REVIEWS

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Topical Application of Drugs Used in Treatment of Oral Lichen Planus Lesions

Miejscowe stosowanie leków w leczeniu zmian liszaja płaskiego błony śluzowej jamy ustnej

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Abstract

Oral lichen planus is a common, chronic mucosal disease associated with a cell-mediated immunological dysfunction. The clinical manifestation is different when various forms, white and red, are considered. Erosive, atrophic, ulcerative lesions require long-term treatment, because of inflammation and severe pain. Since the etiology is still unknown this symptomatic OLP lesions are not curative. The effectiveness of various modalities applied in topical OLP treatment is presented on the basis of the current literature. This treatment in most cases is palliative because of OLP recalcitrant nature. Described agents such: steroids, immunosupressants, aloe vera, hyaluronic acid, antifungal showed beneficial effects. They enhance healing, improve signs and symptoms of lesions and thus improve the quality of patients' life. Topical treatment is recommended mainly because of minimal side-effects **(Adv Clin Exp Med 2013, 22, 6, 893–898).**

Key words: oral lichen planus, topical treatment, drugs.

Streszczenie

Liszaj płaski błony śluzowej jamy ustnej jest często występującą, przewlekłą chorobą błony śluzowej jamy ustnej związaną z dysfunkcją komórek immunokompetentnych. Obraz kliniczny zmian różni się i jest związany z występowaniem białych i czerwonych postaci liszaja. Zmiany erozyjne, atroficzne, wrzodziejące wymagają długotrwałego leczenia w związku z zapaleniem i towarzyszącym silnym bólem. Ponieważ etiologia liszaja jest nadal nieznana, te zmiany są trudne w leczeniu. Na podstawie aktualnych doniesień piśmiennictwa przedstawiono korzyści związane z miejscowym stosowaniem różnych leków w leczeniu liszaja płaskiego błony śluzowej jamy ustnej. Leczenie to jest w większości przypadków objawowe, spowodowane nawrotowym charakterem zmian. Opisano zastosowanie leków wykazujących działanie korzystne: steroidy, leki immunosupresyjne, wyciągi aloesu, kwas hialuronowy, leki przeciwgrzybiczne. Ułatwiają one gojenie zmian, zmniejszają objawy zapalenia i objawy kliniczne, co wpływa na poprawę jakości życia pacjentów. Leczenie miejscowe zmian liszaja płaskiego jest polecane ze względu na występowanie niewielkich skutków ubocznych tej terapii **(Adv Clin Exp Med 2013, 22, 6, 893–898).**

Słowa kluczowe: liszaj płaski, leczenie miejscowe, leki.

Oral lichen planus (OLP) is one of the most common pathology of oral mucosa. It is a chronic inflammatory disease in which cell-mediated immunological dysfunction is underlined. It can persist in some patients for a long time; however, a spontaneous resolve of atrophic lesions was observed. In relation to pathogenesis of OLP, a hypothesis has been proposed involving both antigen-specific and non-specific mechanisms [1]. In antigen-specific mechanisms antigen presentation by basal keratinocytes and antigen-specific keratinocyte killing by CD8 cytotoxic cells are taken into consideration. In non-specific mechanisms mast cells degranulation and matrix metalloproteinase activation is involved. But the initial factor closely related with OLP lesion formation or OLP susceptibility is still unknown. The hypothesis of autoimmune pathogenesis is supported by characteristic features of OLP, such as disease with chronic inflammation, adult onset, association with other autoimmune disorders and also decreased immune privilege, weak expression of TGF-ß1,

increased expression of heat shock proteins by keratinocytes, keratinocyte apoptosis, maturation of Langerhans cells [1]. Clinical and histological OLP features are similar to those seen in chronic graft versus host disease (cGVHD) [2]. A larger number of CD4- and CD8- positive T cells, Langerhans Cells (CD1a) and CD-positive macrophages in the cGVHD and OLP lesions was seen there than in healthy mucosa. However, there were no significant differences in the number of these cells between cGVHD and OLP biopsies [3]. This disease occurs mainly in middle-aged patients and more common in women. OLP can manifest itself in different clinical forms both asymptomatic and symptomatic. The keratotic reticular, papular, plaque- like white patches are often present without any signs or complaints – painless. Erosive, atrophic and ulcerative lesions, which are surrounded by keratotic forms manifest damage epithelium. They are always painful with or without a burning sensation, and this interferes with eating, speaking, swallowing [4].

OLP may be present anywhere in the oral cavity and usually occurs bilaterally/symmetrically on the buccal mucosa, more rarely on lateral borders of the tongue and the gingiva. When in atrophic/erosive form it is present on gingiva, desquamative gingivitis may be diagnosed. It is a descriptive term of inflamed, erythematous and peeling gingiva [4]. In asymptomatic cases of keratotic forms, there may be no need for any treatment. But patients should be checked on regularly. Follow-up control visits are needed every 4–6 months or sooner if any symptoms occur [2, 5].

Numerous different topical and general treatments have been used to relieve pain and reduce or eliminate exacerbations by reducing the signs and symptoms of erosive, atrophic and ulcerative lesions. But current treatment is palliative rather the curative and recurrences are almost always present. Additionally, there were often *Candida albicans* infections present in about 37% to 50% of OLP patients.

In topical treatment the following have been attempted: corticosteroids, immunosupressants – cyclosporin, tacrolimus, antifulgal agents, retinoids [5]. In literature, there have been widely different comparisons observed between different modalities and forms of the same drugs used. Nevertheless, the most favorable topical OLP cure has not been yet established.

Steroids

In general, topical corticosteroids in different formulations are widely used in the treatment of vesiculo-erosive lesions of the oral mucosa as well as in OLP.

As early as in 1980 Lozada and co [6] described the improvement in the treatment of vesiculoerosive diseases, including lichen lesions, when they were treated with fluocinonide 0.05% in an adhesive base. Next a double-blind, placebo controlled study showed the efficacy with complete remission in 20%, and good or partial response in 60% of the topical application of 0.025% fluocinonide [7]. In both investigations no adverse effects were observed during the follow-up period, and it was concluded that fluocinonide used in this form is safe and effective in reducing sings and complaints in OLP lesions. In a further study the effectiveness of topical use of betamethasone has been described [8]. Hegarty and co [9] used two forms of corticoids in the short-term management of lichen lesions: fluticasone propionate spray and batamethasone sodium phosphate mouth rinse. They concluded that both agents were effective and the lesion area was significantly reduced. The spray formula was more acceptable and more convenient in treatment. Also the topical administration of clobetasol propionate in three forms: ointment (0.05%) used three times a day, the clobetasol propionate in an adhesive denture paste in equal amounts (1 : 1) used two times a day and clobetasol propionate in an oral analgesic base (Orabase-B) in equal amounts (1 : 1) used two times a day, gave significant remission. It was concluded that topical application of clobetasol in an adhesive denture paste is an effective drug in ulcerative lesions treatment [10].

Mometasone furoate microemulsion topically used 3 times a day, over 30 days, also significantly reduced the lesions of OLP erythema and ulceration. There were no noted severe adverse effects of any patient [11].

Gonzalez-Moles et al. also found clobetasol 0.05% mouthwash as a safe and efficacious option for the treatment of severe oral erosive lichen planus lesions. In a 48-week period they observed 93.3% total recovery and only two patients showed no response to the treatment [12].

On the basis of the findings that topical application of clobetasol-17-propionate has been reported as an efficacious therapy in atrophic/erosive oral lichen planus, Campisi et al. [13] evaluated the efficacy of new lipid microspheres loaded with 0.025% of clobetasol propionate in comparison with a commonly used formulation – lipophilic ointment in a hydrophilic phase, with the same amount of drug. Authors have suggested that the new formulation of the drug may enhance the remission of atrophic/erosive oral lichen planus lesions. The efficacy of dexamethasone in the treatment of erosive lichen planus was assessed by detecting the levels of

proinflammatory cytokines: interleukin 1-α, IL-6, IL-8 and tumor necrosis factor-alpha in the unstimulated saliva. The topical 0.1% dexamethasone has been used for 6 weeks. As a matter of fact only thirteen patients were enrolled in this study, but the levels of all investigated cytokines were significantly decreased. What is more, the IL-1-α and IL-8 levels following treatment showed no significant differences from control group. Also, the subjects' symptoms evaluated by visual analog scale (VAS) decreased in a significant way [14]. Thongprasom and co [15] investigated the effect of fluocinolone acetonide in orabase (FAO) 0.1% on the expression of tumor necrosis factor-α (TNF-alpha) in patients with OLP. Authors have shown that the number of mononuclear cells positive for TNF-alpha before the treatment was significantly higher than after the treatment and in the normal mucosa of control. They found that topically used FAO 0.1% had an effect on the reduction of TNF-alpha expression.

The most suitable corticosteroid therapy in the management of OLP is the topical therapy. In a comparative study of the effectiveness of systemic and topical corticosteroid treatment of OLP, Carbone and co [16] obtained complete remission of clinical signs in more than 68% in patients treated systemically with prednisone versus over 69% in patients treated with clobetasol ointment in an adhesive medium with simultaneous topical antimycotic therapy.

Steroids in many cases of OLP erosive forms are the first line in controlling symptoms and inducing clinical improvement. However, investigations have shown that different formulations, dosages, time of use have read diversified effects during the treatment. This can be related with different responses for the treatment as the result of individual susceptibility. Regardless of significant reductions in the surface of erythema and ulceration, this treatment does not expose the patient to systemic side-effect. There is no evidence that one steroid is more or less effective. Systemic steroids are considered in exacerbations or widespread lesions. Also, proper oral hygiene control was found to be a very important factor enhancing the healing of the lesions.

It should be underlined prolonged use of topical steroids may lead to the development of candidiasis. That is why candidal cultures are important as routine investigation, before, during or after treatment. Also other rare adverse effects were observed, such as: bad taste and smell, dry mouth, swollen mouth, nausea [9].

Immunosuppresants

Cyclosporin (CsA) is an immunosuppressant which inhibits the proliferation and function of T lymphocytes. Because OLP lesions are related with damage of basement membrane resulting from the production of lymphokines by activated lymphocytes, cyclosporine has been implicated in OLP treatment. However, there are conflicting results when the results of topical use of the cyclosporine are compared [17]. Yoke et al. [18] compared the efficacy of cyclosporin solution treatment in 68 and triamcinolone acetonide in orabase in 71 patients with oral lichen planus lesions. Because they found that clinical improvements of erythema, ulceration and pain between investigated groups were not significant, they concluded that cyclosporine has no better beneficial effect than steroid. In the next similar investigation the effectiveness of both therapies were compared, but on the groups of only six patients treated with cyclosporine and seven treated with triamcinolone acetonide in orabase. On the basis of their investigations Conrotto et al. also concluded that clobetasol is more effective than cyclosporine; however, both drugs have comparable effects on symptoms. Clobetasol treatment gives more frequent side-effects and after the therapy is discontinued, the results are not stable [19]. Nevertheless, the obtained results also confirmed the lack of better therapeutic effect of cyclosporin. In any case, when different trials were reviewed, evidence that cyclosporin may reduce pain and clinical signs of OLP was shown to be weak and ambiguous [20].

Because of the need for a novel therapy of OLP that could be more effective and well-tolerated, topical calcineurin inhibitors (TCIs) were introduced. Pimecrolimus was used in cream form and in an adhesive ointment. The evaluation of the efficacy of 1% pimecrolimus cream in four weeks treatment in fourteen OLP patients has shown that it was effective and well tolerated. Transient burning sensations were noted in some subjects only during first 2 weeks. But the pathology relapsed in each patient 1 month after treatment [21]. The efficacy of 1% pinecrolimus cream in 18 and triamcinolone acetonide 0.1% paste in 17 OLP patients was compared. In both groups, the treatment caused a significant improvement without statistical differences. This was the clue that this calcineurin inhibitor, as well as steroids, may be beneficial in OLP therapy [22]. In the next study it was shown that topical pimecrolimus treatment in oral lichen lesions reduced Fas expression on keratynocytes. Between pre and post treatment specimens were stained and evaluated immunohistochemically. As a result, statistically high significant improvement was identified [23].

Tacrolimus is also known as FK 506. Its immunosuppressive activity is similar to that of CsA, but it has a greater capacity to penetrate the mucosa and

is more potent than cyclosporine. It is available in ointment, cream form (0.1%, 0.03%) or powder in Orabase 0.1% (not available in Poland). In a retrospective study of the treatment of OLP with topical tacrolimus, clinical improvement was noted in more than 90% within 6 weeks [24]. It has been suggested that topical tacrolimus treatment was useful and effective in controlling/reducing the symptoms of erosive OLP [25, 26]. When considering adverse effects, there were noted temporary burning sensations at the beginning of the applications and oral mucosa pigmentation in relation with treatment [27]. But reappearance of the lesions following discontinuation of the use of this drug is a very frequent problem. Recent case reports indicate that topical use of tacrolimus may promote the development of cancer in connection with its immunosuppression. Squamous cell carcinoma (SCC) was diagnosed where tacrolimus had been intermittent used: in plaque form of lateral side of tongue three years after beginning of drug application and five years after OLP diagnosis on one side of the buccal mucasa [28, 29]. In the latter case, the lesion for 3 years has been clinically diagnosed as OLP and histopathological diagnosis described severe lichen planus without malignancy. Reexamination of initial biopsy showed lichenoid lesion (LL). Then, at the follow-up 5 years in clinical presentation was distinct erythema treated with topical steroids, and, because of the unsuccessful treatment, steroids were switched to tacrolimus – 0.1 protopic topical application and was stopped when epithelialization was obtained. In the end, clinically typical ulcerated lesion with indurated borders was present with histopathological diagnosis of SCC. Therefore, it is not clear what was essential for cancer development – possible immunosuppressive effect of topical tacrolimus or oral lichenoid lesions which are considered as dysplastic lesions with higher incidence of cancer development [30].

Topical rapamycin (Sirolimus) used in refractory OLP was effective in 7 described cases, where 4 patients revealed total remission and 2 partial remission of oral erosions. What is important, rapamycin has immunosuppressive and also tumor inhibitor properties, which can decrease the risk of malignance transformation [31].

It has to be underlined that long standing, recalcitrant atrophic, erosive forms are described as lesions with higher malignant potential [32]. The malignant transformation of OLP remains controversial and ranges from 0.4% to 5.6% in numerous studies.

Other Agents

In seeking new solutions for topical treatment of OLP, the efficacy of aloe vera was evaluated in opposition to placebo application. Significant improvement was recorded in the treatment group regarding Oral Health Impact Profile 49 and Hospital Anxiety-Depression scale with no adverse effects in both groups [33]. In the comparison of aloe vera with triamcinolone acetonide 0.1% mouthwash, there were no significant differences in the evaluated data. Both agents significantly reduced pain and burning sensation, score and size of lesions. What is more, control visits 2 months after the start of treatment showed similar degrees of healing in both groups. Therefore, the authors concluded that aloe vera is an effective substitute for triamcinolone treatment [34].

Topical use of hyaluronic acid 0.2% gel (HA) in the management of OLL has also been evaluated. HA forms a protective coat on the oral mucosa and enhances its hydration and accelerates healing. In patients treated with 0.2% HA, a significant reduction in the size of the erosive/ulcerated area was observed, so it may be considered as a safe and useful additional agent in OLL treatment [35].

Topical retinoids such as tretinon, isotretinoin were first used for the treatment of the asymptomatic white OLP lesions. In reticular and plaque-like forms improvement was described. At the same time, the side-effects were rare or non-existent. But in another 10 year study, where the effectiveness of topical use of 0.18% isotretinoin was evaluated, there was a lack of any improvement in clinical and histological state of reticular forms. However, in atrophic-erosive forms, a significant clinical and histological improvement was present. Side effects, such as increased soreness, pain, higher sensitivity to hot foods, were observed only temporary [36]. Topical retinoids seem to have less effectiveness in comparison to corticosteroids treatment and currently are not considered as the agents of great therapeutic importance and are rarely used.

Candida overgrowth can occur as the side-effect of topical OLP therapy, so the candidiasis should be controlled before or during the treatment. When it is present, topical antifungal therapy is required. Antifungal drugs are often employed together with corticosteroids to prevent or treat candida infection. Logi et al. [37] compared clobetasol gel with and without Miconazole gel in OLP treatments. There were no clinical signs of candidosis in the patients taking Miconazole, while 30% of the group treated only with steroids was affected.

On the basis of a meta-analysis of the studies that measured the outcomes of different topical treatment of OLP, strong evidence regarding

efficacy of this treatment was not found. This evaluation should not be considered as reliable, as there were sometimes small size of evaluated trial or some of the trials used the same agent but in different dosage [38].

In any case, topical treatment does appear to be of some benefit in the management of erosive lichen planus.

All described modalities help to control pain, inflammation and discomfort, which improve the quality of patients' lives; despite they know about the chronic character of the disease. A complete cure has not been accomplished, because of the recalcitrant nature of this pathology. However, prolonged contact and respective topical effects on the oral mucosa should be controlled.

In conclusion, general dentist should be aware it is only palliative therapy aimed at relieving pain, through healing erosive and ulcerative forms. Because of chronic autoimmune character of the disease as a result of response to unknown antigens within the oral epithelium, oral lichen planus recurrences are almost always present at a different time after the discontinuation of therapy.

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