divergence was 128°. A light exposure dose was 150 J/cm^2.

The course of treatment was originally planned for the maximum of 10 weekly sessions, or fewer if the therapy was to be successful sooner. A number of lesions (54) showed early response, the remaining ones (74) were given 10 PDT sessions in total.

4. Examination

Prior to the initial appointment, the lesions were photographed and macroscopically measured in millimetres with the use of a periodontal probe PCPUNC 15 (Hu-Friedy, IL, USA). Each lesion's surface area was calculated by taking the distances between the farthest points bordering the healthy mucosa in the width and length of the lesion. For the purpose of this study the lesions were grouped size-wise as follows:

Size Group 0 - no apparent lesion
Size Group I - lesions smaller than 3 cm^2
Size Group II - lesions in the range of 3 to 6 cm^2
Size Group III - lesions ranging from 6 to 9 cm^2
Size Group IV - lesions exceeding 9 cm^2.

Additionally the study included the patients' estimation of the perception of pain and/or discomfort they experienced during the therapy. The intensity of painful reaction typically described as stinging, burning, soreness or tightening was given within a 0–3 scale:

Score 0 - no painful reaction
Score 1 - pain of low intensity
Score 2 - pain of moderate intensity
Score 3 - pain of high intensity

The patients' subjective evaluation of the treatment was collected at every appointment. Additionally, at each odd appointment (3rd, 5th, 7th and 9th) both macroscopic evaluation and photographic documenting took place prior to the illumination. A 12-month observation period started on the completion of the 10-week therapy. Six appointments were scheduled from that point onwards: a week, month, and subsequently 3, 6, 9 and 12 months after the final PDT session.

5. Statistical analysis

All continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test, with Lilliefors correction and Shapiro-Wilk test. Normal distribution of the quantitative variables was not found. The Wilcoxon matched-pairs signed-ranks test was used to compare two related variables. Statistical significance was determined at $p < 0.05$ level. The estimated power of the test was 0.99. All calculations were performed using Statistica 12.0 software (StatSoft, Tulsa, USA).

6. Results

Out of 124 lesions 54 improved at various stages of the therapy: 8 lesions healed after 5 illuminations, 10 more lesions did so after 7 sessions and another 36 lesions needed 9 illuminations to heal. The remaining lesions were given the full 10-session series.

At the initial clinical examination the mean size of the lesions was 3.99 cm^2 ± 3.73. Those on the buccal mucosa and lips were larger, 4.58 cm^2 ± 4.0, than the ones on the gingiva and tongue, whose mean size was 2.93 cm^2 ± 2.91. Most of the lesions in the study group (50.81%) were small and thus fell into Size Group I – 34 on the buccal mucosa and lips, 29 in the masticatory regions. Size Group II was the

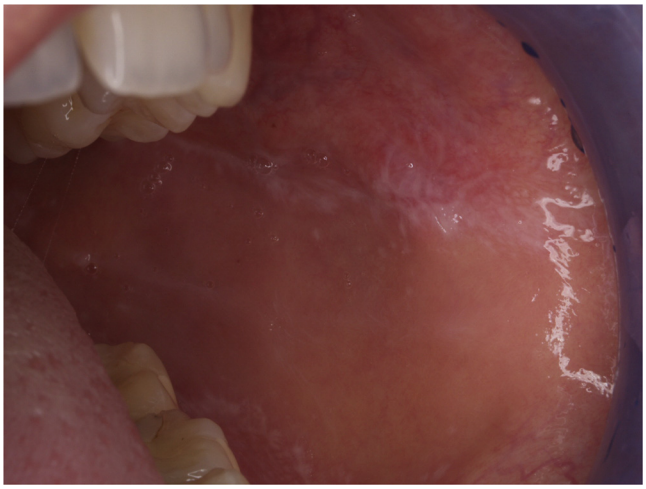

Fig. 1. Female patient, aged 26, before PDT. OLP on the left cheek. Size of the lesion- 2.4 cm x 0.7 cm, surface area 1.68 cm^2.

smallest, with 12 lesions (9.68%) – 10 and 2 on the lining and keratinized mucosa respectively. Size Group II comprised of 35 lesions (28.22%) – 25 on the buccal and labial mucosa, 10 on the gingiva and tongue. The remaining 14 lesions (11.29%) fell into Size Group IV – 11 on the lining mucosa, 3 within masticatory parts.

The mean size values between the female and male patients were 4.05 ± 3.87 and 3.85 cm^2 ± 3.4 respectively. The buccal and labial lesions were larger in women, 4.45 cm^2 ± 4.09, than men, 4.90 cm^2 ± 3.85. The discrepancy in size between the lesions on the gingiva and tongue was even more significant – 3.29 cm^2 ± 3.34 in women against 2.08 cm^2 ± 1.18 in men.

On completion of the treatment 109 lesion showed improvement – 46 healed, 27 of which were buccal and labial and 19 on the gingiva and tongue (Figs. 1–6). Fifteen lesions did not respond to the therapy – 9 and 6 on the lining and masticatory mucosa (Figs. 7–9). In that group, 7 lesions grew in size (4 and 3 on the lining and masticatory mucosa), while remaining in their original size groups. Another 7 lesions (4 buccal and labial, 3 on the gingiva and tongue) enlarged and changed their size groups one up, and 1 buccal lesion moved from Size Group I to Size Group III. One unresponsive lesion on the buccal mucosa did not change its size.

After 10 PDT sessions the mean reduction in size was 62.91%, a figure of statistical significance (p = 0.000000). The figures for reduction in the sites on the lining and masticatory mucosa were 63.54% (p = 0.000000) and 61.43% (p = 0.00078) respectively.

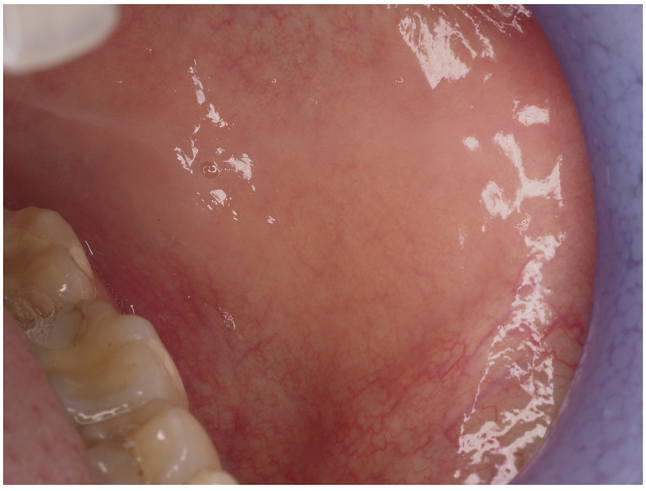

Fig. 2. After PDT- complete remission of the lesion on the left cheek.

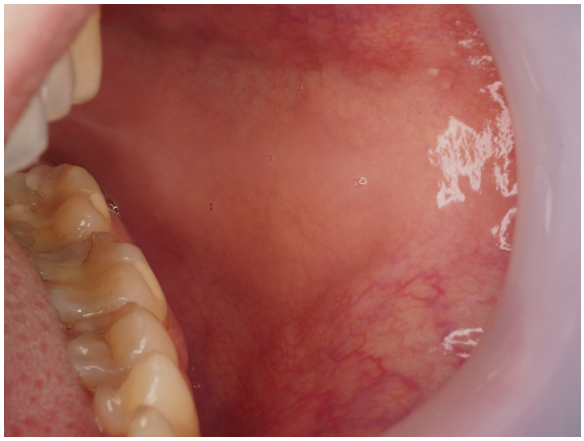

Fig. 3. Twelve months post op - remission on the left cheek maintained.

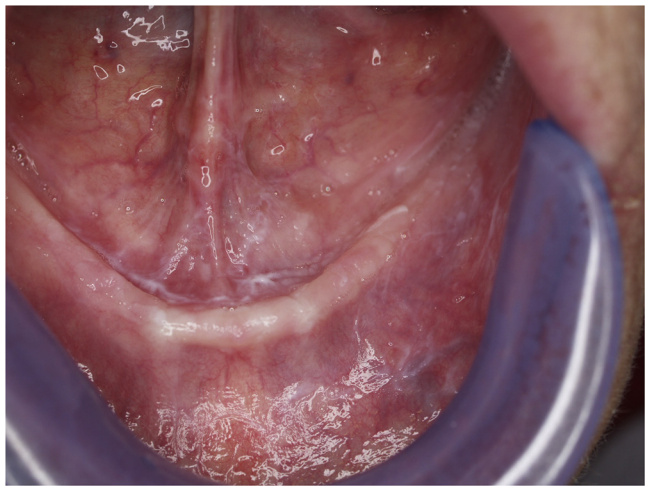

Fig. 4. Female patient, aged 77, before PDT. OLP of edentulous ridge. Size of the lesion – 2.0 cm x 0.6 cm, surface area 1.2 cm^2.

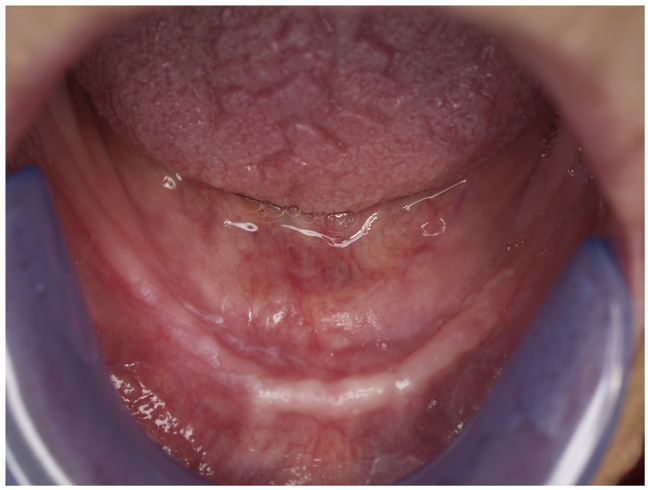

Fig. 5. After PDT- partial remission of the lesion. Size of the remaining lesion – 1.0 cm x 0.2 cm, surface area 0.2 cm^2.

Healing continued, however, during the 12-month follow-up time and resulted in further mean reduction in size – 787% OLP (p = 0.000000), specifically 79.48% (p = 0.000000) within the buccal mucosa and 76.11% on the gingiva and tongue (p = 0.000001). The detailed figures for those changes are given in Tables 1 and 2.

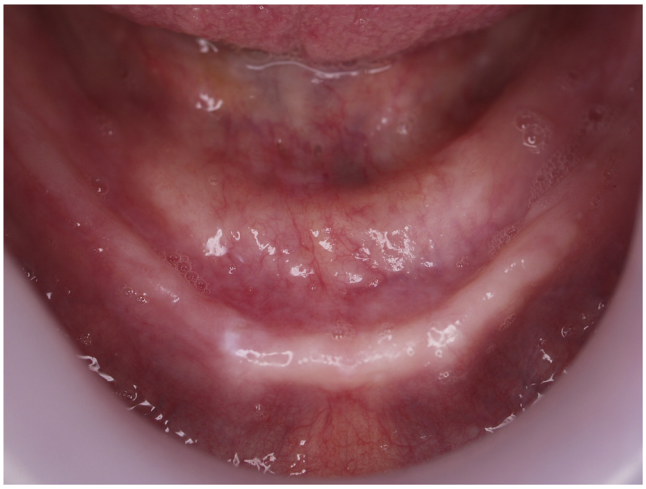

Fig. 6. Twelve months post op – complete remission of the lesion.

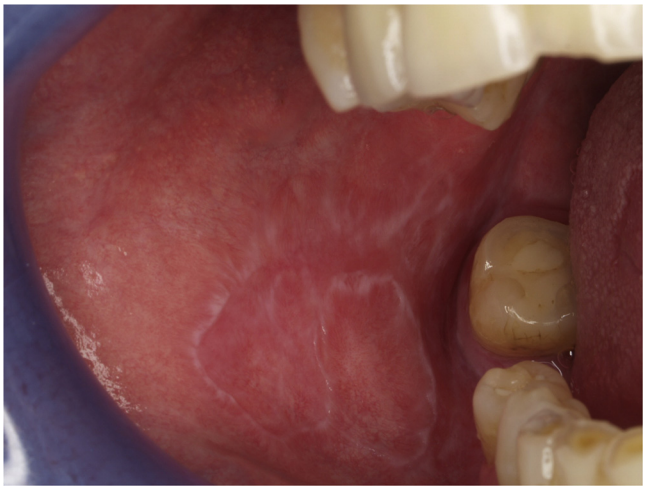

Fig. 7. Male patient, aged 46, before PDT. OLP on the right cheek. Size of the lesion- 2.0 cm x 2.2 cm, surface area 4.4 cm^2.

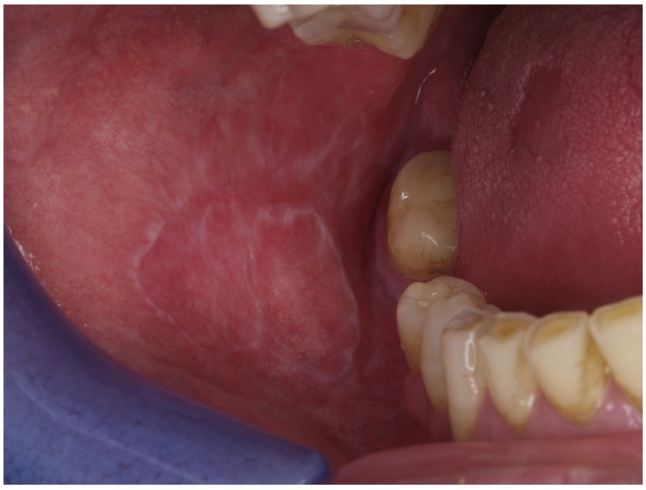

Fig. 8. After PDT – lack of response to treatment.

On completion of the therapy, the lesions within the lining mucosa classified in Size Group IV showed the biggest reduction in size (87.53%), while in those in Size Group I reduction was the smallest (40.00%). A the end of the 12-month monitoring time all lesions on the

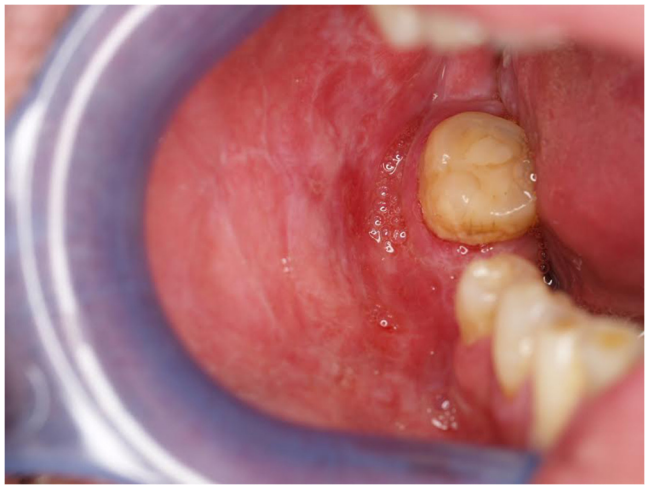

Fig. 9. One year later – extent of lesion area: 2.2 cm x 2.1 cm, surface area 4.62 cm^2.

lining mucosa were progressively healing, thus further reducing in size. Among the lesions on the masticatory mucosa the biggest mean reduction was observed in Size Group IV (92.44%), while the smallest was in Size group III (26.67%). After a year's observation the lesions in Size Groups I and III were still undergoing the process of healing. The former Group showed a two-fold reduction against the values taken directly after the series of 10 illumination sessions. (30.61% vs 68.71%). In Size Group III the respective values for mean reduction rose three-fold (26.67% vs 83.81%). The details of all changes in surface area and mean reduction in all size groups are shown in Table 3.

Significantly, at the end of the 12-month observation, 72 lesions were in remission, surface area of 43 lesions decreased, and 41 of those were now under 3 cm^2 thus in Size Group I (Table 4). Nine out of 80 lesions on the buccal mucosa and lips did not respond to the therapy. Each of them grew in size, 8 remained in their pre-treatment size groups, only one lesion exceeded 9 cm^2 and thus moved from Size Group II to Size Group IV. Among 44 lesions on the masticatory mucosa, 14 reduced their size and 27 healed. During the 12-month monitoring 3 lesions enlarged – one of them remained in its original size group, one moved from Size Group I to Size Group II and the other one was re-classified from Size Group II to Size Group IV.

Comparatively, the applied PDT proved more efficient in the female group, both in case of the lesions on the buccal mucosa and lips (65.84% reduction) and those on the gingiva and tongue (66.26% reduction). Among men, the figures for lesion reduction in both types of mucosa were 57.96% and 42.79% respectively. After the 12-month observation, the efficacy of the therapy was notably greater among women. The mean surface area reduction of the lesions on the lining mucosa was 81.12%, while a corresponding proportion for men was 75.12%. The therapy was even more efficient within the masticatory mucosa. In the female group the mean size reduction was 88.15%, while for the males it was nearly three times smaller – 29.81%. All those discrepancies were statistically significant ($p < 0.0001$).

On completion of the therapy, the records showed that the mean size reduction was bigger in the female than male group (65.93% vs 54.8%). Also, a year after the therapy the proportion was higher on the women's side (83.21%). At that stage, the mean size reduction in the male group was 66.75%, a rise by 11.95% since the immediate post-PDT point. All results were statistically significant ($p < 0.0001$).

7. Patients' perception of treatment

Prior to the therapy 41 patients (82%), 40 women and 1 man, complained of moderately intense pain (Score 2) while 4 patients reported pain of high intensity (Score 3). The remaining group of patients

Table 1
Number and proportion of OLP lesions on completion of treatment and one year later.

Sites	Baseline	On completion						12 months post-therapy					
		Healed		Partly-healed		Unaltered		Healed		Partly-healed		Unaltered	
OLP total	124	46	37.10%	63	50.81%	15	12.09%	72	58.06%	43	34.68%	9	7.26%
Buccal mucosa	80	27	33.75%	44	55.00%	9	11.25%	45	56.25%	29	36.25%	6	7.50%
Female	58	23	39.66%	28	48.27%	8	13.79%	36	62.07%	16	27.59%	6	10.34%
Male	22	4	18.18%	17	77.27%	1	4.55%	9	40.91%	13	59.09%	0	–
Gingiva and tongue	44	19	43.18%	19	43.18%	6	13.64%	27	61.36%	14	31.82%	3	6.82%
Female	31	16	51.61%	10	32.26%	5	16.13%	23	74.20%	6	19.35%	2	6.45%
Male	13	3	23.08%	9	69.23%	1	7.69%	4	30.77%	8	61.54%	1	7.69%

experienced various forms of slight discomfort such as burning, stinging or tightness in mucosa (Score 1). Anticipation of intensified discomfort stopped all patients from eating spicy or/and sour foods, made most of them (29) avoid dry and hard products as well as obstructed their proper oral hygiene.

All patients reported an intense pain (Score 3) occurring after each of the first five PDT sessions, which lasted up to 2 h. In 46 patients (including 8 men) the pain persisted at lower intensity (Score 2) for 3–4 days running. The consecutive PDT sessions triggered less painful reactions. After the 9th illumination 39 patients (78%) experience burning and stinging pain (Score 2) for a few hours only, in 5 other patients it persisted for a maximum of 48 h, and 2 other patients complained of a severe pain (Score 3). After the final 10th illumination 5 persons had no painful reaction while a group of 31 individuals (62%, only women) reported a moderate pain (Score 2) lasting up to 2 h. In 21 of those women the pain stopped within 48 h and the other 10 patients felt subsides discomfort (Score 1) for two more days.

After the 3rd and 5th illuminations 37 patients (74%) a substantial lessening of hitherto pronounced discomfort and symptoms: 12 patients reported some moderate pain (Score 2), 15 – pain of low intensity (Score 1), and 6 – no pain at all (Score 0).

After a series of 7 sessions, 8 patients (16%) described the intensity of pain as moderate (Score 2), 34 (68%) felt it to be mild (Score 1), and the other 8 patients felt no pain (Score 0), even though the lesions were still present.

All patients confirmed that the full series of 10 illuminations reduced their perception of pain notwithstanding the lesions. Two patients (4%) described the pain as moderate (Score 2), for 35 it was mild (Score 1) and 13 did not experience any discomfort (Score 0).

The patients reported that the intensity of pain continued to lessen over the 12-month observation time. It was gone from all the sites on the masticatory mucosa, but persisted within 6 enlarged lesions within the buccal mucosa. Such discomfort was reported by women only and described as moderate (2 lesions) or mild (4 lesions).

8. Discussion

The aim of the presented study was to assess the efficacy of our/authors's own protocol in treatment of reticular form of OLP. At the end of the 10-illumination series 87.91% of OLP lesions either healed or become smaller. Overall, the mean size reduction was 62.91%, which was significant, showing a slightly higher value for the lesions on the buccal mucosa and lips (63.54%) than the gingiva and tongue (61.43%).

There is a great deal of information in the available literature on the efficacy of PDT, reflecting a range of protocols. Maloth et al. [28], who used 5-ALA-mediated PDT, saw 80% of OLP lesions respond to treatment, with mean size reduction by 36.49%. Aghahosseini et al. [20] used PDT mediated by methylene blue (MB) to treat 26 OLP lesions, 12 of which were recognized as the reticular form. The authors achieved improvement in 16 sites while 4 sites were in complete remission and 10 (38.46%) did not respond to treatment. All cured lesions were classified as the reticular variant. The resulting mean size reduction was 443% [20]. Sadaksharam et al. [29] and Prasanna et al. [30] achieved significant reduction while using the same (MB) photosensitizer, 50% and 5333% respectively. In the study by Sobaniec et al. [31] the use of an alternative Chlorin-e6 led to a slightly bigger, 55%, reduction. The authors observed a bigger reduction - 57.6% within the lining mucosa and only 30% reduction in the lesions on the gingiva and tongue. Likewise, Kvaal et al. [32], who used 5-aminolevulinate (MAL), observed post-therapy improvement. They do not, however, provide the figures relevant to the size of lesions and reduction.

A closer analysis of the lesions in presented study established the mean surface area at 3.99 cm^2 ± 3.73. The lesions on the buccal mucosa were larger than those on the gingiva and tongue, 4.58 cm^2 ± 4.01 and 2.93 cm^2 ± 2.91 respectively. After the therapy, the surface area of lesions decreased by 3.14 cm^2 and its mean value was 0.85 cm^2 ± 1.60. The mean size of the lesions on the buccal mucosa and lips decreased by 3.63 cm^2, to a mean size 0.94 cm^2 ± 1.62. The surface area of the lesions on the masticatory mucosa was 2.23 cm^2 smaller, at the mean value 0.70 cm^2 ± 1.58. On completion of the therapy, 15 lesions had not responded favorably to treatment. However, after a year's

Table 2
Mean size, standard deviation and mean reduction of OLP lesions before and after treatment.

Sites	Number of lesions	Mean size[cm^2] and standard deviation			Mean size reduction	
		Baseline	On completion	12 months post-therapy	On completion	12 months post-therapy
OLP total	124	3.99 ± 3.73	1.48 ± 1.98	0.85 ± 1.60	62.91%	78.70%
Female	89	4.05 ± 3.87	1.38 ± 2.07	0.68 ± 1.41	65.93%	83.21%
Male	35	3.85 ± 3.4	1.74 ± 1.75	1.28 ± 1.97	54.8%	66.75%
Buccal mucosa	80	4.58 ± 4.01	1.67 ± 2.04	0.94 ± 1.62	63.54%	79.48%
Female	58	4.45 ± 4.09	1.52 ± 2.05	0.84 ± 1.61	65.84%	81.12%
Male	22	4.90 ± 3.85	2.06 ± 2.01	1.18 ± 1.64	57.96%	75.92%
Gingiva and tongue	44	2.93 ± 2.91	1.13 ± 1.84	0.70 ± 1.58	61.43%	76.11%
Female	31	3.29 ± 3.34	1.11 ± 2.11	0.39 ± 0.86	66.26%	88.15%
Male	13	2.08 ± 1.18	1.19 ± 1.04	1.46 ± 2.50	42.79%	29.81%

Table 3
Surface area and mean reduction of OLP lesions before and after treatment across all size groups.

Size Group	Sites									
	Buccal mucosa					Gingiva and tongue				
	Baseline ($cm^{2)}$	On completion ($cm^{2)}$	Mean size reduction	12 months post-therapy (cm^2)	Mean size reduction	Baseline (cm^2)	On completion (cm^2)	Mean size reduction	12 months post-therapy (cm^2)	Mean size reduction
Group I	1.45 ± 0.87	0.87 ± 1.41	40.00%	0.59 ± 0.83	59.31%	1.47 ± 0.69	1.02 ± 1.50	30.61%	0.46 ± 0.86	68.71%
Group II	4.34 ± 0.68	2.29 ± 1.87	47.24%	1.40 ± 2.23	67.74%	3.79 ± 0.73	1.06 ± 1.18	72.03%	1.48 ± 2.87	60.95%
Group III	6.63 ± 0.68	2.90 ± 3.26	56.26%	1.09 ± 1.30	83.56%	6.30 ± 0.42	4.62 ± 6.53	26.67%	1.02 ± 1.44	83.81%
Group IV	12.91 ± 2.99	1.61 ± 1.92	87.53%	0.80 ± 1.97	93.80%	11.9 ± 2.52	0.09 ± 0.16	92.44%	0.19 ± 0.33	84.03%

observation only 9 lesions remained unresponsive – 6 on the lining mucosa and 3 in the masticatory regions. One of the lesions (on the gingiva) enlarged by 5.61 cm^2 and was now 9.36 cm^2, the size of another one (on the buccal mucosa) increased by 5.4 cm^2 to 9.0 cm^2. Sobaniec et al. [31] achieved comparatively effective results after Chlorin-e6 PDT. Post-therapy the mean size was 2.7 cm^2 ± 2.62, a decrease by 3.3 cm^2, and even bigger reduction by 3.8 cm^2 for the lesions on the buccal mucosa and lips. Aghahosseini et al. [20] and Maloth et al. [28] reported a slightly smaller reduction in lesions' size after MB-mediated therapy, 0.8 cm^2 and 0.85 cm^2 at a lower output value, 1 cm^2 ± 0.9 and 2.2 cm^2 ± 0.79 respectively. The authors of most publications tend to exclude figures for pre- and post-treatment size of OLP lesions, which is a substantial obstacle as far as comparison and reference to our own results is concerned [29,32,33].

The results of our own study attained after the 10-session PDT series indicate a greater efficacy of the therapy in the female group, where, for the lesions on the buccal mucosa and lips, it was 7.88% higher than among the male patients and 23.47% higher for the lesions located on the gingiva and tongue. The gap in efficacy between women and men further increased at the end of the 12-month observation, when the mean size reduction within the lining mucosa was 81.12% and 75.12% respectively. However, the discrepancy was overwhelming within the masticatory mucosa – 88.15% in women against 29.81% in men. Sobaniec et al. [31] observed a reverse outcome of the therapy, a higher efficacy among men, where reduction for the lesions within the buccal mucosa and lips was 68.9% while in women 51.4%. Notably, the female groups in the presented study as well as Sobaniec et al. [31] were over twice as big as than male ones. Also in other two available studies women's dominance was 65% and 92.3% respectively. The authors did not observe, however, statistically significant differences in response to treatment in respect to sex and location of lesions [20,29].

The authors' own protocol included a diode lamp emitting light at 630 nm, 300 mW and 150 J/cm^2. The protocol anticipated a number of illumination sessions sufficient to cure a lesion, but no more than 10 in total. Fifty-four lesions showed early response after the 5th illumination. The majority of lesions required further illuminations and the number of cured lesions grew progressively with each subsequent PDT session. In other studies, responses to therapy varied according to the protocols used. Sobaniec et al. [31] used light at 660 nm and 90 J/cm^2, however, as none of the lesions showed early response, all lesions received 10 illuminations. In a study by Sadaksharam et al. [29] the protocol included the use of Xenon arch lamp emitting the light at 630 nm and 120 J/cm^2 in a series of four therapeutic sessions over the span of 15 days (day 1, 4, 7 and 15). The first three illuminations brought no reaction in the lesions, but after the fourth session 10 out of 20 lesions became reduced in size by 20–49%, a change described by the authors as moderate improvement. Similarly, Aghahosseini et al. [20,33] observed improvement within a week after a single PDT session with the use of a low-energy laser lamp emitting the light at 632 nm and 100 J/cm^2 or 120 J/cm^2.

The secondary aim of the presented study was to evaluate prospects of long-term stability of the therapy's outcome. Over a year-long observation, a process of confirmed healing was taking place in the lesions, while there were not any relapses of the disease. Within that time, the number of cured lesions rose from 46 directly after the therapy to now 72 and the mean reduction in size was now 15.79% bigger (a rise from 62.91% to 78.70%). In 115 out of 124 sites improvement manifested as remission and/or reduction in size by 92.74%. Seventy-two of the healed sites were in complete remission and merely 7.26% of the lesions did not respond to the therapy. The proportion of the lesions in remission was higher on the gingiva and tongue than buccal mucosa and lips. The unresponsive lesions on both the masticatory and lining mucosa made up 6.82% and 7.5% respectively. Overall, a better efficacy of the therapy was observed within the buccal mucosa and lips. PDT resulted in a lesser reduction mean size reduction, 76.11%,within the gingiva and tongue. However, a decrease in surface area occurred on both types of mucosa in relation comparison to the immediate post-therapy results. It needs to be emphasized that all patients managed to keep the regular appointments during the follow-up. Other studies confirm that PDT contributes to lasting remission. Kvaal et al. [32] observed stable results in 10 of 14 patients for four years. There was no record for the other 4 patients who had been lost to the follow-up. Aghahosseini et al. [20,33] claimed that the effects of the therapy can be maintained for a period of 3–9 months, while Sadaksharam et al. [29] estimated such time as 6 months. Prasanna et al. [30] also observed a progressive improvement of lesions between the final PDT session and the end of the follow-up stage. The starting point saw 553% reduction in size while 12 weeks later it rose to 733%.

Table 4
Number of OLP lesions before and after treatment by size.

	On completion of therapy					12 months post-therapy				
	Size Group 0	Size Group I	Size Group II	Size Group III	Size Group IV	Size Group 0	Size Group I	Size Group II	Size Group III	Size Group IV
Size Group I (n = 63)	32	26	4	1	–	38	24	1	–	–
Size Group II (n = 35)	7	15	12	1	–	18	9	6	–	2
Size Group III (n = 12)	2	5	2	2	1	6	5	1	–	–
Size Group IV (n = 14)	5	7	2	–	–	10	3	–	1	–

n – number of lesions observed in given size group.

Sadaksharam et al. [29] and Sulewska et al. [34] attained similar results in their studies where, although over follow-up periods of different-length, they observed constant improvement. Additionally, Prasanna et al. [30] found that there was an overall improvement in all 15 lesions, of which 3 erosive ones turned into milder types. Aghahosseini et al. [20] and Sulewska et al. [34] also observed cases of erosive lesions changing their nature to atrophic, reticular or erythematous. Such transformation can be seen as therapeutic success since it indicates a lesser risk of malignant transformation [21].

The results from the studies above lead to a conclusion that PDT stimulates healing processes, and outcome becomes more evident in longer spans of post-therapy observation, a fact of great significance in a condition as chronic as OLP. This needs confirmation in further long-term studies involving bigger populations of patients. The fact that periods of remission may last up to a year or even longer points to PDT's superiority over pharmacological management of variable efficacy. OLP lesions commonly resist pharmacological treatment and a large proportion of patients relapse soon after it finishes [12–14]. That is why PDT, a non-invasive and practically side-effect-free method, seems to be a good therapeutic option for patients with frequent relapses, extensive lesions, the elderly or those afflicted by systemic diseases.

The available study reports admit that despite being selectively confined to the affected tissue, PDT may cause pain and swelling in the surrounding healthy mucosa [35,36]. A burning or stinging pain may occur during and/or after the illumination and last a few hours [34–37]. Pre- or post-treatment medication can reduce it effectively. In the presented protocol after each of the five initial illumination sessions, all patients reported an intense pain lasting up to 2 h. This post-treatment pain/discomfort subsided with each subsequent PDT session. After the 10th illumination all patients experienced PDT-induced discomfort at a lesser intensity, including those in whom the lesions were still present. Over the 12-month observation period the patients reported further lessening of pain, always of comparatively lower intensity than at the pre-therapy stage. In other studies patients of MAL-mediated therapy also experienced insignificant pain during illumination and some discomfort in the week to follow, with no adverse effects otherwise [32]. A contrary report comes from Chen et al. [38] who had to carry out 5% ALA-mediated PDT under local anesthesia due to a severe throbbing and/or burning pain, which would occur 1–2 hours after the session and last up to 48 h. It transpires that photosensitizers such as Chlorin-e6 or MB cause considerably less discomfort for patients. In a few studies patients did not report intense pain, burning sensation or any other side effects during or immediately after treatment and could do without analgesics [20,29–33]. Aghahosseini et al. [20] observed longer periods of remission bringing improvement to patient's daily lives. They estimated OLP-related pain using 1–10 scale for pre- and post-therapy stages where the figures were 5.1 ± 1.7 and 0.9 ± 1.5 respectively. Prasanna et al. [30] observed the mean pre-PDT symptom score value of 2.5 ± 0.5 drop to 0.4 ± 0.7 during the follow-up, with mean reduction of 2.1 ± 0.8. Overall, 93.3% lesions showed negative symptom scoring, indicating that MB-PDT has a potential to provide excellent symptomatic relief of OLP-related pain. The authors did not notice any recurrences in patients at follow-up appointments.

Both this and other studies' findings confirm that PDT is virtually non-invasive and as such may become an alternative auxiliary method in treatment of reticular OLP. Several other advantages justify its wider use. It is highly effective, non-toxic, allows repeated use, and requires few facilities to carry it out [20,29–35,37,39]. Patients' feedback is favorable as it evidently enhances the quality of their lives, even when lesions are not completely eradicated. However, a variety of currently used PDT protocols and conflicting views on their efficacy make further studies compulsory. Particular attention should be paid to the application of the photosensitizer to the mucosa. Due to the specificity of the oral cavity, the problem of standardization of the quantity of the applied photosensitizer and the maintenance of it on the surface is still a problem. The above technical impediments were also some limitations of the presented study.

Standardization of PDT methods and determination of their effectiveness is also necessary to compare this method with others currently used, including corticosteroids, which have so far been a primary option in OLP therapy. Although a strong topical corticosteroid use seems to be therapeutically effective, a long-term treatment may lead to topical complications such as mucosal atrophy, local hyperpigmentation, candidiasis, xerostomia, prolonged healing or mucosal fragility. On the other hand, systemic complications may involve Cushing's syndrome, hyperglycemia or glycosuria, adrenal insufficiency, gastrointestinal disorders and hypertension [11,19–23,40–47].

Corticosteroids are so effective in OLP therapy due to their anti-inflammatory and immunosuppressive properties through suppression of T cells, controlling autoimmune response and apoptosis in oral mucosa [23,48]. The mechanisms underlying corticosteroid actions and PDT seem to be comparable to some extent. PDT is thought to have an immunomodulatory effect by inducing apoptosis of hyper-proliferating cells in OLP lesions. [33,49]. It is PDT's selective activation of the photosensitizer and precise light targeting the proliferating cells that ensure their predictable necrosis [47]. Bearing in mind both the immuno-inflammatory pathogenesis of OLP and immunomodulatory mechanisms of PDT, it seems reasonable to implement the therapy [33,47,49].

As far as efficacy of PDT against corticosteroids is concerned, the reports from recent years are inconclusive. Mostafa et al. [40] reported a more evident improvement in signs and symptoms among the PDT-treated than corticosteroid group. Bakhitari et al. [50] and Maloth et al. [28] found out that PDT was as effective as topical corticosteroids in management of OLP. However, Jajarm et al. [47] and Saleh et al. [51] reported that corticosteroid treatment brought a significantly greater improvement in symptoms and number of relapses than PDT. Jajarm et al. [23] concluded through meta-analysis that photodynamic therapy failed to show any significant effect on the signs of OLP. These discrepancies between the cited studies may result from different PDT protocols and a different, often short, observation time. That's why, any further RCTs with longer follow-up periods, standardized PDT parameters, taking a comparative approach to PDT and steroid therapy will lead to right conclusions.

9. Conclusions

The results confirmed that ALA-mediated photodynamic therapy using a 630 nm light is effective and can be considered as an optional treatment for symptomatic OLP.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] T.G. Berger, Lichen planus, JAMA Dermatol. 151 (2015) 356.
[2] P. Davari, H.H. Hsiao, N. Fazel, Mucosal lichen planus: an evidence-based treatment update, Am. J. Clin. Dermatol. 15 (2014) 181–195.
[3] D. Di Stasio, A. Guida, C. Salerno, M. Contaldo, V. Esposito, L. Laino, R. Serpico, A. Lucchese, Oral lichen planus: a narrative review, Front Biosci 6 (2014) 370–376 (Elite Ed).
[4] D. Eisen, M. Carrozzo, J.V.B. Sebastian, K. Thongprasom, Oral lichen planus: clinical features and management, Oral Dis. 11 (2005) 338–349.
[5] Ch. Anuradha, B.V. Reddy, S.R. Nandan, S.R. Kumar, Oral lichen planus. A review, N. Y. State Dent. J. 74 (2008) 66–68.
[6] B.J. Schlosser, Lichen planus and lichenoid reactions of the oral mucosa, Dermatol. Ther. (Heidelb) 23 (2010) 251.
[7] P. Córdova, A. Rubio, P. Echeverría, Oral lichen planus: a look from diagnosis to treatment, J. Oral Res. 3 (2014) 62–67.
[8] D. Mostafa, B. Tarakji, Photodynamic therapy in treatment of oral lichen planus, J.

Clin. Med. Res. 7 (2015) 393–399.
[9] J. Dissemond, Oral lichen planus: an overview, J. Dermatolog. Treat. 15 (2004) 136–140.
[10] M. Carrozzo, S. Gandolfo, The management of oral lichen planus, Oral Dis. 5 (1999) 196–205.
[11] F. Gorouhi, A. Solhpour, J.M. Beitollahi, Randomized trial of pimecrolimus cream versus triamcinolone acetonide paste in the treatment of oral lichen planus, J. Am. Acad. Dermatol. 57 (2007) 806–813.
[12] J. Koneru, M. Mahalakshmi, R. Naik, Management of oral lichen planus- A review, Indian J. Appl. Res. 3 (2013) 289–290.
[13] T.A. Hodgson, N. Sahni, F. Kaliakatsou, J.A. Buchanan, S.R. Porter, Long-term efficacy and safety of topical tacrolimus in the management of ulcerative/erosive oral lichen planus, Eur. J. Dermatol. 13 (2003) 466–470.
[14] G. Lodi, M. Tarozzi, A. Sardella, F. Demarosi, L. Canegallo, D. Di Benedetto, A. Carrassi, Miconazole as adjuvant therapy for oral lichen planus: a double-blind randomized controlled trial, Br. J. Dermatol. 156 (2007) 1336–1341.
[15] A. Kuusilehto, R. Lehtinen, R.P. Happonen, K. Heikinheimo, K. Lehtimäki, C.T. Jansén, 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 (1997) 502–505.
[16] R. Kassem, N. Yarom, A. Scope, M. Babaev, H. Traun, F. Pavlotzky, Treatment of erosive oral lichen planus with local ultraviolet B phototherapy, J. Am. Acad. Dermatol. 66 (2012) 761–766.
[17] N. Lavanya, P. Jayanthi, U.K. Rao, K. Ranganathan, Oral lichen planus: an update on pathogenesis and treatment, J. Oral Maxillofac. Pathol. 15 (2011) 127–132.
[18] N. Mollaoglu, Oral lichen planus: a review, Br. J. Oral Maxillofac. Surg. 38 (2000) 370–377.
[19] K. Thongprasom, K. Dhanuthai, Steriods in the treatment of lichen planus: a review, J. Oral Sci. 50 (2008) 377–385.
[20] F. Aghahosseini, F. Arbabi-Kalati, L.A. Fashtami, G.E. Djavid, M. Fateh, J.M. Beitollahi, Methylene blue-mediated photodynamic therapy: a possible alternative treatment for oral lichen planus, Lasers Surg. Med. 38 (2006) 33–38.
[21] F. Aghahosseini, I. Mirzaii-Dizgah, M. Abdollahi, N. Akbari-Gillani, Efficacy of IMOD in oral lichen planus, Open J. Stomatol. 1 (2011) 13–17.
[22] D. Amanat, H. Ebrahimi, M.Z. Zahedani, N. Zeini, S. Pourshahidi, Z. Ranjbar, Comparing the effects of cryotherapy with nitrous oxide gas versus topical corticosteroids in the treatment of oral lichen planus, Indian J. Dent. Res. 25 (2014) 711–716.
[23] H.H. Jajarm, R. Asadi, E. Bardideh, H. Shafaee, Y. Khazaei, M. Emadzadeh, The effects of photodynamic and low-level laser therapy for treatment of oral lichen planus - A systematic review and meta-analysis, Photodiagnosis Photodyn. Ther. 23 (2018) 254–260.
[24] E.N. Lundqvist, Y.B. Wahlin, M. Bergdahl, J. Bergdahl, Psychological health in patients with genital and oral erosive lichen planus, J. Eur. Acad. Dermatol. Venerol. 20 (2006) 661–666.
[25] L. Sharma, M.K. Mishra, A comparative study of PUVASOL therapy in lichen planus, Indian J. Dermatol. Venereol. Leprol. 69 (2003) 212–213.
[26] R. Darlenski, J.W. Fluhr, Photodynamic therapy in dermatology: past, present, and future, J. Biomed. Opt. 18 (2013), https://doi.org/10.1117/1.JBO.18.6.061208 061208.
[27] D.E. Dolmans, D. Fukumura, R.K. Jain, Photodynamic therapy for cancer, Nat. Rev. Cancer 3 (2003) 380–387.
[28] K.N. Maloth, N. Velpula, S. Kodangal, M. Sangmesh, K. Vellamchetla, S. Ugrappa, N. Meka, Photodynamic therapy - a non-invasive treatment modality for pre-cancerous lesions, J. Lasers Med. Sci. 7 (2016) 30–36.
[29] 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 (2012) 97–101.
[30] S.W. Prasanna, E. Ingle, P.R. Aruna, Ch. Pravada, D. Koteeswaran, S. Ganesan, Photodynamic therapy of oral leukoplakia and oral lichen planus using methylene blue: a pilot study, J. Innov. Opt. Health Sci. 8 (2015) 1540005-11.
[31] S. Sobaniec, P. Bernaczyk, J. Pietruski, M. Cholewa, A. Skurska, E. Dolińska, E. Duraj, G. Tokajuk, A. Paniczko, E. Olszewska, M. Pietruska, Clinical assessment of the efficacy of photodynamic therapy in the treatment of oral lichen planus, Lasers Med. Sci. 28 (2013) 311–316.
[32] S.I. Kvaal, E. Angell-Petersen, T. Warloe, Photodynamic treatment of oral lichen planus, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 115 (2013) 62–70.
[33] F. Aghahosseini, F. Arbabi-Kalati, L.A. Fashtam, M. Fatch, G.E. Djavid, Treatment of oral lichen planus with photodynamic therapy mediated methylene blue: a case report, Med. Oral Patol. Oral Cir. Bucal 11 (2006) 126–129.
[34] M. Sulewska, E. Duraj, S. Sobaniec, A. Graczyk, R. Milewski, M. Wróblewska, J. Pietruski, M. Pietruska, A clinical evaluation of the efficacy of photodynamic therapy in the treatment of erosive oral lichen planus: a case series, Photodiagnosis Photodyn. Ther. 18 (2017) 12–19.
[35] H. Gursoy, C. Ozcakir-Tomruk, J. Tanalp, S. Yilmaz, Photodynamic therapy in dentistry: a literature review, Clin. Oral Invest. 17 (2013) 1113–1125.
[36] F.H. van Duijnhoven, R.I. Aalbers, J.P. Rovers, O.T. Terpstra, P. Kuppen, The immunological consequences of photodynamic treatment of cancer, a literature review, Immunobiol. 207 (2003) 105–113.
[37] K. Konopka, T. Goslinski, Photodynamic therapy in dentistry, J. Dent. Res. 86 (2007) 694–707.
[38] H.M. Chen, C.H. Yu, P.C. Tu, C.Y. Yeh, T. Tsai, C.P. Chiang, Successful treatment of oral verrucous hyperplasia and oral leukoplakia with topical 5-aminolevulinic acid-mediated photodynamic therapy, Lasers Surg. Med. 37 (2005) 114–122.
[39] M.A. Biel, Photodynamic therapy in head and neck cancer, Curr. Oncol. Rep. 4 (2002) 87–96.
[40] D. Mostafa, E. Moussa, M. Alnouaem, M, Evaluation of photodynamic therapy in treatment of oral erosive lichen planus in comparison with topically applied corticosteroids, Photodiagnosis Photodyn. Ther. 19 (2017) 56–66.
[41] S. Patil, S. Khandelwal, N. Sinha, S. Kaswan, F.R. Tipu, Treatment modalities of oral lichen planus: an update, Jpn. J. Oral Diagn. / Oral Med. 1 (2012) 47–52.
[42] R. Kini, D.V. Nagaratna, A. Saha, Therapeutic management of oral lichen planus: a review for the clinicians, World J. Dent. 2 (2011) 249–253.
[43] S.A. Al-Maweri, S. Ashraf, B. Kalakonda, E. Halboub, W. Petro, N.A. AlAizari, Efficacy of photodynamic therapy in the treatment of symptomatic oral lichen planus: a systematic review, J. Oral Pathol. Med. 47 (2018) 326–332.
[44] G. Chamani, M. Rad, M.R. Zarei, S. Lotfi, M. Sadeghi, Z. Ahmadi, Efficacy of tacrolimus and clobetasol in the treatment of oral lichen planus: a systematic review and meta-analysis, Int. J. Dermatol. 54 (2015) 996–1004.
[45] Z. Akram, F. Javed, M. Hosein, M.A. Al-Qahtani, F. Alshehri, A.I. Alzahrani, F. Vohra, Photodynamic therapy in the treatment of symptomatic oral lichen planus: a systematic review, Photodermatol. Photoimmunol. Photomed. 34 (2018) 167–174.
[46] M. Carbone, E. Goss, M. Carrozzo, S. Castellano, D. Conrotto, R. Broccoletti, S. Gandolfo, Systemic and topical corticosteroid treatment of oral lichen planus: a comparative study with long-term follow-up, J. Oral Pathol. Med. 32 (2003) 323–329.
[47] H.H. Jajarm, F. Falaki, M. Sanatkhani, M. Ahmadzadeh, F. Ahrari, H. Shafaee, A comparative study of toluidine blue-mediated photodynamic therapy versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus: a randomized clinical controlled trial, Lasers Med. Sci. 30 (2015) 1475–1480.
[48] M. Radwan-Oczko, Topical application of drugs used in treatment of oral lichen planus lesions, Adv. Clin. Exp. Med. 22 (2013) 893–898.
[49] H.H. Jajarm, F. Falaki, O. Mahdavi, A comparative pilot study of low intensity laser versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus, Photomed. Laser Surg. 29 (2011) 421–425.
[50] S. Bakhtiari, S. Azari-Marhabi, S.M. Mojahedi, M. Namdari, Z.E. Rankohi, S. Jafari, Comparing clinical effects of photodynamic therapy as a novel method with topical corticosteroid for treatment of Oral Lichen Planus, Photodiagnosis Photodyn. Ther. 20 (2017) 159–164.
[51] W.E. Saleh, O.H. Khashaba, S.El nagdy, M.D. Moustafa, Photodynamic therapy of oral erosive lichen planus in diabetic and hypertensive patients, Mansoura. J Dent. 1 (2014) 119–123.