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LITERATURE REVIEW

The Photodynamic Treatment of Oral Lichen Planus: A Literature Review

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ABSTRACT
Lichen planus (LP) is a chronic, relapsing, non-infectious inflammatory disease affecting the skin and mucous membranes. The exact origin of oral lichen planus (OLP) is not well known. Complete spontaneous healing is rare. The treatment of oral OLP is palliative; there is no curative treatment so far, which is a therapeutic challenge for practitioners. The goals of treatment are the control of pain, signs, and symptoms. Local corticosteroids remain the first-line treatment. In case of failure of drug therapy, other treatments can be considered, such as photodynamic therapy (PDT). Material and methods: Our work was carried out using the PubMed, Science Direct, and EBSCO search engines to explore the literature on the efficacy of PDT in the treatment of lichen planus. Conclusion: PDT appears to have some effect in the treatment of OLP in adult patients. However, further randomized controlled trials with a long follow-up period, standardized PDT parameters, and comparison of PDT efficacy with steroid therapy are warranted to obtain strong conclusions in this regard.

KEYWORDS: Lichen planus; Photodynamic treatment; Photosensitizers.

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INTRODUCTION

OLP is a chronic inflammatory mucocutaneous disease of unknown etiology and polymorphic appearance (1). Erasmus Wilson first described LP condition in 1869 as a chronic disease with a rare possible malignant transformation (2-3). Oral lesions often precede skin lesions and, in many cases, they remain the only manifestation of the disease. In rare cases, LP can affect the nasal, laryngeal, esophageal, genital or anal mucosa; the disease may also present lesions on the scalp or nails (1-3). The prevalence of this pathology is estimated to be between 1% and 2%. It affects more women than men and the majority of cases are identified in middle-aged people between 30 and 60 years of age. (1-4-7-8).

LP in children is rare, the clinical signs and characteristics resemble those of a LP in adults. However, the prognosis for OLP in children generally appears to be more favorable than in adults (5-6-8).

Patients with OLP develop coincident skin lesions in 44% of cases, and more than 70% of patients with cutaneous LP develop coincident OLP. OLP is more common, persistent and resistant to treatment than the cutaneous form (8).

The etiology is still uncertain. Data in the literature point to the autoimmune origin of the LP. An immunological process is triggered by the existence of an antigen capable of modifying the antigenic specificity of basal keratinocytes of the oral mucosa, making them targets for cell-mediated immunity (1- 9). This triggering factor may be of external origin induced by systemic drugs, contact allergies, mechanical trauma, dental restorations, viral or bacterial infection... or of internal origin induced by psychological disorders, genetic factors etcetera.

Antimalarials, antihypertensives, non-steroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors have been associated with oral lichenoid reactions. Other drugs have been implicated such as diuretics, oral hypoglycemic agents, gold salts, penicillamine, beta-blockers, and antiretroviral drugs for the treatment of HIV (10).

A possible association between LP and infection with HIV and hepatitis C virus (20-21) has been suggested, but it could be related to zidovudine or ketoconazole therapy for HIV infection (19) or modern therapy for patients with chronic liver disease that includes interferon-gamma and ribavirin drugs often considered a cause for triggering lichenoid reactions (1).

Researchers have found that contact of dental restorative materials with oral tissue may be associated with the development of lichenoid reactions that clinically and histologically resemble to OLP but have an identifiable etiology. Amalgam (12-13), composite resins (14), cobalt, nickel, palladium and gold, have been implicated as causes

of oral lichenoid reactions, even flavors and plastics may play an important role in the pathogenesis of its lesions (11-15). On the other hand, other authors show that the replacement of the incriminated materials by other restorations did not have a beneficial effect on the lesions of the LP, which may point us towards the involvement of other factors. Trauma is an exacerbating factor by which other etiological factors may exert their effect; this partly explains why OLP lesions develop in sites prone to trauma, the oral mucosa or the lateral surfaces of the tongue (2-11). Psychosomatic disorders and their association with the LP remains controversial. Studies by Vilar-Villanueva M (16) and Zucoloto ML (17) have found that psychological disorders and increased anxiety levels play an important role as a trigger for OLP and are responsible for many relapses by increasing the severity of the lesions. Patients with OLP may benefit from complementary therapeutic treatments, such as psychological and/or psychiatric care, in conjunction with specific treatment of oral lesions. Psychological support would be desirable in order to improve their mental health, as this would have a positive impact on their quality of life and lead to a better progression of the disease. On the other hand, the results of a study by Adamo D (18) reported no statistically significant association between symptomatic reticular LP and anxiety. Mood disorders could modulate the perception of pain or that patients could develop two different associated oral diseases such as stomatodynia and LP.

The treatment of OLP is palliative, there is no curative treatment until today which is a therapeutic challenge for practitioners. The goals of treatment are the control of pain, signs and symptoms. Local corticosteroids remain the first-line treatment (45). Systemic corticosteroids are also to be prescribed as first-line treatment in severe and extensive forms of OLP, or in case of resistance to local corticosteroid therapy. Other drug treatments such as retinoids (46), tacrolimus, cyclosporine and Aloe Vera can be used as second-line therapy in case of contraindication to corticosteroid therapy or resistance to this treatment. In case of failure of the drug therapy, other treatments can be considered such as laser, surgery, psychotherapy and PDT.

CONCEPTS OF PDT

Photodynamic therapy is a therapeutic modality that has been used for the management of many lesions such as oral cancers and potentially malignant lesions, particulary OLP. This approach requires three essential elements, which are a photosensitizer (PS), a light source and oxygen. Light at a specific wavelength activates the PS molecule from a stable state to an unstable singlet state of short duration. To return to its stable ground state, the PS molecule transfers energy to oxygen, which causes the release of reactive oxygen species, in a singlet or triplet electronic state that seeks to gain or lose an electron that gives it stability. Its radical reactions are very fast (< 0, 04 us) and of short action (< 0, 02 um) provoke the destruction and the death of the abnormal cells, without causing damages to the cells and the healthy tissue.

MATERIALS AND METHODS

A comprehensive literature researches were performed in the Pubmed (MEDLINE), Scopus, Cochrane, Sciencedirect and google scholar databases. The Keywords were used: Lichen planus; Photodynamic treatment; Photosensitizers. Article have been selected based on title, abstract, material and methods. The minimum inclusion requirements were studies on patients diagnosed with OLP and treated with PDT after topical administration of a PS, randomized controlled trials. Studies that did not meet the inclusion criteria, in vivo studies were excluded. The focused question was "Is PDT effective in the treatment of OLP?

RESULTS:

12 studies that met the inclusion criteria were included in this work. The number of subjects ranged from 8 to 50 patients. In 7 of the 12 studies, the patients had erosive and/or atrophic OLP.

The types of light sources were diode lasers in 3 studies, light-emitting diodes (LED) in 5 studies, GaAlAs (Gallium-Aluminum-Arsenide) laser in 2 studies, while one study used a low-level laser and a xenon arc lamp respectively.

The wavelengths depended on the PS used and ranged from 600 to 670 nm. Methylene blue (5%) was used as PS in 5 studies and toluidine blue was used in 3 studies with a similar wavelength between its 2 PS which varied between 630 and 660 nm. 5-Aminolevulinic acid (5-ALA) was used in 3 studies with a wavelength between 600 and 670 nm and metyl aminolevulinic (MAL) in 1 study, with a wavelength between 600 and 660.

The studies reported a total number of PDT sessions ranging from 1 to 10 applications. 5 studies included local corticosteroid therapy as a control group. The results of 4 studies showed that PDT treatment of OLP is as effective as corticosteroid therapy. One study showed that the effect of corticosteroids was more benign than PDT, but that PDT was an effective treatment option.

Pre-treatment clinical parameters were pain perception, quality of life, and lesion extension. Several studies confirmed the safety of PDT during active treatment sessions and follow-up periods ranged from 4 weeks to 4 years.

DISCUSSION

The exact mechanism of action of dynamic phototherapy is not clear. It seems to act on hyperproliferating cells, such as those present in malignant tumors that selectively absorb photosensitizers (PS). It has been suggested that PDT may have immunomodulatory effects and may induce apoptosis in inflammatory, hyperproliferating cells that are present in the LP. This could reverse hyperproliferation and inflammation of the LP.

Recently, the use of PDT is gaining importance due to its minimal toxicity on normal tissues and several studies have shown an effective reduction of OLP lesions after PDT, 11 studies included in the present literature review showed that PDT resulted in a clinically significant improvement of the OLP lesion, therefore it is confirmed that PDT has some effect in the management of LP. However, it is important to evaluate several factors that may influence the efficacy of PDT because there is a great deal of heterogeneity between studies with respect to the wavelength of the light source, the type of PS used, the duration of treatment or number of sessions and the duration of follow-up and observation.

Table 1: General characteristics and outcome of the included studies

Author	Type of lichen	Type of Photosensitizers (PS)	Light source and Wavelength (nm)*	Number of PDT sessions	Number of patients	Follow-up time	Treatment report
N. Rakesh et al. (2018) (34)	Erosive refractory	5 - Aminolevulinic acid	Laser diode 600-670 nm	Not specified	10	4 years	Reduced reticulation, erythema, ulceration (from 5 to 3) and recorded burning sensation by the visual analogue scale (pre-treatment VAS ranged from 5 to 8, post-treatment VAS was 0 to 1)
Sedigheh Bakhtiari et al. (2017) (35)	Not specified	methylene blue (MB)	LED 630 nm	4	30	90 days	Photodynamic therapy was as effective as dexamethasone mouthwash in the treatment of lichen planus. It could be used as a safe modality in the treatment of oral lichen planus lesions without side effects.
Sana Mirza (2018) (36)	Erosive-atrophic oral lichen planus	Toluidine blue (1 mg/ml)	GaAlAs diode Laser 630nm	8	15	1 year	PDT is effective in treating erosive-atrophic forms of OLP in adult patients.
Sigrid I et al. (2013) (37)	white streaks and erythematous and ulcerated area on the mucous membrane	Methyl 5-aminolevulinate (MAL)	LED 600-660 nm	1	14	4 years	Oral lichen planus treated with MAL-PDT showed improvement after only one treatment.
Raluca Cosgarea (2020) (32)	Not specified	Methylene blue (MB)	Low level laser 660nm	4	20	56 days	PDT treatment in OP results in reduced lesions and improved quality of life, and induces local and systemic anti-inflammatory effects. The study identifies PDT as a new treatment option in OLP.
Saleh et al. 2020 (44)	Erosive	Methylene blue MB	LED 660nm	8	10	4 weeks	PDT is as effective as topical steroids
Hasan Hoseinpour Jajarm et al. (2014) (41)	Erosive-atrophic	Toluidine blue	GaAlAs laser 630 nm	2	11	1 month	Traditional corticosteroid therapy has been shown to be more effective than PDT-TB.
Fatemeh Lavaee (2019)(38)	Not specified	Toluidine blue	Laser diode 660nm	3	8	7 weeks	PDT is as effective as topical steroids
Diana Mostafa 2017 (39)	Erosive	Methylene blue (MB)	Diode Laser 660 nm	8	10	2 months	The results of this study lead to the conclusion that MB-PDT is considered a better treatment for OELP compared to CT because it is very effective in reducing pain and lesion regression.
Magdalena Sulewska (2017) (40)	Erosive	5-aminolevulinic acid (5-ALA) (5%)	LED 630 nm	10	12	12 months	The results suggest that PDT offers a non-invasive treatment of the lesions and can become an alternative and complementary method to those currently used.
Jayachandran Sadaksharam (2012) (42)	Symptomatic lichen planus	5% Methylene blue	Xenon arc lamp 630nm	4	20	4 weeks	There was a satisfactory reduction in the signs and symptoms of oral lichen planus.
Magdalena Sulewska (2019) (43)	Erosive, refractory	5-aminolevulinic acid (5-ALA) (5%)	LED 630 nm	10	50	12 months	Significant reduction in pain and injury size after PDT is stopped
Diana Mostafa 2017 (39)	Erosive	Methylene blue (MB)	Diode Laser 660 nm	8	10	2 months	The results of this study lead to the conclusion that MB-PDT is considered a better treatment for OELP compared to CT because it is very effective in reducing pain and lesion regression.

Apart from light and oxygen, one of the three essential elements of PDT is the presence of a photosensitizer. These dyes are defined as substances capable of absorbing light with a specific wavelength, causing photochemical or photophysical reactions (24-25).

The PS found in the 11 articles included (Table 1) can be divided into two PS groups: dyes and hematoporphyrin derivatives. 5-aminolevulinic acid (5-ALA), a second-generation PS, is an endogenous substance, an intermediate product of porphyrinea metabolism with a low molecular weight, a short phototoxicity period, good tissue penetration and high singlet oxygen levels (27). In PDT treatment with 5-ALA, 5-ALA is applied topically to the lesion area, exhibits excellent tissue selectivity and is absorbed by hyperproliferative epithelial cells, and is then converted to protoporphyrin IX (PPIX) with high photosensitivity. After the use of a light source at specific wavelengths, a large amount of singlet oxygen and free radicals are produced, causing apoptosis and cell necrosis in the area of the lesion, without causing damage to the surrounding normal tissues and cells (28).

The use of methylene blue is justified by its relative stability to light, which makes it an important generator of singlet oxygen (31). The action of methylene blue in PDT is dependent on the target tissue and targets mainly mitochondria and lysosomes but possibly also other cellular organelles (26-29). Methylene Blue has also shown promising results in the treatment of a variety of superficial cancerous and non-cancerous skin lesions (26). Cosgarea et al. found that the use of methylene blue induced local and systemic anti-inflammatory effects by causing a decrease in the relative numbers of CD4+ and CD8+ T cells in mucosal OLP lesions, in the number of activated peripheral CD4 + CD137+ T cells, and in the number of CD8 + CD137+ T cells and IL-17-secreting T cells (32).

Luan e al demonstrated that toluidine blue PDT gave an antimicrobial effect in periodontal tissue without damage to healthy tissue (30). The advantage of these PS is that they are readily available on the market and can be applied to the oral mucosa in the form of mouthwash or gels before light irradiation (29).

The maximum absorption of light by a PS should be at wavelengths between 600 nm and 800 nm. Absorption of light at wavelengths above 800 nm does not provide sufficient energy to stimulate oxygen in its singular state and the production of other reactive oxygen species, and the minimum absorption in the range of 400 nm to 600 nm prevents possible excessive photosensitivity caused by sunlight (25). The types of light sources in our review were broad spectrum lamps, diode lasers and diode LED. Wavelengths depended on the PS and the range was 600-660 nm.

According to Hess J et al (29), a wavelength range of 630-660 nm is the best choice, taking into account both absorption and depth of penetration into the tissue under consideration. Daylight has been used in cutaneous PDT, but is not applicable to oral tissues (33).

It has been shown that the frequency of laser application also affects the overall effectiveness of PDT (22-23). This is also reported by clinical studies 32,34, 36, 38, 39,43 (Table 1) which showed a wide variety in the number of sessions (between 1 and 10 sessions) but no explanation was given for repeated treatments. It is therefore difficult to determine a threshold for the number of times photodynamic sessions should be applied to achieve favorable results in the treatment of LP.

The results of studies 39, 38, 44 (Table 1) showed that PDT for the treatment of OLP is as effective as corticosteroid therapy. Furthermore, PDT does not cause undesirable side effects and is a safer treatment modality since the results of PDT were similar to those of the known standard and since it does not need to be used as frequently, and is easier to use and without complications, it can surely be used as an alternative or complementary treatment for corticosteroids (4)

CONCLUSION

With recent developments in PS and light delivery systems, photodynamic therapy appears to have some effect in the treatment of OLP. This technique can be used to treat large and recurrent lesions with minimal impact, it is simple, and is highly accepted by patients. However, further randomized controlled trials with a long follow-up period, standardized PDT parameters, and comparison of PDT efficacy with steroid therapy are warranted to obtain strong conclusions in this regard.

AUTHORS' CONTRIBUTIONS

All the authors have actively participated in the redaction, the revision of the manuscript, and provided approval for this final revised version.

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COMPETING INTERESTS

The authors declare no competing interests with this study.

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