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PLENARY ABSTRACT

The management of oral lichen planus: symptom control at what risk?

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At best, health care professionals palliate the symptoms associated with oral lichen planus (OLP). A variety of topical and systemic therapies have been used in the management of OLP but the majority of these have not been evaluated in randomised controlled clinical trials. The risks associated with such therapeutic interventions should therefore always be assessed against the intended benefits.

In palliative care the patient is the focus of treatment, not the disease. Although clinicians strive to achieve lesion resolution, if the condition has little impact on the individual then the relative risks associated with treatment may outweigh the therapeutic benefits. Primary outcomes of therapy thus need to concentrate on symptom reduction and quality of life improvement. A step wise approach to OLP management is advocated, with the level of entry into the treatment algorithm being dictated by disease severity and response to therapeutic intervention.

The merit of histopathological diagnosis in the management of OLP remains contentious. Although a biopsy may confirm the presence of epithelial dysplasia in a clinically suspicious area or provide useful diagnostic information concerning the aetiology of a desquamative gingivitis, there is very little benefit to be gained by its routine use in asymptomatic reticular disease. As with all mucosal conditions, the selection of biopsy site and efficient tissue sampling is fundamental to the success of histopathological diagnosis. The pathologist is only able to report on the tissue excised and consequently the experience of the clinician requesting and performing the biopsy is critical to the latter's overall diagnostic value.

Prior to initiating treatment for OLP, the patient should understand the aetiology and nature of the condition including the relative risk of malignant transformation. As with other chronic inflammatory dermatoses, education is central to management and is essential to establishing realistic patient expectations of the intended therapeutic intervention. Any discussion should be accompanied by a leaflet to emphasise the information given and contain references to a number of peer reviewed websites.

Oral lichenoid reaction (OLR) may be clinically and histopathologically indistinguishable from OLP. Diagnosis is suggested by the onset of clinical signs and symptoms coinciding with the institution of drug therapy or placement of a dental restoration. An assortment of drugs has been linked to the development of OLR and in symptomatic patient's consideration should be given to changing to a structurally unrelated drug with a similar therapeutic effect. This should be done only after consultation with the individual's medical physician. A systematic management protocol for amalgam associated lichenoid reaction has been previously reported (Thornhill *et al*., 2006). In cases where the lichenoid lesion is thought to be due to a type IV contact hypersensitivity reaction, replacement of the restoration under isolation with a dental rubber dam may result in partial or complete resolution of the lesion.

The risk of malignant transformation in OLP is likely to be minimised with smoking cessation and moderation of alcohol consumption. The additional benefits of a balanced diet and good oral health should also be promoted. Plaque control can be optimised by regular visits to a hygienist who has expertise in the management of individuals with mucosal disease (Lo Russo *et al*., 2009; López-Jornet and Camacho-Alonso, 2010). Patients should also be encouraged to report symptoms different to those routinely experienced and to actively monitor their oral mucosa.

Individuals should also consider the role of stress in symptom exacerbation of OLP (Manolache *et al*., 2008; Krasowska *et al*, 2008). Despite mild disease, a few patients may present with disproportionate discomfort and alternative diagnoses including psychological co-morbidity must be considered. It is unwise to treat this patient group in the absence of significant mucosal disease as symptomatic improvement is not likely. Instead, time should be taken to explore the origin of the altered perception in these individuals which may include an underlying fear of malignancy or cancer phobia.

When initiating therapy for OLP, disease severity needs to dictate the primary intervention. Asymptomatic OLP does not require active treatment. Mild to moderate disease may be managed successfully with topical therapies. Severe disease, however, requires the introduction of systemic agents with further management being dictated by the response to initial treatment. The confidence a patient has in his or her clinical team will be severely impaired if an inadequate treatment strategy is employed.

Typically, first line intervention in OLP is topical corticosteroid therapy. Despite no particular product being associated with Level A evidence (multiple randomised controlled trials), several agents achieve Level B (single randomised or several non-randomised trials) (Al-Hashimi *et al*., 2007). The most frequent local adverse effect associated with topical therapy is candidosis and this may be prevented by the use of concomitant antimicrobial or antifungal agents. A potential serious side-effect of topical corticosteroid use is suppression of the hypothalamic-pituitary-adrenal (HPA) axis and this has recently been reported to occur with clobetasol (Gonzalez-Moles and Scully 2010). Hence, the use of topical corticosteroids (such as fluticasone) which have a high ratio of topical to systemic activity, high first pass metabolism and no HPA suppressive effect would seem preferable (Fowler *et al*., 2002). The selection of topical preparation should also be guided by both the site and severity of the lesions as well as the patient's degree of manual dexterity, cognitive function and overall lifestyle. Compliance with topical corticosteroid regimens is dependent on ease of use and minimum frequency of application. Furthermore, individuals ought to be advised not to eat or drink for at least 30 minutes following topical corticosteroid use.

Topical ciclosporin is expensive and has little efficacy compared with topical corticosteroids in the management of OLP (Conrotto *et al*., 2006). In contrast, topical tacrolimus and pimecrolimus appear to be efficacious in the short term and are predominantly associated with localised adverse effects (Al Johani *et al*, 2009; López-Jornet *et al*, 2010). The recent publication of a second squamous cell carcinoma in the setting of OLP treated with topical tacrolimus suggests potential long term risks of therapy which need to be monitored further (Mattsson *et al*., 2010). All calcineurin inhibitors can be systemically absorbed following topical oral use and it is therefore difficult to separate the local from systemic effects of the drug on the disease. Sirolimus (rapamycin) has both immunosuppressive and tumour inhibitory properties and could theoretically reduce malignant transformation in the context of OLP (Soria *et al*., 2009).

Severe cases of OLP require systemic agents and as previously described these may be selected as first line therapy for individuals in whom topical drugs would not rapidly improve symptom control. Systemic corticosteroids are indicated in OLP for severe erosive and recalcitrant disease. Pulsed therapy (0.5-1.0mg per kg daily) with rapid tapering is tolerated best, followed by the introduction of a steroid sparing agent and / or concomitant topical therapy. The most common adverse effects of short term corticosteroid use are mood disturbance, gastro-oesophageal irritation and increased appetite leading to weight gain. Long term systemic corticosteroid therapy can generally be avoided in the majority of cases, but when necessary consideration should be given to providing these patients with adequate bone and gastro-intestinal protection.

There is limited evidence to support the 'steroid-sparing' action of azathioprine in the management of OLP (Al-Hashimi *et al*., 2007). Prior to commencing the drug, the thiopurine methyltransferase (TPMT) level should be assayed to evaluate the potential risk of drug-induced bone marrow aplasia. Weekly monitoring of white and red blood cell indices along with the platelet count and liver biochemistry should take place for the first month following therapy initiation. Once the desired therapeutic dose is achieved monthly or three-monthly blood tests are acceptable. Many individuals experience a transient increase in liver transaminase activity on commencing azathioprine which often resolves without drug cessation. However, the clinician needs to remain vigilant for persistent and increasingly raised enzyme levels particularly following dose escalation. Long term risks of azathioprine therapy include infection and neoplasia (Schiavo *et al*., 2010).

The efficacy of mycophenolate mofetil (MMF) as a 'steroid sparing' agent in OLP is limited to a single case report (Dalmau *et al*., 2007) although there is more extensive evidence supporting its use in this way for the management of cutaneous disease. Whilst the adverse effect profile of MMF is better than azathioprine, long term concerns regarding haematological and cutaneous malignancies remain (Schiavo *et al*, 2010). MMF therapy requires blood monitoring in a similar manner to azathioprine.

Currently, limited evidence is available for the use of chloroquine and hydroxychloroquine in OLP. Other recently reported therapeutic interventions include: phototherapy, purslane (Agha-Hosseini *et al*., 2010) and BCG-PSN (Xiong *et al*., 2009).

In summary, currently there is insufficient data to determine an evidence based algorithm for OLP management. Asymptomatic OLP does not require treatment. For mild to moderate disease a topical corticosteroid of moderate potency is the treatment of choice with the mode of administration being dependent on both patient and disease-related factors. Treatment failure should be considered if the clinical response has been poor and drug compliance has been adequate for at least 3 months. Second line topical therapy is presently limited to the use of a calcineurin inhibitor with

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subsequent reversion to a topical corticosteroid. For severe or recalcitrant disease it is appropriate to consider systemic corticosteroid therapy as first line treatment along with the use of a 'steroid sparing' agent. Once disease control is achieved, topical therapy may then be introduced. With all interventions the potential short and long term adverse effects must be explained to the patient and appropriate clinical and drug monitoring undertaken.

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