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Review

Photodynamic therapy as a new therapeutic approach of oral lichen planus

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Abstract

Oral lichen planus (OLP) is a chronic, immunologically mediated disease, defined by periods of exacerbation and quiescence. The disease is associated with a low mortality risk, but in some instances, morbidity can be important, especially in extensive, erosive forms, with a significant impact on the quality of life.

OLP is a chronic T-cell mediated inflammatory disease involving the oral cavity, the most common lesions being located on the oral mucosa, tongue and gums. Its etiology remains in part unknown, but several factors proved to be involved in the development of the disease (drugs, dental materials, infectious agents, psychological factors, autoimmunity and genetic predisposition).

The therapeutic approach should take into account the type of lesion and the extent of the disease, as well as the possible adverse effects. Although several therapies are available, OLP treatment still remains a challenge. Photodynamic therapy (PDT) is widely used in dermatology, finding applicability in the treatment of an increasing number of conditions. Recent research has shown the role of PDT in the treatment of OLP. It is a minimally invasive therapy with few side effects and promising results.

Keywords : oral lichen planus, photosensitizer, therapy

Highlights

- ✓ The therapeutic approach in the OLP remains a challenge; although many therapies are available, none of them can still be considered the ideal therapeutic approach.
- ✓ PDT seems to be a promising therapy, but with heterogeneous results due to lack of standardization (the available studies using different sources of light, wavelengths and photosensitizers).

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Introduction

Oral lichen planus (OLP) affects 0.5-2% of the general population (1). OLP is a chronic T-cell mediated inflammatory disease involving the oral cavity, the most common lesions being located on the oral mucosa, tongue and gums. Its etiology remains unknown, but several factors proved to be involved in the development of the disease including drugs, dental materials, infectious agents, psychological factors, autoimmunity and genetic predisposition (2-5). There are numerous studies attesting the role of hepatitis C virus infection in the pathogenesis of OLP; the presence of viral RNA was revealed in the samples from the oral mucosa of OLP patients (6). It seems that lymphocytes, the main cells involved in the pathogenesis of OLP, are activated under the action of an internal or external factor, which will lead to the release of high amounts of mediators of inflammation, resulting in the apoptosis of keratinocytes (7-9).

From a clinical point of view, several forms of OLP have been described, namely reticular, papular, plaque-like, atrophic, bullous and erosive. The atrophic, erosive and bullous forms associate pain as the main symptom, which is often a therapeutic challenge (10). Several therapies are available, but none is curative. The most important objective of the therapy should be the reduction of the inflammatory process and consequently, the alleviation of pain (11). Topical corticosteroids (with moderate or high potency) are the first-line treatment in OLP, systemic corticosteroids being recommended only in severe or non-responsive cases to topical therapy as well as in cases when the patient associates cutaneous lesions (12). The most important side effect of local steroid therapy is oral candidiasis; therefore, it is often recommended to associate corticosteroids with an antifungal drug. The atrophy of the oral mucosa has rarely been reported (11).

In chronic cases, when corticosteroids are used for long periods of time, although the level of absorption is low, there is a risk of adrenal suppression; therefore, these patients should be carefully monitored (13). Other topical therapeutic options are calcineurin inhibitors and retinoids. Immunosuppressant drugs including methotrexate, cyclosporine and azathioprine have also been used (1, 13). Since OLP lesions resistant to corticosteroids have been reported, it is necessary to use other therapies. In this context, several authors have studied the efficacy of photodynamic therapy (PDT) in OLP treatment. It seems that PDT is effective in the treatment of OLP by inducing the apoptosis of inflammatory cells, which are the most important players in OLP pathogenesis (14).

Discussions

The psychological impact of oral lichen planus on the patient's life quality

Disorders of the oral cavity are associated with a significant impact on the patient's life quality. Fadler et al. conducted a study on 149 patients and evaluated the psychological impact of oral mucosal disorders. They found that bullous diseases of the oral mucosa and OLP had had the greatest impact (15). Radwan-Oczko et al. analyzed 42 OLP patients with a mean duration of the disease of 43 months. Several questionnaires were used in order to assess the impact of OLP on the patients' life quality. There was a positive correlation between the duration of the disease and the level of perceived stress and a negative correlation between the duration of the disease and the quality of life (16).

Lopez-Jornet et al. demonstrated that psychological discomfort and social disability are increased in OLP patients (17). Another recent study showed that psychiatric disorders such as anxiety and depression are more common among these patients (18). Moreover, Karbach et al. compared OLP patients with those with oral cancer and identified a higher pain score of the lesions and a lower social disability score among OLP patients (19). A study revealed that the degree of stress is higher among patients with erosive OLP than among those with non-erosive OLP (20). Interestingly enough, a case control study evaluated the psychological profile of OLP patients and highlighted that low self-control and depression are more strongly associated with mild forms of OLP (reticular and papular) than with severe forms. This might have a role in the progression of OLP lesions (21).

Stress seems to contribute to the development of OLP lesions (22). It has been suggested that the oral mucosa has increased reactivity to psychological stimuli (23). Stress, both acute and chronic, induces changes in the immune response. However, it should be taken into account that the disorder itself is a stressful factor for the patient (24).

Photodynamic therapy – a promising therapy

Photodynamic therapy is a therapeutic approach that is increasingly used in a broad spectrum of disorders. In dermatology, there are various diseases that may benefit

from this therapy (25-27). In 1900, the medical student Oscar Raab and his professor Von Tappeiner described PDT as an antimicrobial therapy, observing *Paramecium*'s photoinhibition. They noticed that acridine, which is chemically inert under dark conditions, is activated by sunlight leading to the destruction of the *Paramecium* species (28, 29). In 1999, the FDA approved PDT in the treatment of precancerous lesions of the face and scalp (30-32). PDT has the advantage of being a minimally invasive technique that preserves the normal tissue (33, 34).

PDT can be regarded as a particular form of photochemotherapy, based on a photochemical reaction, which uses a photosensitizer, a source of light and oxygen, exerting a selective cytotoxic effect (35, 36). The activation of the photosensitizer by light results in the generation of reactive oxygen species, especially singlet oxygen, leading to tissue necrosis and apoptosis (37, 38).

The main steps of the technique include the administration of the photosensitizing agent, which will accumulate selectively in the target cells, followed by the illumination of the respective area with a light source. Numerous light sources are employed in PDT, including coherent and non-coherent light sources. The main sources that can be used are ultraviolet light (330-400 nm), red light (600-700 nm) and near infrared light (700-100 nm). Longer wavelength light penetrates deeper into the tissue (33). Most of the photosensitizers are activated at a wavelength between 630-700 nm (39).

A series of photosensitizers have been used in time, initially systemically and then topically. Nowadays, 5-aminolevulinic acid (ALA) remains one of the most used topical agents. ALA is endogenously converted into protoporphyrin IX, a photosensitizing molecule, which leads to the formation of reactive oxygen species after exposure to an appropriate wavelength (400-410 nm, 635 nm) (40). Besides ALA, one of the most used agents is its derivative, methyl aminolevulinate (MAL) (41). Other photosensitizers are phenothiazines such as toluidine blue and methylene blue (620-700 nm) that are especially used in dentistry (39).

In most cases, PDT is well tolerated, the main side effects being pain, erythema and, in some cases, urticaria. Scar formation or other allergic reactions may occur less frequently (42, 43).

The role of photodynamic therapy in oral lichen planus

The results of the studies on PDT efficacy in the treatment of OLP, are heterogeneous. This can be explained by the fact that different photosensitizers (ALA, methylene blue, toluidine blue, etc.) and various light sources (diode laser, light emitting diode) are employed (44). Grandi et al. reviewed the data on the efficacy of PDT in OLP therapy. They analyzed one case series, three prospective single-arm and five open-label randomized clinical trials and noticed that a wide range of photosensitizers and different modalities to evaluate the patients were used. The analysis concluded that beneficial effects of PDT were observed in all studies, but the overall response rate varied between 0 and 29%. There were no notable side effects during the treatment. Grandi et al. draw attention to the fact that the effects of PDT might increase weeks or months after application, thus the follow-up period is very important and could have repercussions on the outcomes of the studies (45).

A systematic review by Akram et al. on the role of PDT in OLP treatment showed that none of the analyzed studies evaluated histopathological changes after PDT. In addition, the authors pointed out that the assessment of PDT efficacy is difficult given that there is no consensus on the parameters which should be used and in most studies the follow-up period was too short. Furthermore, they emphasized the need to compare the results with a control group consisting of patients treated with corticosteroids (46).

The meta-analysis by Jajarm et al. focused on comparing the effectiveness of corticosteroid therapy with new phototherapy methods including low-level laser therapy and PDT. They observed that low-level laser therapy is effective in relieving pain and clinical signs. However, there were no differences when these two parameters were analyzed in comparison with the results obtained in patients treated with corticosteroids. Low-level laser therapy was superior to corticosteroids only when the effect on the severity of lesions was evaluated. With respect to the reduction in size of OLP lesions, similar results were obtained when PDT was compared with corticosteroids (47).

Methylene blue-mediated PDT

Methylene blue is an agent that has been used in medicine for over 100 years. It is used in various diseases such as methemoglobinemia or urolithiasis; the compound has low toxicity on human tissue. It is best absorbed at wavelengths higher than 620 nm (48). Aghahosseini et al. evaluated the efficacy of PDT in OLP in a study that included 26 lesions from 13 patients with histopathologically confirmed OLP, refractory to previous treatments, including topical application of corticosteroids or cyclosporine. They used 5% methylene blue as a photosensitizer and the irradiation was performed using light laser with a wavelength of 632 nm. An improvement was obtained for 16 lesions. The mean reduction in lesion

size was 44.3% at 12 weeks after the therapy. Favorable results have also been obtained regarding the pain level (49). Another recent study using methylene blue as a photosensitizer and a light source with a wavelength of 630 nm included 20 OLP patients. After 4 sessions, 10 patients experienced a moderate improvement and the rest of the patients were unresponsive. Moreover, they evaluated the patients two weeks after therapy and observed that the lesions significantly improved in 5 patients, 12 underwent moderate improvement and 3 were unresponsive. The results were significantly better four weeks after the therapy, a fact which indicated that the PDT effect should also be quantified during follow-up visits (50).

Bakhtiari et al. evaluated the efficacy of methylene blue-mediated PDT in comparison with topical steroid therapy in 30 patients diagnosed with erosive or reticular OLP. In the corticosteroid group, 0.5 mg dexamethasone solution was used in 5cc water. They showed that PDT is as effective as the dexamethasone solution in the OLP treatment (51). Mostafa et al. also compared the efficacy of methylene blue-mediated PDT with corticosteroids in patients with erosive OLP. They included 10 OLP patients treated with topical corticosteroids and 10 OLP patients treated with PDT in the study (the light source used was 630 nm diode laser). In patients treated with PDT, a greater reduction in the pain level and lesion size was observed when compared to the corticosteroid group. Therefore, the authors concluded that PDT is more effective than steroid therapy, having the role of reducing pain, thus alleviating a symptom (52). Regarding the efficacy of topical corticosteroids versus laser phototherapy, Akram performed a systematic review in order to determine whether the efficacy of low-level laser therapy is higher compared to topical corticosteroids in OLP patients. Five studies were included, in 3 of them topical corticosteroids were superior to low-level laser therapy, one study revealed greater improvement using low-level laser therapy and one showed similar results between the studied groups. These heterogeneous results denote that further studies are needed (53).

ALA-mediated PDT

ALA interacts with the light source and leads to the release of reactive oxygen species (54, 55). It is a second-generation photosensitizer, synthesized in the laboratory, acting as a prodrug, with a good specificity for tumor tissue (56).

A recent study used ALA to assess the efficacy of PDT in the treatment of OLP. The complete resolution of lesions was achieved in 50% of cases and a partial response in 35.7% of them. The symptoms (pain, discomfort during speech) disappeared in all patients (57). The study conducted by Sulewska et al., which included 50 patients with reticular OLP, evaluated 5% ALA PDT (the illumination source was represented by a diode lamp with a high-power LED emitting light at 630 nm), over a period of 10 weeks, one session per week. Out of the 124 lesions, 46 were completely healed. At the end of the therapy, the mean reduction in size of the lesions was 62.91%, and after 12 months, 78.7% respectively (58). Rakesh et al. highlighted the utility of PDT in the case of 10 patients with relapsing erosive OLP. They used 4% ALA and red light (wavelength of 600-670 nm). Gingival lesions had the poorest response (59).

PDT was employed in the treatment of premalignant oral lesions (60). Thus, the study conducted by Maloth included 13 patients with oral leukoplakia and 8 patients with OLP. Regarding oral leukoplakia, PDT led to lesion resolution in 16.6% of patients and 66.6% of them observed partial resolution, the rest of the patients did not respond to therapy. In the case of OLP patients, 80% had a partial response and 20% had no response. They used ALA and blue light with a wavelength of 420 nm. The study also compared PDT with conventional therapy, and better results were achieved when PDT was used in patients with oral leukoplakia; however, in the case of OLP the results were similar (61). A systematic review evaluated the available data on the efficacy of PDT in premalignant lesions, including leukoplakia, erythroplakia, erythro-leukoplakia and verrucous hyperplasia. Thirteen trials were analyzed and the number of the studied patients ranged from 5 to 147. The complete response to PDT varied between 27% and 100%. No response to PDT was recorded in 0 - 25% of cases (62).

Kvaal et al. studied the efficacy of MAL-PDT (red light at a wavelength of 600 to 660 nm) on 17 patients with OLP. One side of the mouth was treated with MAL-PDT and the other side was considered the control side. The improvement of the lesions was achieved after a single session and there was a long-term effect, the patients being followed-up for 4 years (63).

Other photosensitizers

Jajarm et al. analyzed the efficacy of PDT using toluidine blue as a photosensitizer in comparison with topical corticosteroids in OLP patients, with the erosive-atrophic form. No significant differences were found when the sign scores of changes were compared between the two groups. However, better results have been obtained regarding the improvement of the symptoms and

efficacy indices in the patients treated with corticosteroids. Additionally, the rate of relapse was lower among these patients (64). The study by Mirza analyzed toluidine blue-mediated PDT, using GaAlAs laser with 630 nm wavelength and low-level laser therapy, using diode laser with wavelength of 630 nm in comparison with conventional corticosteroid therapy in patients with OLP. A total of 45 patients were divided into 3 groups. Group 1 was treated with toluidine blue-mediated PDT, group 2 with low-level laser therapy and group 3 performed 5-minute rinses with dexamethasone. The results highlighted the favorable effects of PDT and laser therapy, but corticosteroids were more effective on pain relief. The authors concluded that corticosteroids remain the gold standard in OLP therapy (65).

Sobaniec et al. used chlorine e6 (Photolon®) consisting of 20% chlorine e6 and 10% dimethyl sulfoxide, as a photosensitizer, and a semiconductor laser with a wavelength of 660 nm. The patients underwent 10 sessions at a 2-week interval. Among the 23 patients, 48 lesions were identified and treated. The mean reduction in lesion size was 55% and 14 lesions were completely healed. Better results were obtained for lesions localized on the cheeks and lips, compared to those on the tongue and gums (66).

Conclusions

The therapeutic approach in OLP still remains a challenge. Although several therapies are available, none of them can be considered the ideal therapeutic approach. PDT seems to be a promising therapy; however, the results are heterogeneous. This is the result of a lack of standardization, the available studies using different sources of light, wavelengths and photosensitizers. Further studies are needed to determine which parameters are optimal in order to achieve the best results.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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