Outcomes of therapy of immunologically-mediated diseases of the oral mucosa

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Abstract

Immune-mediated diseases (IMDs) can give rise to long standing painful oral mucosal disease which adversely affect oral function and perhaps lessens quality of life.

The present series of studies, retrospectively determine the clinical presentation and long-term efficacy and safety of treatment of large groups of patients with oral lichen planus, mucous membrane pemphigoid, pemphigus vulgaris and orofacial granulomatosis. These diseases are some of the challenging disorders to be managed by oral medicine specialists.

It was found that patients with oral lichen planus (OLP) rarely have extra-oral manifestations of LP. The symptoms of OLP can generally be controlled with topical corticosteroids and/or tacrolimus. While tacrolimus is not notably better than topical corticosteroids for the management of OLP, it does not seem to increase any risk of malignant transformation. Adverse side effects are uncommon with topical corticosteroids, while 21% of patients with OLP may have adverse side effects with tacrolimus, particularly unpleasant taste.

In the present cohort of 49 patients with orofacial granulomatosis (OFG) the onset of disease was characterised by facial swelling in 50% and the long-term behaviour of OFG was characterised by the development of further clinical manifestations with most patients developing orofacial swelling and/or intra-oral ulceration. The response of OFG to therapy was typically remitting and although a lessening of soft tissue swelling oral ulceration could generally be achieved with topical and/or systemic therapy. Complete remission of facial swelling occurred in 50% of patients within 3 years of therapy but may be achieved quicker when intra-lesional corticosteroids are used. Spontaneous remission was rare. Significant adverse side effects to therapy were rare.

In a cohort of 62 patients, mucous membrane pemphigoid typically manifested as recurrent oral mucosal ulceration and/or desquamative gingivitis and 32.3% patients had some extra-oral involvement.

Treatment generally lessened painful symptoms however gingival lesions rarely resolved. Adverse side effects affected 50% of patients; however in the majority of affected individuals these were minor.

In a cohort of 40 patients with pemphigus vulgaris the mouth was often the initial site of involvement but other mucocutaneous sites could be affected. Management necessitated topical and systemic therapy. Adverse side effects occurred in 50% patients and were mainly associated with systemic immunosuppressive agents (e.g. azathioprine).

The results of this present study indicate that the long-term treatment of IMDs of the oral mucosal are challenging to both the patients and clinicians. While many patients do experience an improvement in their disease status, many do not. The precise impact of IMDs upon the quality of life of affected individuals remains unclear.

DECLARATION

Except for the help listed in the acknowledgements, the contents of this thesis are entirely my own work. This has not previously been submitted, in part or in full, for a degree or diploma of this or any other university or examination board.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGUERS

ABBREVIATION

ASE	Adverse side effect
BMZ	Basement membrane zone
DIF	Direct immunofluorescence
FDA	Federal Drug Agency
GDP	General dental practitioners
GI	Gastrointestinal
GP	General dental practitioners
GvHD	Oral lichenoid lesions of graft-versus-host disease
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
IEN	Intra-epidermal neutrophilic
IgA	Immunoglobulin A
IgM	Immunoglobulin M
IIF	Indirect immunofluorescence
IMDs	Immune-mediated diseases
IMSEBDs	Immune-mediated subepithelial blistering diseases
IVIg	Intravenous immunoglobulin
LP	Lichen planus
MMF	Mycophenolate mofetil
MMP	Mucous membrane pemphigoid
NHS	National Health Service
OFG	Orofacial granulomatosis
OLCLs	Oral lichenoid contact lesions
OLDRs	Oral lichenoid drug reactions
OLP	Oral lichen planus
OMFS	Oral and Maxillofacial Surgery
OSCC	Oral squamous cell carcinoma
PNP	Paraneoplastic pemphigus
PV	Pemphigus vulgaris
PF	Pemphigus foliaceus
RCTs	Randomised controlled trials
SD	Standard deviation
SPD	Subcorneal pustular dermatosis
SPSS	Statistical Package for the Social Sciences
Th2	T-helper2
TNF-α	Tumour necrosis factor-alpha
UCL	University College London
UCLH	University College London Hospital
WHO	World Health Organization

CHAPTER 1
GENERAL INTRODUCTION

GENERAL INTRODUCTION

A wide range of disorders can give rise to oral mucosal disease, particularly infection, malignant disease and immunologically-mediated diseases. While infections generally give rise to transient oral symptoms (e.g. painful ulceration) and potentially malignant disease is often asymptomatic, immunologically-mediated diseases can be symptomatic and long standing and thus can adversely impact upon a patient's quality of life. Some of these disorders are very common (e.g. recurrent aphthous stomatitis and oral lichen planus) however there seems to be an increase in the prevalence of other less common diseases such as orofacial granulomatosis and pemphigus vulgaris.

Immunologically-mediated disorders comprise a group of disorders that give rise to wide variety of cutaneous and/or oral lesions. The most common oral mucosal lesions are ulceration/erosions and other clinical manifestations (e.g. labial swelling of orofacial granulomatosis). Mucous membrane pemphigoid and pemphigus vulgaris can also give rise to oral vesicles and bullae, however this may rarely be seen in the mouth as most break down before the patient is seen by the clinician.

Immunologically-mediated disorders can be difficult to diagnosis and treat. They may share the similar clinical manifestations (e.g. desquamative gingivitis and/or oral ulceration) and as a consequence there may be a delay in the definitive diagnosis.

As noted above many of these disorders seem to be lifelong and can be distressing to affected individuals and as a result adversely affect quality of life (Hegarty et al., 2002). Also the disease can have an impact upon the patient's family (e.g. worry) and necessitate lifelong care and may result in the loss of employment time due to attending clinics. Finally the long-term clinical management could potentially place additional pressure upon health care resources.

The chronic nature of these disorders necessitates patients requiring extended periods of treatment with different potent topical and/or systemic medication which may be associated with adverse side effects. Corticosteroids for example can give rise to short- and/or long-term adverse side effects that, perhaps frustratingly, limit their prescription to patients with severe or recalcitrant disease and those without controlled diabetes mellitus or hypertension.

The long-term adverse outcomes of therapy of immunologically-mediated diseases of the oral mucosa have rarely been reported and existing reports, for example of oral lichen planus, do not detail the adverse outcome of therapy (Ingafou et al., 2006). Certainly however the treatment of immunologically mediated diseases can adversely affect patients, for example 2 of 55 patients with oral pemphigus vulgaris may have died as a consequence of adverse effects of therapy (Scully et al., 1999). There are few systematic reviews of the therapy of immunologically-mediated diseases and yet perhaps as a consequence of increased longevity of life and changing attitudes towards medical care, increasing numbers of patients are referred to oral medicine units for the treatment of such diseases.

The overall aims of this work is to retrospectively determine the clinical manifestations of large groups of patients with well defined oral mucosal diseases; examine the outcome of therapy, and to detect the nature and frequency of adverse effects of therapy. With such information it may be possible to establish the optimum and safe treatment of such diseases. It will also give insight into the likely course of disease and hence provide patients with a greater understanding of their disease.

The study has focused upon 4 significant immunologically-mediated oral mucosal disorders: oral lichen planus, orofacial granulomatosis, mucous membrane pemphigoid and pemphigus vulgaris.

Lichen planus (Chapter 2) is the most common cutaneous disorder that can affect the oral mucosa and oral lichen planus (OLP) is one of the most common chronic immunologically-mediated oral mucosal diseases. It represents one of the most challenging disorders that oral medicine physicians have to manage on a regular basis (Mignogna et al., 1998; Gonzalez-Moles et al., 2003; Mignogna et al., 2005). The aims of this chapter were to determine: the clinical outcomes of long-term therapy of OLP and to report the frequency and nature of adverse side effects of therapy and the malignant transformation rate of OLP.

Orofacial granulomatosis (OFG) (Chapter 3) is a chronic inflammatory disease with the potential to adversely affect the quality of life of patients by the persistent labial and/or facial swelling, painful oral ulcerations, and/or occasional neurological manifestations (Wiesenfeld et al., 1985; Somech et al., 2001; Leao et al., 2004). The aims of this chapter are to describe the early and late clinical features and other clinical characteristics of a large number of patients with OFG together with the clinical outcomes of long-term therapy and the frequency and nature of adverse side effects of therapy of OFG.

Mucous membrane pemphigoid (MMP) (Chapter 4) is a rare mucocutaneous disorder which often affects oral mucosal surfaces. MMP usually affects people in their middle to late life (Laskaris et al., 1982; Silverman et al., 1986; Gallagher and Shklar, 1987). The aims of this chapter are to describe the long-term outcomes of therapy in a substantial cohort of MMP patients attending single clinical centre in addition to the frequency and nature of adverse side effects of therapy of MMP.

Pemphigus vulgaris (PV) (Chapter 4) although uncommon is the most common and severe form of pemphigus and was considered a fatal condition before the immunosuppressive therapy era. PV affects all ethnic groups; however it frequently affects Ashkenazi Jewish (Gazit and Loewenthal, 2005; Mimouni et al., 2008). It gives rise to vesiculobullous

lesions of the skin and/or mucous membranes. The overall aims of this chapter are to describe the long-term outcomes of therapy in a large cohort of PV patients in addition to the frequency and nature of adverse side effects of therapy of PV.

CHAPTER 2

ORAL LICHEN PLANUS

2.1 INTRODUCTION

Oral lichen planus (OLP) is a common chronic mucocutaneous disorder of middle to late life affecting approximately 0.1% to 4% of the population (Scully et al., 1998; Xue et al., 2005) and is found more frequently in women than men (Eisen, 2002; Mignogna et al., 2005) with a reported ratio of around 2:1 (Xue et al., 2005) (Table 2.1). In a recent study conducted to assess frequency of diagnostic biopsies from UK general dental practitioners, 1.0% of the examined biopsies were lichen planus or lichenoid reaction (Franklin and Jones, 2006). Although OLP in children is uncommon (Laeijendecker et al., 2005) it has been reported (Sharma and Maheshwari, 1999; Alam and Hamburger, 2001; Patel et al., 2005; Xue et al., 2005) and the prognosis is suggested to be better than in adults (Laeijendecker et al., 2005).

In contrast to cutaneous LP which is usually self-limiting, oral lichen is a chronic disease and rarely disappears completely, although it may change in appearance over time (Thorn et al., 1988; Eisen, 2002). In a recent study, about 30% of the lesions resolved, but the authors noted that the disease could re-emerge (Roosaar et al., 2006).

2.1.1 Prevalence of oral lichen planus

Lichen planus (LP) commonly affects the oral mucosa (Mignogna et al., 1998) and OLP is one of the most common oral mucosal disorders (Mignogna et al., 2005). It represents one of the principle and most challenging disorders that oral medicine physicians treat on a regular basis (Gonzalez-Moles et al., 2003). Many studies have reported the prevalence and/or incidence of OLP; however, its true prevalence is unknown as most data are of symptomatic patients referred to hospitals or specialized dental units. OLP and other extra-oral involvement are thought to be underreported since many patients are asymptomatic (Mignogna et al., 1998; Chainani-Wu et al., 2001; Bidarra et al., 2008; McCartan and Healy, 2008). However a critical review (McCartan and Healy, 2008) concluded that the true prevalence of OLP is difficult to

determine from published reports as most are methodologically inadequate (e.g. lack of diagnostic clinical and histopathological criteria, absence of histological confirmation and inclusion of lichenoid reactions). Nevertheless on a day to day basis OLP remains one of the most common disorders to be managed by specialist in oral medicine in the world.

2.1.2 Clinical features of oral lichen planus

The clinical presentation of OLP differs from patient to patient and ranges from asymptomatic reticular lesions (usually not detected by the patient) to widespread painful erosive or ulcerative mucosal lesions. Six clinical variants have been described: reticular, papular, plaque, atrophic, erosive and bullous (Andreasen, 1968). Eisen combined these six types into three groups; white striae, plaques, and papules representing asymptomatic reticular type, and two symptomatic groups, atrophic/erythematous and erosive, including ulcerations and bullae (Eisen, 2002). Piboonniyom and co-workers (2005) have suggested OLP be classified into three main variants: reticular/hyperkeratotic, erosive/erythematous, and ulcerative forms (more details are discussed below).

It is common to have more than one mucosal site involved at same time (Ingafou et al., 2006) and it is not unusual to find more than one type in the same patient where it is can classified according to the most severe form. Bilateral buccal mucosal involvement is the most common presentation of OLP followed by disease of the tongue, lower lip, and gingivae (Gorsky et al., 1996; Xue et al., 2005). Unilateral lesions have been reported in 1.8% and 5.2% in different OLP patient cohorts (Andreasen, 1968; Eisen, 2002). OLP may affect any oral mucosal surface; however it rarely affects lips, the palatal mucosa or floor of the mouth (van der Waal, 2009). A recent study of 808 patients reported that OLP affected the buccal mucosa (73%), tongue (44%) and gingivae (33%) much more frequent than the floor of the mouth (4. 6%), labial

mucosa (1. 8%), palate (1. 8%) or oropharynx (0. 7%) (Carbone et al., 2009a).

Most patients with oral lichen planus who are referred to tertiary clinics have mucosal pain and discomfort. A recent report (Ingafou et al., 2006) found about 62.5% of a OLP cohort had oral soreness or discomfort while another study estimated mouth discomfort to be present in 69.5% of the patients (Brown et al., 1993).

2.1.3 Oral lichen planus forms

There are many classifications of OLP, however the most common one is Andreasens's classification with the six subtypes or forms; reticualr, papular, palque, erosive, atrophic and bullous forms (Andreasen, 1968).

The reticular form is the most common variety of OLP and may more prevalent among women. It usually presents as asymptomatic bilateral white keratotic lines (Wickham's striae) on the buccal mucosa (Dusek and Frick, 1982; Xue et al., 2005).

The papular form usually presents as multiple, raised, small (<1 mm) white lesions and is often found with other types (Dusek and Frick, 1982).

The plaque form presents as symptomatic multiple, raised, flat lesions on the oral mucosa, usually on the tongue or buccal mucosa. The clinical appearance of plaque OLP resembles multiple hyperkeratotic mucosal lesions (Dusek and Frick, 1982; Edwards and Kelsch, 2002).

The erosive form may be more likely in older individuals and represents the second most frequent type. It is usually painful, of long duration and usually presents as slightly erythematous, depressed areas of the oral mucosa with partial loss of the epidermis usually with surrounded radiating keratotic lines which usually affect many oral mucosal surfaces (Dusek and Frick, 1982; Xue et al., 2005).

The atrophic form presents as multiple erythematous, thinning areas of oral mucosa. White keratotic striae usually surround the atrophic areas. As with the erosive form, it is usually painful and requires treatment to decrease patient discomfort (Dusek and Frick, 1982; Edwards and Kelsch, 2002).

In some reports “atrophic” disease is described as “erosive” and “erosive” as ulcerative. Hence there can sometimes be confusion in the exact description of disease. Nevertheless these aforementioned types are the most common to give rise to painful symptoms.

The bullous form is rare and presents as circumscribed swellings which may rupture due to mechanical trauma to leave an area of erosion (Dusek and Frick, 1982).

Gingival involvement of OLP is common. Gingival lesions may present as desquamative gingivitis or as keratotic reticular or plaque lesions. Desquamative gingivitis is the term used to describe gingival atrophic lesions caused by a group of disorders which includes lichen planus. Patients may complain of mild to severe pain accompanying gingival lesions. In one study of 700 OLP patients (Mignogna et al., 2005), 336 (48%) had gingival lesions. 0.1% to 10% of OLP patients can have lesions solely affecting the gingivae (Scully and el-Kom, 1985; Xue et al., 2005).

2.1.4 Extra-oral involvement

Extra-oral involvement in the course of LP is well documented. The skin, nails, scalp, and mucosal surfaces of the oesophagus, pharynx, larynx, conjunctiva, genitals, and bladder (albeit it rarely) can be involved in the course of the disease (Tunca et al., 2004) however most of patients usually have just one extra-oral site involvement (Bidarra et al., 2008). In a recent study extra-oral involvement was reported to affect 40% of the 87 OLP patients (Bidarra et al., 2008).

Cutaneous lichen planus can affect any part of the skin; however, it commonly presents as pruritic areas on the flexor surfaces of forearms and pre-tibial skin of the lower legs and may affect about 16% to 20% of patients with OLP (Gorsky et al., 1996; Eisen, 1999; Bidarra et al., 2008). The cutaneous lesions are usually self-limiting and remission takes place after periods ranging from a few weeks to years often leaving areas of hypermelanotic pigmentation. The classic form presents with pruritic symmetrically distributed polygonal erythemamatous papuloplaques on the legs, wrists, and back (Eisen, 1999; Sharma and Maheshwari, 1999). Scalp involvement of LP is uncommon but can give rise to scarring alopecia, termed lichen planopilaris (Eisen, 1999).

Nail involvement has been reported in 2% of OLP patients (Eisen, 1999). The nail plates may become itchy, thin and atrophic, with rough, striated ridging, fissuring and splitting of the nail edge. Subungual hyperkeratosis and ptyergium may occur (Eisen, 1999; Yokozeki et al., 2005). Lichen planus is uncommon in children; however, nail involvement is common in those diagnosed with the condition. In one series, 11% of LP patient with nail lesions were children (Tosti et al., 2001).

Oesophageal LP may cause pain and persistent dysphagia resulting from esophagitis and stricture formation. This may be more common in females and the actual frequency of oesophageal involvement is thought to be underestimated (Abraham et al., 2000).

Genital lesions seem to be more common in women than men; in one study 19% of women and 4.6% of men with OLP had genital disease (Eisen, 1999). In women, white, reticulate, lacy lesions are the classical finding and disease may be most likely in the posterior vulvar vestibule (Buffon et al., 2009). Dysuria, dyspareunia, postcoital bleeding, mucosa adherence, synechiae, and obliteration of vagina are possible complications and can cause painful sexual intercourse (Moyal-Barracco and Edwards, 2004; Buffon et al., 2009). Affected men usually have

lichen planus-like lesions of the external genitalia, probably of the glans penis.

2.1.5 Oral lichen planus-related disorders

2.1.5.1 Oral lichenoid contact lesions (OLCLs)

OLCLs are the result of dental restorations, especially amalgam, and can be recognized by proximity to the restoration and by their unilateral and limited distribution. Removing the restoration usually results in resolution of the lesions within months (Issa et al., 2004). OLCLs have the same histopathological characteristics as OLP (Al-Hashimi et al., 2007). There have been occasional reports of other metallic and non-metallic dental restoration materials giving rise to contact lesions (Ostman et al., 1996; Tosti et al., 1997; Koch and Bahmer, 1999).

2.1.5.2 Oral lichenoid drug reactions (OLDRs)

OLDRs are caused by systemic drugs such as angiotensin-converting enzyme inhibitors, sulphonylureas, and non-steroidal anti-inflammatory drugs (NSAIDs) (Rice and Hamburger, 2002). As with OLCLs, the lesions are clinically and histopathologically indistinguishable from OLP, it has been suggested that basal epithelial cell cytoplasmic autoantibodies may be detected (Lamey et al., 1995) and that the subepithelial infiltrate is deeper and more diffuse within the connective tissue, and contains a more mixed infiltrate of eosinophils and plasma cells (Rice and Hamburger, 2002). It has been suggested that the lesions of OLDRs may resolve after the medication is discontinued (Al-Hashimi et al., 2007) but there are few reports to substantiate this suggestion.

2.1.5.3 Vulvovaginal gingival lichen planus

Concurrent involvement of the gingivae and genital mucosa, known as vulvovaginal gingival or less common peno-gingival syndrome, is a rare, or more likely underreported, variant of lichen planus. Patients may complain of painful erosions and/or ulceration of the vulva, vagina, in

addition to desquamative gingivitis (Eisen, 1994; Rogers and Eisen, 2003).

2.1.5.4 Oral lichenoid lesions of graft-versus-host disease

The oral mucosa may be involved in both acute and chronic graft-versus-host disease (GvHD); however, it is more commonly observed in the latter. The lichenoid lesions of GvHD can affect any site of oral mucosa but the buccal mucosa may be the first and most commonly affected oral site of chronic GvHD (Ferrara et al., 2009). The clinical and conventional histopathological features of GvHD are generally similar to those of OLP (Al-Hashimi et al., 2007).

2.1.5.5 Lichenoid dysplasia

Lichenoid dysplasia describes lesions that have histopathological features of dysplasia and a band like lymphocytic infiltrate in the lamina propria mimicking that of LP. Histopathologically, unlike OLP, lichenoid dysplasia may have an intact basal cell layer, rounded epithelial ridges with abnormal cytology (Fatahzadeh et al., 2004). It is unlikely however that lichenoid dysplasia is the underlying cause of the malignant potential of OLP as it is a rare entity.

2.1.6 Diagnosis of oral lichen planus

The diagnosis of OLP is based on clinical and histopathological examination. Some authors consider the classical clinical features (e.g. bilateral distribution of white patches) alone are adequate to provide a diagnosis (Ingafou et al., 2006; Al-Hashimi et al., 2007; Pakfetrat et al., 2009). A biopsy is recommended when the clinical presentation is perhaps atypical and to exclude dysplasia or malignancy (van der Waal, 2009). However, other authors recommend that histopathological studies should always be undertaken even if the classical clinical presentations are present (Xue et al., 2005; Rad et al., 2009). Indeed van der Meij and van der Waal (2003) reported a lack of correlation between clinical and histopathological diagnosis of OLP and proposed revised diagnostic

criteria for OLP and oral lichenoid lesions. In view of the suggested malignant potential of OLP it would seem clinically sensible to have histopathological confirmation of the diagnosis of OLP. This would thus lessen any medicolegal repercussions if a patient ultimately develops an oral squamous cell carcinoma.

Both immunofluorescence and immunohistochemical studies are not useful in the diagnosis of OLP (van der Waal, 2009) although they are indicated when there is a possibility of disease such lupus erythematosus, pemphigus vulgaris or mucous membrane pemphigoid (Leao et al., 2008).

2.1.7 Histopathological features of oral lichen planus

The histopathological features of OLP lesions comprise epithelial changes of parakeratosis and acanthosis with Civatte bodies, liquefaction degeneration, and eosinophilic deposits at the basement membrane. The so called “saw-toothed” rete pegs may be more likely with cutaneous than oral disease. When there is erosion or ulceration there will be loss of epithelial depth or histopathological evidence of frank ulceration. One of the characteristic features of LP is a dense band of cellular infiltrate (mainly T lymphocytes as demonstrated by immunobiochemistry) in the superficial layer of connective tissue (Kramer et al., 1978; Porter et al., 1997).

However, van der Meij et al. (1999) reported that histopathological assessment of OLP biopsy material could at times be subjective, inadequately differentiating LP from other similar histopathological process such as OLDRs and OLCLs and possibly be non-reproducible (van der Meij et al., 1999). Similarly recently Rad and co-workers (2009) found a lack of correlation between the WHO histopathological and clinical diagnostic criteria. Despite these possible shortcomings histopathology remains the most common method worldwide to confirm the clinical diagnosis of OLP. Ultimately diagnosis requires the collation of all aspects of the history, clinical presentation and results of any

additional investigations. In addition the treatment of symptomatic OLP is usually similar to that of allied disorders such as lupus erythematousis affecting the oral mucosa.

2.1.8 Aetiology of oral lichen planus

Discussion of the aetiopathogenesis of OLP is out with the remit of this review but certainly OLP has a strong immunological basis. As noted above, the lesions are histopathologically characterized by a dense T lymphocyte infiltrate, which may represent a cell-mediated immune-response to an unknown antigen. The initial triggers for the T cell immune response are still unknown, although a variety of mechanisms have been postulated (Porter et al., 1997). It has been suggested OLP may be induced by systemic drugs (oral lichenoid drug reactions) or dental restorative materials (oral lichenoid contact lesions) as discussed above.

The role of Hepatitis C in the aetiology of OLP is a controversial issue. Several studies reported association between OLP and hepatitis (Table 2.2). Hepatitis C infection was commonly detected in OLP patients in Italy (Mignogna et al., 1998; Mignogna et al., 2000), Brazil (Grossmann et al., 2009), Taiwan (Chung et al., 2004), and Japan (Nagao et al., 1995) but not in the UK (Ingafou et al., 1998; Roy et al., 2000) or the Netherlands (van der Meij and van der Waal, 2000). The high number of OLP patients with hepatitis C in some groups may reflect the prevalence of hepatitis C in these populations (Mignogna et al., 2000) or a true association between the two disorders (Mignogna et al., 1998). In a recent study of a large cohort of OLP patients in Italy, 21% of those who underwent hepatic examination had liver abnormalities, most of who were ultimately found to have hepatitis C infection (Carbone et al., 2009a).

An immunogenetic susceptibility to HCV-related OLP has been proposed (Carrozzo et al., 2005) that may explain the geographic variation in an association between HCV and OLP, but at present the precise association between the two disorders remain unclear.

2.1.9 Malignant transformation of oral lichen planus

The precise association of OLP with risk of oral squamous cell carcinoma (OSCC) remains undetermined. However OSCC does not always arise at the site of OLP (van der Waal, 2009), is not always associated with erosive or ulcerative disease (Ingafou et al., 2006) and the risk can be independent of risk factors such as tobacco use (Gandolfo et al., 2004). Although the malignant potential of OLP remains a controversial issue it would seem appropriate all patients with OLP are made aware of this malignant potential, given appropriate advice about relevant lifestyle change (e.g. avoidance of tobacco and alcohol) and are regularly reviewed by competent clinicians.

There is little information as to the actual malignant transformation rate and the behaviour and outcome of squamous cell carcinomas (OSCCs) arising from OLP lesions. One report states that the site of the malignancy is not restricted to that of the pre-existing OLP (van der Waal, 2009).

Malignant transformation has been reported in several studies (Table 2.3). It reported to range between 0% to 12.5% of OLP patients (Lodi et al., 2005a; Gonzalez-Moles et al., 2008). The standardized incidence ratio (i.e. the ratio of observed to expected instances) ranged between 2.6 (95% CI: 0.1 to 14.8) to 45.3 (95% CI: 21.2 to 87.3) (Roosaar et al., 2006; Carbone et al., 2009a). However, in a long-term population-based study, there was minimal increased risk of oral malignancy in patients with oral lichen lesions (Roosaar et al., 2006).

2.1.10 Treatment

As OLP is likely to be lifelong disease the principle goal of treatment is to lessen the painful symptoms (Chainani-Wo et al., 2001; Gonzalez-Moles et al., 2002). Intervention is recommended when patients complain of burning sensations and irritation which may interfere with eating and speech and, consequently, their quality of life (Hegarty et al., 2002;

Rozycki et al., 2002). Such patients are likely to have erosive or ulcerative lesions.

Although many OLP patients are asymptomatic, follow up visits, explanation, patient education, and oral hygiene instruction are important. A review of the patient's drug history may identify medications associated with lichenoid reactions, such as angiotensin-converting enzyme inhibitors, sulphonylureas and non-steroidal anti-inflammatories (Rice and Hamburger, 2002) and it may be possible for these to be changed to agents less likely to cause or worsen OLP.

A systematic review on oral lichenoid lesion healing after amalgam restorations were replaced reported complete healing ranged from 37.5% to 100%, with lesions in direct contact with the original amalgam showing the greatest improvement (Issa et al., 2004). The same review noted a wide range of patch test results: 16% to 91% of patients were positive to patch testing for at least one mercury compound (Issa et al., 2004). The authors concluded that a patch test is of limited value in diagnosing lichenoid lesions; although other groups have suggested that patch testing is important to support clinical decisions (Pigatto and Guzzi, 2005).

2.1.10.1 Therapeutic agents

A wide range of topical and systemic therapies have been evaluated or suggested for treatment of OLP including topical corticosteroids (Voute et al., 1993); ciclosporin (Eisen et al., 1990; Sieg et al., 1995); retinoids (Laurberg et al., 1991); and systemic modalities such as corticosteroids (Carbone et al., 2003), hydroxychloroquine (Eisen, 1993), mycophenolate mofetil (Nousari et al., 1999), thalidomide (Camisa and Popovsky, 2000), dapsone (Kumar et al., 1994), heparin (Stefanidou et al., 1999; Femiano et al., 2003), photochemotherapy (Lundquist et al., 1995), and methylene blue-mediated photodynamic therapy (Aghahosseini et al., 2006).

However, there is little evidence of the efficacy and superiority of any of these agents as they have in general not been evaluated in well-designed randomised controlled clinical trials and most studies had small patient cohorts (Zakrzewska et al., 2005).

A detailed discussion of the different agents used in the managing OLP is not the scope of the present section; however, the most common modalities and the new agents recently introduced or suggested over the last few years are discussed. More details on treatment of OLP can be found in Table 2.4

Topical corticosteroids

Topical corticosteroids represent the mainstay of treatment of OLP (Carbone et al., 2003), while topical retinoids and calcineurin inhibitors (e.g. tacrolimus and pimecrolimus) may be considered to be a second-line therapies (Al-Hashimi et al., 2007).

There are numerous reports on the efficacy of topical corticosteroids in the management of OLP, including a recent review by Thongprasom and Dhanuthai (2008).

Among the many topical corticosteroids preparations and forms that have been suggested as effective in treating OLP are fluocinolone acetonide (Buajeeb et al., 2000; Thongprasom et al., 2003), clobetasol propionate alone (Carbone et al., 2003) or in an adhesive denture paste (Lo Muzio et al., 2001) and triamcinolone acetonide 0.1% (Endo et al., 2008).

The most commonly used formulations are ointment, cream, mouthwash, and spray. A mouthwash (e.g. betamethasone sodium phosphate dissolved in water) may be used if the patient has extensive mucosal involvement, especially in areas where it is difficult to easily apply an ointment or cream, or the medication may not be retained on the oral mucosal lesions (Gonzalez-Moles et al., 2002). Similarly clobetasol as an aqueous mouthwash may be effective (Gonzalez-Moles et al., 2003).

Some clinicians prefer occlusive therapy with custom-made trays for gingival disease as this may extend the contact time of the topical agents (Lu et al., 1998; Gonzalez-Moles et al., 2003; Mignogna et al., 2005; Endo et al., 2008).

In addition to being effective and non-costly, topical corticosteroids give rise to fewer minor adverse side effects (ASEs) than systemic corticosteroids (Carbone et al., 2003), although severe adverse side effects ASEs can occasionally arise with potent agents such as clobetasol (Gonzalez-Moles et al., 2002). The most common ASEs of topical corticosteroids are superficial candidal infections particularly with the more potent topical creams, ointments and mouthwashes. As a consequence some clinicians recommend the use of antimycotic agents, such as nystatin or miconazole when highly potent corticosteroids agents are prescribed (Gonzalez-Moles et al., 2003; Carbone et al., 2009a; Carbone et al., 2009b).

Other ASEs of topical potent agents have included mild moon face and hirsutism. The former reduces when frequency of application is reduced, while the latter can be managed by cosmetic depilation (Gonzalez-Moles et al., 2003). Nevertheless as such ASEs can affect 13% of patients (Gonzalez-Moles et al., 2003) there is a need to prescribe such agents with caution and ensure patients are aware of common ASEs. Although topical corticosteroids are the mainstay of therapy of OLP worldwide, even potent agents do not cause complete resolution of painful symptoms hence the need for alternative (e.g. calcineurin inhibitors) or adjuvant therapies (e.g. systemic corticosteroids and/or systemic immunosuppressants).

Intralesional corticosteroids

Intralesional corticosteroids has been suggested for many years to be a potential means of managing persistent OLP lesions, however there are few detailed studies to confirm this. A recent report did however observe that intralesional triamcinolone acetonide injection (40 mg/ml) was an

effective and safe means of managing ulcerative OLP that had not been responsive to topical corticosteroids (Xia et al., 2006).

Systemic corticosteroids

Systemic corticosteroids (e.g. prednisolone or deflazacort) may be employed for severe erosive/ulcerative OLP or when there is also non-oral involvement (Carbone et al., 2003). Systemic corticosteroids are usually prescribed to control acute flare ups (Lu et al., 1998). There is a significant risk of ASEs if these are prescribed for long-term use.

Topical calcineurin inhibitors

T-cell activation is central to the pathogenesis of OLP (Lodi et al., 2005b), hence blockage of calcineurin function might be expected to lessen the severity of such disease.

Topical ciclosporin

Although it has been reported to be effective in the management of OLP (Frances et al., 1988; Eisen et al., 1990; Harpenau et al., 1995), topical ciclosporin appears to be less effective and more expensive than topical corticosteroid in controlling OLP lesions (Yoke et al., 2006; Conrotto et al., 2006). The details of the precise impact of topical ciclosporin in the management of OLP are reviewed elsewhere (Al Johani et al., 2009).

Topical tacrolimus

There are many reports of the efficacy of tacrolimus in the management of OLP. Effectiveness has been assessed via open-label prospective studies (Kaliakatsou et al., 2002; Olivier et al., 2002; Lozada-Nur and Sroussi, 2006), randomized trials (Corrocher et al., 2008; Radfar et al., 2008), retrospective studies (Hodgson et al., 2003; Thomson et al., 2004), case series (Morrison et al., 2002; Rozycki et al., 2002), and described in several case reports (Lener et al., 2001; Shen et al., 2004; Shichinohe et al., 2006).

Initial studies were conducted in patients with symptomatic OLP who were recalcitrant to topical corticosteroids or at risk of adverse side effects from corticosteroids. Eleven of the 13 OLP patients who were prescribed topical tacrolimus (mean duration of 6.5 months) had either complete resolution or partial improvement of painful oral mucosal lesions within four weeks from the start of the treatment although 2 patients had no benefit (Rozycki et al., 2002). Both 0.1% and 0.3 % concentrations of tacrolimus were able to induce complete healing of OLP lesions and cause relief of painful symptoms while 0.03% formulation led to partial response only (Rozycki et al., 2002). Symptomatic and clinical improvement is observed usually within 2 weeks (Kaliakatsou et al., 2002). Adverse side effects were uncommon and minimal but recurrences were observed within one to two weeks of cessation of tacrolimus therapy (Rozycki et al., 2002).

Hodgson and colleagues (2003) in a retrospective analysis of 50 OLP patients with erosive/ulcerative OLP recalcitrant to topical corticosteroids demonstrated the long-term (mean: 19.8 months) efficacy and safety of 0.1% topical tacrolimus. Most of the patients (94%) having either complete or partial resolution of mucosal erosions. Most of the ASEs were intra-oral burnings sensation and taste disturbance.

Topical tacrolimus was suggested for OLP patients who are recalcitrant to topical corticosteroids, patients at risk of adverse side-effects from systemic immunosuppressant agents or at risk of oral candidosis (Lener et al., 2001; Lozada-Nur and Sroussi, 2006; Chaudhry et al., 2007).

Two randomized trials reported that tacrolimus was more effective than triamcinolone (Laeijendecker et al., 2006) and clobetasol (Corrocher et al., 2008) in controlling painful symptoms of erosive OLP. However, Radfar and co-workers (2008) in a randomized, double-blind study found no significant differences between tacrolimus and clobetasol in the management of symptomatic OLP. In addition relapse is common after

the drug was discontinued and can occur quickly (Olivier et al., 2002; Morrison et al., 2002).

At present there remains little strong evidence to demonstrate that tacrolimus is notably superior to topical corticosteroids for the treatment of oral lichen planus. Moreover, available data should be evaluated with caution as studies often employed dissimilar preparations and concentrations of tacrolimus ranging from mouthwash (Olivier et al., 2002) to paraffin- or mineral oil-based ointments (Kaliakatsou et al., 2002; Morrison et al., 2002). Overall however, tacrolimus can be considered effective in controlling the extent of mucosal lesions and the related symptoms of OLP. It has few adverse side-effects but relapses may arise after discontinuation of therapy. Therefore the maintenance of disease remission necessitates continued intermittent use of topical tacrolimus, the frequency of application being different from one patient to another (Hodgson et al., 2003). Additional details on studies reporting the efficacy of topical tacrolimus in OLP in Table 2.4.

Pimecrolimus

Pimecrolimus shares the same cellular binding protein (FKBP-12) as tacrolimus and blocks the transcription of cytokines by inhibiting the calcineurin pathway. There is very limited data of the potential of topical pimecrolimus for the treatment of oral mucosal disease. Pimecrolimus has been suggested to be effective in the management of symptoms and erosions/ulcerations of OLP (Dissemond et al., 2004; Esquivel-Pedraza et al., 2004; Scheer et al., 2006; Swift et al., 2005). A significant pain reduction in erosive OLP is reported by patients treated with pimecrolimus in comparison to placebo (Swift et al., 2005). Another study of 12 patients found that 1% pimecrolimus cream was more effective in lessening symptoms and signs of erosive OLP in comparison with vehicle only (Passeron et al., 2007).

Twice daily application of a mixture of 1:1 of pimecrolimus 1% cream with a hydrophilic adhesive gel base has been suggested to be safe and

effective treatment of OLP (Dissemond et al., 2004; Swift et al., 2005) with clinical improvement usually observed from 2 to 5 weeks (Esquivel-Pedraza et al., 2004). The drug was well-tolerated with only transient burning sensation arising in 2 of the 6 patients using pimecrolimus. However, relapse was observed in all patients within 4 weeks of cessation of therapy (Passeron et al., 2007).

A randomized clinical trial found that pimecrolimus 1% cream was no better than topical triamcinolone acetonide in lessening the symptoms and signs of OLP when applied 4 times daily for 2 months (Gorouhi et al., 2007). Moreover, a transient oral burning sensation was reported by 10% of patients who received pimecrolimus (Gorouhi et al., 2007). A recent randomized vehicle-controlled small study showed that topical pimecrolimus was effective in controlling pain due to OLP erosions/ulceration during and up to 30 days after cessation of therapy (Volz et al., 2008). Similar results were reported in other studies, (Dissemond et al., 2004; Esquivel-Pedraza et al., 2004; Swift et al., 2005). Pimecrolimus was also used effectively in association to tacrolimus in a patient with cheilitis glandularis superimposed on OLP (Erkek et al., 2007).

Topical pimecrolimus may thus be of some benefit, at least in the short-term in the treatment of symptomatic OLP. However its relative effectiveness and safety when compared to topical tacrolimus or corticosteroids are not known. Further investigations are needed to confirm its suggested prolonged long-term efficacy.

In 2004 the US Federal Drug Agency (FDA) reported 19 and 10 patients who received topical tacrolimus and pimecrolimus respectively developed malignant tumours. The 10 malignancies associated with topical pimecrolimus included; non-Hodgkin’s lymphoma, paniculitis-like T-cell lymphoma, granulomatous lymphadenitis with hyperplasia, squamous cell carcinoma, intraductal papilloma of the nipple and basal cell carcinoma.

Two of the 10 pimecrolimus-associated malignancies occurred at the same site of local application.

In patients who received topical tacrolimus, 9 patients developed lymphomas and 10 developed cutaneous malignancy (mainly squamous cell carcinoma, sarcoma, and malignant melanoma). Most of the cutaneous tumours (70%) developed in the same area of tacrolimus application (Anonymous, 2004). Tacrolimus was the suspected causative agent of oral squamous cell carcinoma (OSCC) of the tongue in a 56-year-old woman who was prescribed tacrolimus (0.1% twice daily) to control her OLP (Becker et al., 2006). The OSCC developed after 3 years of topical tacrolimus commencement and 6 years following the diagnosis of OLP. In addition another paper reported the development of genital SCC in a 57-old male with a 2 years history of balanoposthitis. The patient developed the tumour after 2.5 months of therapy with topical tacrolimus which necessitate surgical intervention with skin graft (Langeland and Engh, 2005). Both of these mucosal tumours developed at sites of tacrolimus application. This data may suggest that tacrolimus may be a promoter or accelerator of mucoucutaneous carcinogenesis (Niwa et al., 2003; Langeland and Engh, 2005). However, this should be considered with caution as histopathological description of the lesions before tacrolimus application was not always provided and hence it is not known whether or not the carcinogenetic process had already commenced before the therapy (Berger et al., 2006; Qureshi and Fischer, 2006). A more recent case-control study did not find any increased risk of lymphoma in atopic dermatitis patients treated with topical tacrolimus and/or pimecrolimus (Arellano et al., 2007).

In January 2006, the US FDA approved the inclusion of a potential risk of cancer in the labelling of tacrolimus and pimecrolimus cream, and recommends the use of these agents as second-line therapies. In addition, the FDA recommended refraining from using these treatments in children under 2 years of age (Anonymous, 2006a).

There remains little information of the carcinogenic potential of tacrolimus or pimecrolimus, and the new recommendations from the European Medicines Agency state that the benefits of these calcineurin inhibitors outweigh the risks (Anonymous, 2006b). The European Medicines Agency however recommends that intermittent use of the topical tacrolimus with the lowest strength possible and only for short periods of time. Certainly with regard to OLP, a clear diagnosis should be established before the use of topical tacrolimus as early squamous cell carcinoma may clinically mimic lichenoid lesions or develop in the context of lichen planus (Lozada-Nur and Sroussi, 2006).

Retinoids

Although often mentioned in non-systematic reviews, there are few reports of the benefit of retinoids. Twice daily application of topical tazarotene gel 0.1% has been suggested to be effective in the management of hyperkeratotic OLP (Petruzzi et al., 2002) although, as this was likely to be asymptomatic the exact benefit to the patient is unclear. In a randomized trial, topical isotretinoin was found effective in managing atrophic and erosive oral lichen planus with dysplasia. Transient mucosal soreness and sensitivity to hot foods has been reported with isotretinoin topical therapy (Scardina et al., 2006).

Thalidomide

Thalidomide in a dose of 100 mg/day was found to be effective in managing erosive lesions of OLP; however, when the dose was increased to 200 mg/day, patients started to develop side effects such as dizziness and skin rash (Camisa and Popovsky, 2000). Thalidomide should be reserved for the most severe cases of OLP due to its adverse side effects such as teratogenic effects, proximal myopathy and neuropathy (Camisa and Popovsky, 2000; Macario-Barrel et al., 2003).

Efalizumab

Efalizumab, an inhibitor of T cell interactions, is a recombinant humanized IgG1 monoclonal antibody that binds to CD11a and is used primarily in the treatment psoriasis (Joshi et al., 2006). Efalizumab (0.7 mg/kg/week followed by 1 mg/kg/week) has been used successfully in the management of patient who developed cutaneous LP and symptomatic oral lesions and who did not respond to a short course of systemic prednisone and topical tacrolimus. Both cutaneous and oral mucosal lesions improvement was evident within 5 weeks and substantial improvement was reported within 10 weeks (Cheng and Mann, 2006).

Heffernan and co-workers (2007) reported on four patients with erosive OLP who had been prescribed subcutaneous efalizumab (initial dose; 0.7 mg/kg for a week followed by 1 mg/kg weekly for 11 weeks). All patients' oral mucosal lesions responded favourably to treatment. The mean reduction in the total mucosal lesional surface area was 71.1% (range; 57.3–96.8%) with improvement in the patient-centred outcomes of 82% and 69.3% in visual analogue scale and oral health impact profile-14, respectively. One patient discontinued therapy as she developed subacute cutaneous lupus erythematosus and another developed urticaria and a staphylococcal abscess of an artificial hip joint.

Alefacept

Alefacept may lessen the severity of many disorders by inhibition of activated T cells. It was approved by the US Food and Drug Administration for the treatment of moderate to severe psoriasis. It prevents T cell activation and initiates T cell apoptosis (Sugiyama et al., 2008).

Intramuscularly injected alefacept (15 mg/week for 12 weeks) was used in the management of two patients with widespread mucocutaneous LP, that also affect the oral mucosa, who did not respond to a variety of topical and systemic agents, including antihistamines, hydroxychloroquine sulfate, topical tacrolimus, topical and systemic corticosteroids,

azathioprine, ciclosporin, mycophenolate mofetil, griseofulvin, and ultraviolet-B (Fivenson and Mathes, 2006). Neither of the 2 patients developed ASEs and both were disease free after completing the treatment protocol. There was no flare-up after discontinuation of therapy up to 12 to 20 weeks (Fivenson and Mathes, 2006).

Other agents

A wide variety of other agents (alone or in combination with others) have been proposed in the management of OLP. These include adalimumab (Chao, 2009), etanercept (Yarom, 2007), hydroxychloroquine (Eisen, 1993), mycophenolate mofetil (Nousari et al., 1999; Dalmau et al., 2007), dapsone (Kumar et al., 1994), rapamycin (Soria et al., 2009), levamisole (Sun et al., 2007), heparin (Stefanidou et al., 1999; Femiano et al., 2003; Femiano and Scully, 2006), photochemotherapy (Lundquist et al., 1995; Guyot et al., 2007), aloe vera (Choonhakarn et al., 2007), Ignatia (Mousavi et al., 2009), hyaluronic acid (Nolan et al., 2009), CO2 laser (van der Hem et al., 2008), and methylene blue-mediated photodynamic therapy (Aghahosseini et al., 2006).

2.1.10.2 Surgery

Surgery have a very limited role in the treatment of OLP, however palatal grafts may be used to treat recalcitrant gingival lichen planus or lichenoid lesions (Axell and Henriksen, 2007). In one case report a patient had complete disappearance of gingival lesions after 3.5 years (Tamizi and Moayedi, 1992).

2.1.11 Clinical follow-up and outcome of oral lichen planus

2.1.11.1 Clinical follow-up

The review interval is a controversial issue in OLP patients and there are no widely accepted guidelines available. Eisen (2002) and Al-Hashimi and co-authors (2007) recommended regular follow-up of OLP patients to detect any malignant transformation and to improve prognosis. Some oral medicine units regularly review patients whom they believe are at higher risk of malignancy; however, this observation is not based on evidence but personal clinical experience. Carbone and co-workers (2009) reviewed patients according to clinical presentation and treatment needs; patients with white lesions (reticular, papular or plaque forms) were seen twice a year for the first 2 years after diagnosis and then annually; patients with red lesions (erosive or atrophic) were usually seen twice annually and with active disease undergoing therapy were seen every 2 months until their disease stabilized.

However due to the limited number of oral medicine specialists and the high cost of follow-up, there is doubt over exact frequency of visits to improve prognosis. Some authors recommend involvement by general dental practitioner in the long-term management of OLP patients (Ingafou et al., 2006; Mattsson et al., 2002).

2.1.11.2 Outcome of oral lichen planus

OLP is chronic disorder (Chainani-Wu et al., 2001) and flare up of oral lesions is common (Eisen, 2002; Roosaar et al., 2006). In a long-term population-based study, one-third of the lesions had spontaneous remission (Roosaar et al., 2006). In the Carbone et al. study (2009), most of the 808 patients (76.6%) had the same clinical presentation as that found in first visit of the study; 2.5% had complete healing for at least 12 months after presentation; and 6% of the study group reported worsening of their disease. Fifteen per cent of the patients had resolution of atrophic/erosive lesions which changed to reticular, plaque, or papular lesions; while 6% had their white lesions (reticular, popular, or plaque) altered to atrophic or erosive forms (Carbone et al., 2009a). In another

large cohort (690 patients), only 13% had complete resolution of symptoms and signs after a median of 35 months (Ingafou et al., 2006).

While there is considerable data concerning the clinical presentation of OLP the long-term outcomes of patients receiving contemporary care of OLP remains unknown. In addition the frequencies of adverse events with therapy are not well detailed. Hence the aim of this chapter was to describe the long-term outcomes of therapy and malignant transformation rate in a large cohort of OLP patients attending a single clinical centre.

2.2 AIMS

The aims of this chapter were to determine:

1. The clinical outcomes of long-term therapy of oral lichen planus in a cohort of patients with oral lichen planus that had been treated with corticosteroids and/or topical tacrolimus.
2. The frequency and nature of adverse side effects of therapy of oral lichen planus in this cohort of patients.
3. The malignant transformation rate of oral lichen planus.
4. To compare clinical, haematological and serological outcome and malignant transformation rate between patients who had treated with and without topical tacrolimus.

2.3 PATIENTS AND METHODS

2.3.1 Patients group

The study group consisted of 186 subjects managed by the Oral Medicine Unit of UCL Eastman Dental Institute and UCLH Eastman Dental Hospital UCLH NHS Trust between 1985 and 2006, found to have clinical and/or histopathological features of oral lichen planus (OLP) based upon WHO histopathological criteria (Kramer et al., 1978).

2.3.2 Methods

The medical chart of each patient was examined using multiple data extraction forms for details of demographics, past medical and drug histories, extra-oral and intra-oral clinical features and clinical progress data. Details of diagnostic and monitoring investigations were also systematically extracted. These included: histopathology, full blood cell count, differential white cell count, hepatic and renal biochemistry and details of the different topical and systemic therapies employed in the management of each patient (Appendices 1-5).

In the second section of this study, patients were divided into two groups according to wether they had received topical tacrolimus during the course of their treatment.

Outcomes of therapies

Analyses were restricted to patients with OLP-related mucosal ulceration/erosion and desquamative gingivitis. Three outcome analyses were used in the present study:

1. Analysis 1 was relevant to patients on topical corticosteroids (group A) and patients on topical tacrolimus (group B) as separate groups. The presence of oral ulceration/erosion and/or desquamative gingivitis between baseline and last clinical review for each group was used as outcome measure.

2. Analysis 2 consisted of comparison between group A and group B. The presence of symptoms (pain, soreness, or discomfort) and clinical signs

(oral ulceration/erosion and/or desquamative gingivitis) in group A versus group B at baseline and on last clinical review were used as outcome measures.

3. Analysis 3 was restricted to group B. Serial measurements of disease status during 6-months reviews were conducted and identified the most common disease status (> 50% of reviews) during the observation period. The disease status was considered separately for symptoms and signs.

The symptoms-related disease status was defined as a 3-point scoring system: 0 (asymptomatic/mild pain), 1 (presence of moderate pain), 2 (presence of severe pain), as reported by the patients.

The sign-related disease status was defined as a 3-point scoring system: 0 (absence/or presence of erosive areas on <30% of oral mucosa surface), 1 (presence of erosive areas on 30-70% of oral mucosa surface), 2 (presence of erosive areas >70 of oral mucosa surface) as reported by the clinician. The score was retrospectively collected for each clinical review on the bases of clinical notes and photographs.

Malignant transformation rate

The rate of malignancy transformation was detected by recording the number of patients who developed oral squamous cell carcinoma at least 6 months after the diagnosis of OLP.

Statistical analyses

The differences between females and males in relation to duration of oral symptoms before attending to Oral Medicine clinics and duration of the treatment were analyzed using Student's t-test.

McNemar test was used to compare symptom and signs scores between the two treatment groups (Group A and B). Descriptive and analytical statistics were undertaken using the SPSS program (SPSS for Windows:

(Statistical Package for the Social Sciences) software, version 12.0).

2.4 RESULTS

2.4.1 Patient demographics

Age and gender

The mean age of the patients when they attended for first time in the oral medicine unit was 54.7 years (SD 13.4, median 55.0), this being 54.0 for males (SD 14.3), and 54.9 for females (SD 13.1). There was an age range of 18.3 to 92 years. The onset of the clinical features of oral lichen planus was usually in the fifth to seventh decades of life (Table 2.5). There were a higher number of females (133; 71.5%) than males (53; 28.5%), with a female to male ratio of 2.5:1.

Ethnic group

The majority of patients were white British (90; 48.4 %) (Self-reported, according to 2001 Census) (Office for National Statistics, 2003). The second most common ethnic group who had OLP was Indian (32; 17.2%). Additional details of ethnic background of this cohort of patients are provided in Table 2.6.

Marital status

Marital status was stated under four categories; married which included married patients and patients with civil partnership; single, divorced and widowed patients. One hundred and twenty one (65.1%) patients were married or living with a partner. 37 (19.9%) were single, 13 (7.0%) were widowed, 9 (4.8%) were divorced and the marital status was not reported in the case note of 6 patients.

Tobacco use and Alcohol consumption

Forty eight (25.8%) of the patients were previous tobacco users and 20 (10.8%) were current users of tobacco. The mean number of self-reported cigarettes per day was 15.3. One hundred and seventeen (62.9%) of the group currently drank alcohol, the mean total weekly consumption being 11.9 units.

Sources of referral to oral medicine

One hundred and three (55.4%) of the patients had been referred to the oral medicine unit by general dental practitioners. Thirty five patients were referred by oral maxillofacial or oral surgeons, 12 patients were referred by general medical practitioners and the remaining patients were referred by different medical and dental specialists as detailed in Table 2.7. All patients had been referred for the diagnosis and/or management of their oral lesions. The mean time from referral to initial attendance in oral medicine was 0.29 years (SD 0.53).

2.4.2 Past medical and drug histories

2.3.2.1 Past medical history

A quarter of this cohort of patients had a history of allergic disease. Eighteen (9.7%) patients were allergic to penicillin, two to aspirin and 19 were allergic to a variety of other agents. Fifty patients had history of cardiovascular disease and 24 patients had respiratory diseases. Thyroid dysfunction and other endocrine conditions were common among this cohort of patients. Additional details of past medical history are provided in Table 2.8.

2.3.2.2 Past drug history

The patients were receiving a wide range of medication at the time of their clinical consultation in the Oral Medicine Unit. As expected from the medical history, the most common drugs were anti-hypertensives, endocrine and anti-asthmatic agents (Table 2.9).

Some of these agents were being used to control oral and/or mucocutaneous lesions likely to be due to OLP. A wide range of topical and/or systemic agents had been prescribed to the present cohort of patients before attending the Oral Medicine clinic. Triamcinolone acetonide (Adcortyl in Orabase) was prescribed to 28 patients, hydrocortisone sodium succinate and chlorhexidine gluconate were prescribed to 24 patients. Patients also were prescribed other

preparations of topical corticosteroids, systemic corticosteroids, antimicrobial and/or analgesic agents. Additional details on different agents used to control the patients' disease before attending Oral Medicine clinics are summarised in Table 2.10.

2.4.3 Histopathological features

Histopathological examination of lesional tissues was undertaken for 158 (84.9%) patients. 127 (68.3%) had just one biopsy, 24 had two and 5 had three, one patient had 4 and another had 7 biopsies. The histopathological reports of the remaining 28 patients were not available in their clinical notes. Additional details on the histopathological features of the present cohort are provided in Table 2.11.

2.4.4 Clinical features

2.4.4.1 Presenting clinical signs and symptoms

Most patients complained of oral discomfort, soreness and pain or mouth ulcerations (133; 71.5%). The buccal mucosa, tongue and the gingivae were the most affected sites. Gingival involvement, ranging from redness of the gingivae to painful ulcerated gums, was reported by 51.1% of the patients. Asymptomatic white patches (4 detected by GDP, two by GP and 4 by patients) were the cause of referral of 10 patients and three patients were complaining of oral dryness in addition to oral pain or ulceration. The patients had had oral symptoms from few weeks to more than 22 years before attending Oral Medicine Unit. The average duration of symptoms prior to clinical presentation in oral medicine was 31.9 months (SD 47.8).

2.4.4.2 Distribution of OLP lesions

Bilateral involvement of the oral mucosa and/or gingivae was observed in 132 patients and when it was unilateral, it was affecting the left side (11 patients) more than the right side (9 patients). The distribution of oral lesions was not reported in the remaining 34 patients. The buccal mucosa was the most commonly affected site (68.3%) followed by the gingivae

(51.1%). Additional details of the intra-oral distribution of OLP lesions are provided in Table 2.12.

2.4.4.3 Extra-oral involvement

In this cohort of patients, extra-oral involvement of possible LP was self-reported by 25 patients (13.4%). Eleven patients had cutaneous disease while 6 patients had vulva or vaginal involvement. Three patients had both cutaneous and genital involvement. Four patients had scalp involvement. One patient had widespread mucocutaneous lesions affecting skin, scalp, nails and genitals. Seven of the patients with extra-oral LP reported that the mouth was the first site of involvement while skin or genital lesions preceded oral lesions in 5 patients. One patient had simultaneous onset of oral and extra-oral disease. The temporal relationship of the oral/extra-oral disease of the remaining 12 patients was not recorded.

2.4.5 Duration of therapy

The duration of treatment of OLP provided by the Oral Medicine clinic differed between patients and ranged from a few months to more than 20 years (until data collection ceased) with a mean of 4.2 SD (3.7) years. Sixty four (34.4%) patients were followed-up for less than 2 years, 76 (40.9%) from 2 to 6 years, 32 (17.2%) from 6 to 10 years and 14 (7.5%) patients were followed-up for more than 10 years.

2.4.6 Analysis of outcome according to prescribed therapies

In the following section patients are divided into two groups (Group A or B) according to whether they did or did not receive topical tacrolimus as part of their therapy.

Patients not prescribed topical tacrolimus (Group A)

One hundred patients received topical treatment other than topical tacrolimus. Only 4 of this group received systemic corticosteroids and/or systemic immunosuppressant. Details of the different topical and systemic agents used to control OLP in this group of patients are provided in Table 2.13.

Patients prescribed topical tacrolimus (Group B)

The remaining 86 patients received topical tacrolimus treatment in addition to other topical agents and 18.6% of this group had also received systemic corticosteroids and/or systemic immunosuppressant in an attempt to control their disease (Table 2.14). One or both topical tacrolimus concentrations (0.03% and/or 0.1 %) had been prescribed to all this group of patients. The mean duration of treatment with tacrolimus was 2.2 years with a range of 2 weeks to more than 6 years.

2.4.6.1 Analysis 1: Presence of oral ulceration/erosions and desquamative gingivitis at baseline vs. last clinical examination for group A and group B separately

Patients on topical corticosteroids (Group A)

Among the forty three patients with oral mucosal ulceration/erosions 32.6% (14/43) had persisting lesions after therapy whereas complete healing was observed in 29 patients (29/43; 67.4%).

Most of the patients with desquamative gingivitis (33/44; 75%) had persisting gingival lesions after therapy, whereas in only 25% of cases complete healing was observed (11/44) (Table 2.15).

Patients prescribed topical tacrolimus (Group B)

Among the 52 patients with oral mucosal ulceration/erosions 44.2% (23/52) had persisting lesions after therapy whereas complete healing was observed in 29 patients (29/52; 55.8%).

Half of patients (20/41; 48.8%) with desquamative gingivitis had persisting lesions after therapy, whereas in only 51.2% of cases complete healing was observed (21/41) (Table 2.16).

2.3.6.2 Analysis 2: comparison between group A and group B

Symptoms

Most patients of group A had improvement of their painful symptoms with almost 71% of individuals reported no pain after therapy. This percentage was slightly lower in group B (49/86; 57%).

Clinical signs

Mucosal ulceration/erosion

Both groups of patients exhibited significant improvement in the prevalence of oral mucosal ulceration. In group A, 43/100 (43%) initially had mucosal ulceration/erosions and after treatment this was reduced to 32.6% (14/43) ($P< 0.001$). In group B, 52/86 (60.5%) initially had ulcers and/or erosions and this reduced to 23/52 (44.2%) after treatment ($P< 0.001$).

Comparison between the 2 groups showed that patients in group B had significantly more mucosal ulceration/erosion before therapy than group A ($P=0.03$). However at the end of the observation period, there was no statistical difference between the 2 groups in regard to their mucosal ulcerations ($P=0.33$).

Gingival involvement (desquamative gingivitis)

There was significant improvement in desquamative gingivitis only in group B. In group A, 44/100 (44%) initially present with gingival involvement and after treatment this was reduced to 33% (P=0.65). In group B, 41% initially had gingival involvement and this reduced to 23.3% after treatment (P= 0.006).

There was no significant difference between the 2 groups of patients in their gingival involvement in the start or at the end of the study (P=0.72 and 0.09 respectively).

2.3.6.3 Analysis 3: First, last and serial measurements of group B (i.e those receiving tacrolimus)

Symptoms before therapy vs. last review

Of the 15 patients who had disease symptoms status of 2 (severe pain) at start of tacrolimus therapy, 12 (80%) reported a reduction of pain to disease status 0 (11/12; 91.7%) or 1 (1/12; 8.3%). Three patients reported persistence of disease status 2.

Of the 50 patients who had disease symptoms status 1 (moderate pain), 43 (86%) reported reduction to disease status 0. One patient had an increase to disease status 2 and 6 patients reported persistence of moderate pain.

Of the 16 patients who had disease symptoms status of 0 (no/mild pain) at start of tacrolimus therapy, 15 (93.8%) reported stable disease (status 0) at the end of therapy. One patient reported disease status 1.

Serial measurements of symptoms

Analysis of patients' symptoms calculated upon serial measurements of symptoms during 6-month reviews shows absence of/mild pain (disease status 0) was the most common disease status during therapy. It was present in 66/81 (81.5%) patients. Disease status 1 and 2 were the most

frequent disease status in 11/81 (13.6%) and 4/81(4.9%) patients respectively.

Signs before therapy vs. last review

Of the 14 patients who had disease signs status of 2 (erosions affecting >70% of oral mucosa) at the start of tacrolimus therapy, 11 (78.6%) reported a reduction of disease status to status 0 (9/11; 81.8%) or 1 (2/11; 18.2%). 3 patients reported persistence of disease status 2.

Of the 57 patients who had disease signs status 1(erosions affecting 30-70% of oral mucosa), 49 (86%) reported reduction to disease status 0. One patient disease status increased to 2 and 7 patients reported persistence of pre-therapy disease status.

Of the 10 patients who had disease signs status of 0 at start of tacrolimus therapy, 9 (90%) reported stable disease at the end of the therapy. One patient had an increase of disease status to 1.

Serial measurements of signs

Analysis of the response to topical tacrolimus calculated upon serial measurements of disease signs status during 6-month reviews shows that disease status 0 was the most common disease status (>50% of reviews) it was reported in 65/81 (80.2%) patients. Disease status 1 and 2 were the most frequent in 12/81 (14.8%) and 4/81 (4.9%) patients respectively.

2.4.7 Adverse side effects and malignant transformation

Twenty nine (15.6%) patients had adverse side effects (ASEs). In the majority of instances, patients had only 1 ASE (19/29; 65.5%). Four patients had 2 ASEs (4/29; 13.8%), 5 (17.2%) had 3 ASEs and 1 had 4 ASEs. Most adverse effects in this cohort of OLP patients were associated with topical tacrolimus.

Patients not prescribed topical tacrolimus (Group A)

Only two patients in this group had adverse side effects. One complained of burning sensation, due to topical application of fluticasone propionate 0.05%, and one had worsening of his gastroesophageal reflux which necessitated the cessation of betamethasone mouthwash.

Patients prescribed topical tacrolimus (Group B)

Twenty seven patients reported adverse side affects. Eighteen patients (20.9%) complained that the topical tacrolimus gave rise to oral side effects that included local burning (3 patients), tingling sensation (6), a peppery taste (3), other taste disturbances (2), a stinging sensation (2) or local irritation (2).

All 5 patients in this group who had systemic azathioprine developed side effects including cutaneous rash (1 patient), fever (1), nausea (2) vomiting (3), dizziness (1) and headache (1).

In one patient (who also had type I diabetes mellitus) fluticasone propionate spray caused an elevation of plasma glucose. Other side effects had been reported such as diarrhoea, angular cheilitis, dryness of the mouth, panic-anxiety, tiredness, shaking, bladder irritation and haematuria. Additional details on adverse side effects of different therapies used in this cohort of patients in Table 2.17.

Malignant transformation

One patient (72.4 year old male) who did not receive topical tacrolimus developed reactive atypia while another patient on topical tacrolimus developed oral squamous cell carcinoma (48 year old female).

2.5 DISCUSSION

Oral lichen planus (OLP) is a common oral mucosal disorder that adversely affects the patients' quality of life (Tabolli et al., 2009). Although OLP is common, there still controversy surrounding its diagnostic criteria, association with hepatitis, and potential for malignant transformation. In addition, there is no consensus on long-term management or strong evidence on the most effective therapy. The aim of the present chapter has been to determine the outcomes and safety of current OLP management in one tertiary centre.

The demographics of the present patient cohort confirmed recent reports from Italy (Mignogna et al., 1998; Carbone et al., 2009a), USA (Chainani-Wu et al., 2001; Eisen, 2002), UK (Ingafou et al., 2006), Iran (Pakfetrat et al., 2009), and China (Xue et al., 2005) that OLP is primarily a disease affecting middle to late age females. Although OLP is most commonly diagnosed in fifth and sixth decades of life, it can affect younger people (Sharma and Maheshwari, 1999; Nnoruka, 2007; Woo et al., 2007; Mathew et al., 2008) as demonstrated in the present group of patients.

The mean duration of symptoms before patients attended oral medicine was 31.9 months, suggesting perhaps that misdiagnosis or delay in referral may be a frequent occurrence. The referral delay may indicate that some patients were managed by general dental practitioners (GDPs), general medical practitioners, or medical specialist (e.g., dermatologist). Some GDPs may be familiar with OLP, as it is one of the most common mucocutaneous disease affecting the mouth, and may have prescribed topical agents such as benzydamine hydrochloride or topical corticosteroids to control symptoms, especially if the disease was mild (López-Jornet et al., 2009). However, as a substantial number of this cohort presented initially with only gingival lesions, it could be surmised that many GDPs assumed that the clinical condition represented plaque-related gingivitis, hence underlying the delayed referral (Mignogna et al., 2005).

The oral clinical features of OLP have been described in detail in several large cohorts (Mignogna et al., 1998; Chainani-Wu et al., 2001; Eisen, 2002; Xue et al., 2005; Ingafou et al., 2006; Carbone et al., 2009a; Pakfetrat et al., 2009). In the present study, OLP gave rise to multiple areas of erosions/ulceration usually with a lichenoid background characterised by red and white lesions and the presence of the classical Wickham's striae. The lesions most commonly affected buccal mucosa, gingivae, and tongue as previously reported (Pakfetrat et al., 2009). The tongue was more commonly affected than the gingivae in some studies (Gorsky et al., 1996; Xue et al., 2005; Ingafou et al., 2006).

A recent study reported 12% of patients had extra-oral involvement (Carbone et al., 2009a). Twenty-five (13.4%) patients of the present cohort had a history of clinical and/or histopathological evidence of extra-oral OLP. Most of the patients presented with only one extra-oral site involvement in agreement with others (Bidarra et al., 2008), with the skin the most commonly affected site (19; 10.2%), similar to the results of Chainani-Wu et al. (2001) and Carbone et al. (2009), who reported skin involvement in 11.4% and 7.8%, respectively. This small number of patients with cutaneous involvement may reflect a referral bias, as patients with predominately skin lesions will be referred to a dermatologist, and those referred to oral medicine specialist have mainly oral mucosal involvement. The genitalia, especially in women, is another site which may be affected and underreported by cohort from dental tertiary units (Eisen, 1994; Bidarra et al., 2008).

LP may affect the oral mucosa before, after, or simultaneously with extra-oral involvement. Although all three situations were reported in the current cohort, OLP commonly preceded the appearance at other mucocutaneous sites as reported previously (Ingafou et al., 2006; Pakfetrat et al., 2009), but of course this may simply reflect a bias of patients with oral disease being referred to an oral medicine unit.

In summary, the clinical picture of OLP in this cohort of patients was dominated by oral erosions/ulceration, desquamative gingivitis, and less frequently by associated mucocutaneous involvement.

Both diabetes mellitus and hypertension have been suggested to be associated with lichen planus (Grinspan et al., 1966; Lamey et al., 1990). In present cohort, 21 (11.3%) and 42 (22.6%) patients had diabetes or hypertension, respectively. In 2005/2006, the prevalence of diabetes mellitus and hypertension was estimated to affect 3.6% and 12.0% of the UK population, respectively (UK-Quality and Outcomes Framework for GP databases). Therefore, the prevalence of both disorders is considerably higher in our cohort patients. However, the age group of the present cohort may account for these observations.

There are no widely accepted guidelines for treating OLP. A systematic review in the Cochrane database (Chan et al., 2000) concluded that there is weak evidence to support any agent over a placebo. The authors recommend that large, well designed placebo-controlled randomised trials were necessary determine the efficacy of different therapeutic agents to assist clinicians in identifying appropriate medications to treat OLP.

Although patients were prescribed different topical and/or systemic agents before attending to Oral Medicine clinics they still complained of pain and active disease. The failure may be due to wrong diagnosis, failure to use the appropriate agent or dosage or it could reflect the severity of the disease.

A wide variety of preparations, forms, and concentrations of topical corticosteroids were employed in present cohort of patients depending on disease severity, clinical presentation, and/or patient's preference (as they used these agents for extended periods). Most patients were initially managed with topical corticosteroids, the conventional OLP treatment (Donovan et al., 2005), which reduced the symptoms of most (71%) patients in group A (patients not received topical tacrolimus) who received

these agents. However, the remaining patients (86 patients) required topical tacrolimus and/or systemic agents to control symptoms.

Topical tacrolimus has been reported to be effective in the management of OLP (Kaliakatsou et al., 2002; Olivier et al., 2002; Hodgson et al., 2003; Thomson et al., 2004; Lozada-Nur and Sroussi, 2006; Radfar et al., 2008; Corrocher et al., 2008). However, there are little substantial data on the long-term benefits.

The results of the present study demonstrate that topical corticosteroids, particularly the high potent agents, and topical tacrolimus are effective to the same degree in managing symptomatic OLP. Both agents induce lessening of symptoms and oral mucosal lesions. However, corticosteroids may be more acceptable than topical tacrolimus as many patients who receive the latter complained of local adverse side effects.

Recently 2 randomized controlled studies have been conducted to investigate the efficacy of topical tacrolimus in comparison with 2 different preparations of topical corticosteroids in the management of OLP. The studies assessed the efficacy of 0.1% topical tacrolimus ointment in comparison with 0.1% triamcinolone acetonide ointment 4 times daily (40 patients over a 6-week period) (Laeijendecker et al., 2006) and clobetasol 0.05% (30 patients over a 6-week period) (Radfar et al., 2008) in the management of OLP. The first study found that topical tacrolimus was more effective, in short-term than triamcinolone acetonide. While the later found no difference between clobetasol and tacrolimus. This result may partially explain as clobetasol is more potent than triamcinolone acetonide. At the end of observation period of the present study, there was no statistically significant difference in symptoms between the two groups. This might reflect the fact that patients on tacrolimus presented initially with more severe oral mucosal erosions and ulcerations.

Topical tacrolimus resulted in rapid pain control in some patients (data not shown), suggesting that there is some short-term benefit as reported

previously (Laeijendecker et al., 2006). Thus it may be considered for patients' recalcitrant to corticosteroid treatment to control painful symptoms. Both the US Food and Drug Administration and The European Medicines Agency recommend intermittent, short-term (i.e., 2 week) use of topical tacrolimus. In the present cohort tacrolimus was used to control the pain quickly and to manage flare-ups and the patient then reverted to the first line treatment, topical corticosteroids.

OLP is a chronic disorder with periods of remission and relapse (Xue et al., 2005; Roosaar et al., 2006) and spontaneous remission is rare (Bidarra et al., 2008). A substantial number of present patients still had oral mucosal lesions, mainly white or atrophic lesions, at the end of the data collection period. However, persistence of these lesions does not necessarily correlate with symptoms and considered improvement from the original status (Carbone et al., 2009a). Erosion and ulceration are commonly resolved with treatment; while other lesions, such as the lichenoid and white lesions, are more persistent and perhaps unlikely to resolve with any topical and/or systemic agents.

Most of the patients who experienced ASEs were prescribed topical tacrolimus (18 patients). Topical tacrolimus is associated with a number of local ASEs (Corrocher et al., 2008) however most of these are transient and resolve when the patient stops the medication or have resolution of their mucosal erosions. Patients reported tingling, peppery taste and taste disturbance, stinging sensation, and irritation. There were minimal ASEs reported by patients receiving topical corticosteroids, and included burning sensation and worsening of gastroesophegeal reflux developed in 2 patients reflecting the high safety profile of these agents.

The malignant potential of OLP is an area of controversy (Lodi et al., 2005a). In the present study after a mean observation period of 2.2 years, one patient developed neoplasia in the 86 patients treated with tacrolimus while none of the 100 patients receiving other therapies developed any oral tumors in pre-existing OLP lesions. However both dysplasia and

neoplasia, which developed in patients who received tacrolimus therapy, developed in sites other than the original site of the biopsy thus it, cannot be concluded that the tacrolimus was the cause of malignant transformation. Although the atrophic and erosive forms of OLP have been reported to present a higher malignancy risk compared with other forms of the disease, (Markopoulos et al., 1997), a recent report (Carbone et al., 2009a) found that atrophic and erosive lesions are not at higher risk than other OLP forms and the presumed malignant potential is not affected by the type of the therapeutic agents used in the management of OLP. Although these authors did not investigate the risk of topical tacrolimus these observations may give weight to the notion that tacrolimus is not a significant co-factor in the malignant transformation risk of OLP.

The main limitation of the present study is its retrospective design and associated methodological inadequacies, including differences in reporting clinical features and outcomes, and variations in diagnostic and monitoring procedures.

There is a need to uniformly define terms such as relapse, flare-up, and resolution therapeutic response and to conduct well-designed, controlled randomized studies. A standardized method of reporting signs and symptoms during routine clinical reviews is important to obtain maximum benefit of patient's observations as this represents a useful source of information for evaluating long-term outcomes and the efficacy of different therapies. Clinicians should include clear information on dosage, form and preparation, and duration of the therapeutic agents used in different treatment stages in each patient chart.

Patient records should also contain all clinical, histopathological, serological, haematological test results. A clear clinical charting of the mucosal lesions utilizing the appropriate scoring systems, at least one of the available invalidated systems used in previous published papers. The present study showed the need of establishing a simple, widely accepted

standardized scoring system to record the oral lesions of immune-mediated disorders, including OLP, which will help researchers and practitioners better evaluate a patient's condition and needs and to evaluate the efficacy of different agents used in the management of oral mucosal lesions.

In addition, establishment of national and international registers (although there are some in some countries) for rare diseases will help us to understand various aspects of these disorders including the most effective treatment options.

2.6 CONCLUSION

The results of this study indicate that symptomatic OLP remains difficult to manage. Tacrolimus is not superior to topical corticosteroids, and malignant transformation is rare with topical corticosteroids and/or tacrolimus.

Table 2.1 Example of some studies that reported patients with oral lichen planus*

Author year	No. of patients	Age (range) years	Gender		F:M ratio	Gingivae	Skin	Genitalia
			F	M				
Carbone et al., 2009a	808	Men (58.3) and women (61.4) (45.9-74.7)	493	315	1.6:1	33%	63	24
Bermejo-Fenoll et al., 2009	550	56.4 (42.8-70)	442	128	3.5:1	-	-	-
Pakfetrat et al., 2009	420	41.6 (13-75)	273	147	1.9:1	-	15.5%	-
Camacho-Alonso et al., 2007	213	NR** (14-90)	170	43	4:1	82 (38.4%)	0	0
Ingafou et al., 2006	690	52 (16-83)	439	251	1.8:1	145	-	11
Xue et al., 2005	674	50.4 (10-78	444	230	1.9:1	205	77 (11.4%)	-
Mignogna et al., 2005	700	NR (18-83)	420	280	1.5:1	336 (48%)	-	-
Eisen, 2002	723	NR (13-82)	544	179	3.1:1	401	-	-
Chainani-Wu et al., 2001	229	55 (NR)	154	75	2.1:1	-	26 (11.4%)	-

* Cohorts of >200patients in last 10 years. ** NR: Not reported

Table 2.2 Studies reporting the prevalence of Hepatitis C virus in patients with lichen planus

Study	Year	Country	Study group (LP)			Control group		
			Patients		HCV seriopositive	No	Origin	HCV seriopositive
			Total	Pts with OLP				
Stojanovic et al.,	2008	Slovenia	173	71	2	218	Dermatology patients	0
Michele et al.,	2007	Italy	79	79	9	466	Acute trauma (orthopaedic)	25
Amer et al.,	2007	Egypt	30	NR	21	30	Dermatology patients	1
Ali and Suresh	2007	Saudi Arabia	40	40	0	40	Dental patients	0
Yarom et al.,	2007	Israel	62	62	3	65	Other oral mucosal lesions	1
						225452	Volunteer blood donors	240
Das et al.,	2006	India	104	NR	2	150	HIV-I and II and HCV negative?	0
Laeijendecker et al.,	2005	Netherlands	100	100	0	100	Psoriasis vulgaris	0
Rahnama et al.,	2005	Iran	66	NR	1	140	Blood donors	3
Asaad and Samadani	2005	Saudi Arabia	114	7	30	65	Volunteers from relatives	3
Karavelioglu et al.,	2004	Turkey	41	NR	2	18360	Blood donors	459
Ghodsi et al.,	2004	Iran	146	NR	7	319375	Blood donors	309
Harman et al.,	2004	Turkey	128	52	8	128	Healthy persons	1
Bokor-Bratic,	2004	Serbia	48	48	0	60	Dental patients	0
Chung et al.,	2004	Taiwan	32	32	14	1034	Community-based sample	287

Table 2.2 (Cont.) Studies reporting the prevalence of Hepatitis C virus in patients with lichen planus

Study	Year	Country	Study group (LP)			Control group		
			Patients		HCV seriopositive	No	Origin	HCV seriopositive
			Total	Pts with OLP				
Lodi et al.,	2004	Italy	303	303	58	278	Dental patients	9
Denli et al.,	2004	Turkey	140	NR	7	280	Dermatosis other than LP	4
Gimenez-Garcia and Perez-Castrillon	2003	Spain	101	53	9	99	Dermatology patients	2
Klanrit et al.,	2003	Thailand	60	60	4	60	Dental healthcare workers	0
Garg et al.,	2002	Nepal	64	29	0	43	Unknown	0
Daramola et al.,	2002	Nigeria	57	NR	9	24	A. Dermatology patients	6
						24	B. Healthy subjects	0
Figueiredo et al.,	2002	Brazil	68	68	6	726	Sao Paulo residents	14
Beaird et al.,	2001	USA	24	NR	4	20	Dermatology patients	1
Erkek et al.,	2001	Turkey	54	7	7	54	Dermatology patients	2
Kirtak et al.,	2000	Turkey	73	27	5	73	Dermatology patients	1
Ibrahim et al.,	1999	Egypt	43	NR	9	30	Dermatology patients	3
Tucker et al.,	1999	UK	45	13	0	32	Dermatology patients	1
Chuang et al.,	1999	USA	22	NR	12	40	Psoriasis patients	10
						149756	Volunteer blood donors	255
Mignogna et al.,	1998	Italy	263	263	76	100	Dental patients	3
Ingafou et al.,	1998	UK	55	0	0	110	Dental healthcare worker	0
Ilter et al.,	1998	Turkey	1998	75	0	75	Dermatology patients	0

Table 2.2 (Cont.) Studies reporting the prevalence of Hepatitis C virus in patients with lichen planus

Study	Year	Country	Study group (LP)			Control group		
			Patients		HCV seriopositive	No	Origin	HCV seriopositive
			Total	Pts with OLP				
Bagan et al.,	1998	Spain	100	100	23	100	Healthy individuals	5
Dupin et al.,	1997	France	102	102	8	306	Surgical patients	14
Imhof et al.,	1997	Germany	84	45	13	87	Dermatology patients	1
Sanchez-perez et al.,	1996	Spain	78	56	16	82	Dermatology patients	2
Carrozzo et al.,	1996	Italy	70	70	19	70	Unrelated oral keratosis	3
Tanei et al.,	1995	Japan	45	37	17	45	Surgical patients	3
Gimenez-arnau	1995	Spain	25	NR	11	18	NR	1
Bellman et al.,	1995	USA	30	NR	7	41	Dermatology patients	2
Cribier et al.,	1994	France	52	4	2	112	Dermatology patients	3
Santander et al.,	1994	Spain	50	NR	19	27	Dermatology patients	1
Narayan et al.,	1998	India	75	NR	2	30	Healthy controls	0
Chuang et al.,	1999	USA	22	NR	12	40	Psoriasis patients	10
						149756	Volunteer blood donors	255

*Modified from Lodi et al., 2004 and Shengyuan et al., 2009

Table 2.3 Studies reporting the malignant potential and systemic disorders that may be associated with OLP

Authors year	Patients No.	Malignancy	Liver disease	Diabetes	Hypertension
Carbone et al., 2009a	808	15 (1.9%) patients (3 men and 12 women; mean age; 67 [range; 57.7-67.3 years])	More than 164 (20%) patients had liver abnormalities 137 were hepatitis C positive	1	12
Bermejo-Fenoll et al., 2009	550	5 (0.9%)	17% had positive hepatitis C markers	NR	NR
Fang et al., 2009	2119	23 (1.1%) (mean age; 52 years; 12 women and 11 men).	NR	NR	NR
Pakfetrat et al., 2009	420	Dysplasia (7.1%), OSCC (0.07%) (2 males, 1 female)	NR	NR	NR
Ingafou et al., 2006	690	OSCC (12 pts) and carcinoma in situ (1 pt)	NR	NR	NR
Xue et al., 2005	674	4 (0.6%)	NR	78 (11.6%)	NR
Mignogna et al., 2005	700	21 (3%)	NR	NR	NR
Eisen, 2002	723	6 (0.8%)	4 patients had hepatitis C	5%	21%
Chainani-Wu et al., 2001	229	4 (1.7%)	Hepatitis C in 14/31 tested patients	10	43
Bagán-Sebastián et al.,1992	205	-	40 patients had chronic liver disease	27	-

Table 2.4 Studies reporting the efficacy of different therapeutic agents in the management of oral lichen planus

Agent	Study/Year	Dose	Study type	No of Pt's	Results	Adverse side effects
Clobetasol propionate (0.025 or 0.05%) + miconazole gel + 0.12% chlorhexidine mouth rinse	Carbone et al., 2009	Twice a day for 2 months	Randomized controlled trial	25	No difference between the 2 formulations	No ASEs.
Clobetasol ointment + miconazole + 0.12% chlorhexidine ± prednisone	Carbone et al., 2003	Clobetasol 1-2 times/day Prednisone (50 mg/day)	Comparative study	49	Effective	All ASEs associated with systemic prednisone and including: elevation of blood pressure, epigastric pain, and water retention.
Clobetasol propionate ointment (different preperations)	Lo Muzio et al., 2001	2-3 times/day	Randomized	24/54	Effective	Pseudomembranous candidiasis.
Clobetasol ointment (0.05%)/ fluocinonide ointment (0.05%) + miconazole gel and 0.12% chlorhexidine mouthwashe	Carbone et al., 1999	-	Placebo-controlled, comparative	60	Effective	None.
Fluocinolone acetonide (0.1% solution and/or orabase)	Thongprasom et al., 2003	1-3 times/day	Retrospective	97	Effective	Oral candidiasis.
Fluticasone propionate spray/ betamethasone sodium phosphate mouthrinse	Hegarty et al., 2002	4 times/day	Randomize, crossover	48	Effective	All ASEs associated with fluticasone spray and including: nausea, swollen mouth, bad taste and smell, difficulty in spray application, dry mouth, sore throat, red, painful tongue and pseudomembranous candidosis.

Table 2.4 (Cont.) Studies reporting the efficacy of different therapeutic agents in the management of oral lichen planus

Agent	Study/Year	Dose	Study type	No of Pt's	Results	Adverse side effects
Fluocinonide gel (0.05%)/ fluocinonide ointment in Orabase (0.05%)/ clobetasol gel (0.05%)/ clobetasol ointment in orabase (0.05%)	Chainani-Wu et al., 2001	1-4 times/day	Retrospective, descriptive	229	Effective	Oral candidiasis.
Fluocinolone acetonide (0.1% gel or oral base)	Buajeeb et al., 2000	4 times/day	Randomized	48	Effective	No significant ASEs.

Table 2.4 (Cont.) Studies reporting the efficacy of different therapeutic agents in the management of oral lichen planus

Agent	Study/Year	Dose	Study type	No of Pt's	Results	Adverse side effects
Topical pimecrolimus	Volz et al., 2008	Twice/day Pimecrolimus 1% cream	Randomized controlled	20	Effective	Burning sensations and slight paraesthesia in 5/10 patients
	Dissemond, 2008	Twice/day Pimecrolimus adhesive ointment (0.5%) (1:1 of 1% cream and a hydrophilic adhesive gel base)	Case report	1	Effective	None
	Erkek et al., 2007	Pimecrolimus 1% cream	Case report	1	Effective (used for remission maintenance	Not reported
	Gorouhi et al., 2007	4 times/day Pimecrolimus 1% cream	Randomized	40	Effective	Transient burning sensation in 2 patients
	Passeron et al., 2007	Twice/day Pimecrolimus 1% cream	Randomized controlled	12	Effective	Transient burning sensation in 2 patients
	Scheer et al., 2006	Twice/day Pimecrolimus 1% cream	Case series	5	Effective	Difficult application
	Swift et al., 2005	Twice/day Pimecrolimus 1% cream	Randomized controlled	20	Effective	Transient burning sensation in 1 patient
	Dissemond et al., 2004	Twice/day Pimecrolimus 1% cream	Case report	1	Effective	Transient burning sensation
	Esquivel-Pedraza et al., 2004	2-5 times/day Pimecrolimus 1% cream	Case series	3	Effective	None

Table 2.4 (Cont.) Studies reporting the efficacy of different therapeutic agents in the management of oral lichen planus

Agent	Study/Year	Dose	Study type	No of Pt's	Results	Adverse side effects
Topical tacrolimus	Corrocher et al., 2008	0.1% ointment 4 times/day	Controlled, randomized,	32	Effective	Transient (4-5 days) worsening of burning sensation in 9/16 patients.
	Radfar et al.,2008	1-4 times/day	Controlled, randomized	30	Effective	-
	Tavassol et al., 2008	0.1% ointment twice daily	Case series	11	Effective	Rare and minor (not specified)
	Erkek et al., 2007	-	Case report	1	Effective	-
	Chaudhry et al., 2007	0.1% ointment twice daily	Case report	1	Effective	-
	Rabanal et al., 2007	0.1 % ointment twice daily	Case report	1	Effective	-
	Becker et al., 2006	0.1% ointment twice daily	Case report	1	Effective	Development of squamous cell carcinoma at the same site of application of tacrolimus.
	Lozada-Nur et al, 2006	0.1% tacrolimus in Orabase, 3 times/day for 14 days	Case series	10	Effective	Recurrent headache (1 patient), transient burning sensation (1).
	Shichinohe et al., 2006	0.1% tacrolimus, twice daily	Case report	2	Effective	None.
	Laeijendecker et al., 2006	0.1% ointment, 4 times/day for 6 weeks.	Randomized controlled	40	Effective	Temporary burning/stinging sensation in 8/20.
	Riano Arguelles et al., 2006	0.1% tacrolimus once daily	Case report	1	Effective	-
	Donovan et al., 2005	0.1% tacrolimus	Case report	1	Effective	-

Table 2.4 (Cont.) Studies reporting the efficacy of different therapeutic agents in the management of oral lichen planus

Agent	Study/Year	Dose	Study type	No of Pt's	Results	Adverse side effects
Topical tacrolimus	Fricain et al., 2005	1% tacrolimus, twice/day for 8 weeks	Case report	1	Effective	Mucosal pigmentation.
	Byrd et al., 2004	0.03% and/or 0.1% tacrolimus	Retrospective	37	Effective	Local irritation (4 patients), burning (5), tingling sensation (3), and dysgeusia (2).
	Shen and Pedvis-Leftick, 2004	0.1% ointment twice/day for 9 months	Case report	1	Effective	Temporary brown discoloration of oral mucosa.
	Thomson et al., 2004	0.1% tacrolimus in Orabase, 1-2 times/day	Retrospective	23	Effective	Parasthesia and burning sensation (6), dysguesia (1), dysguesia and nausea (1).
	Hodgson et al., 2003	0.1% tacrolimus in paraffin ointment twice/day	Retrospective	50	Effective	Burning sensation (8), dysgeusia (5), and headache (2).
	Olivier et al., 2002	Tacrolimus mouthwash (0.1 mg/100 mL of distilled water). 4 times/day for 6 months	Case series	8	Effective	Transient burning sensation (3), dry mouth (2).
	Kaliakatsou et al., 2002	0.1% tacrolimus in a paraffin ointment base	Case series	17	Effective	Tingling and burning sensation, altered taste sensation, slight nausea, mild headache and constipation.
	Morrison et al., 2002	Tacrolimus 0.1% ointment or in mineral oil. 2-3 times/day for 3 months	Case series	6	Effective	None
	Rozycki et al., 2002	Tacrolimus ointment (0.03%, 0.1%, and 0.3%).	Retrospective	13	Effective	Burning sensation (1 patient), sore throat (1).
	Lener et al., 2001	0.1% Tacrolimus, twice/day for 3 months	Case report	1	Effective	-
	Vente et al., 1999	0·1% ointment, twice/day for 4 weeks	Case series	4	Effective	Burning sensation.

Table 2.4 (Cont.) Studies reporting the efficacy of different therapeutic agents in the management of oral lichen planus

Agent	Study/Year	Dose	Study type	No of Pt's	Results	Adverse side effects
Rapamycin	Soria et al., 2009	Topical rapamycin (1 mg/ml) twice a day for 3 months	Open prospective	7	Effective	Local discomfort and detectable blood sirolimus levels.
Hyaluronic acid 0.2%	Nolan et al., 2009	-	Randomized, placebo-controlled, double blind trial	124	Effective	-
Topical isotretinoin (0.05% and 0.18% concentrations)	Scardina et al., 2006	Twice/day	Randomized	70	Effective	Transit increase in soreness, pain and sensitivity to hot foods
Sulodexide	Femiano and Scully, 2006	Oral sulodexide (250 units) 1-2 times/day	Open trial	12	Effective	Dizziness, vomiting, and hot flushes.
Intralesional triamcinolone acetonide	Xia et al., 2006	0.5 ml (40 mg/ml)	Controlled, short-term	45	Effective	None.
Methylene blue-mediated photodynamic therapy	Aghahosseini et al., 2006	Patients gargle with 5% methylene blue solution in water for 5 minutes and after 10 minutes mucosal lesions irradiated by laser light (lambda = 632 nm, light exposure dose = 120 J/cm^2).	Open label	13	Effective	Mild burning sensation.
Tazarotene gel 0.1%	Petruzzi et al., 2002	Twice/day	Randomize, controlled	12	Effective	Transit burning sensation and taste abnormalities.
Prednisone ± azathioprine	Chainani-Wu et al., 2001	Prednisone 40-80 mg/day Azathioprine 50-100 mg/day	Retrospective, descriptive	229	Effective	Insomnia, mood swings, fatigue and water retention, headaches, nausea, dizziness, diarrhea, increase in urinary frequency and increased appetite.

Table 2.5 Age of 186 oral lichen planus patients

Age	Male	Female	Frequency	%
10-19	2	0	2	1.1
20-29	1	4	5	2.7
30-39	5	13	18	9.7
40-49	10	30	40	21.5
50-59	21	37	58	31.2
60-69	7	31	38	20.4
70-79	6	15	21	11.3
80-89	0	1	1	0.5
90-99	1	2	3	1.6
Total	53	133	186	100

Table 2.6 Ethnicity of patients with oral lichen planus

Ethnic group	Frequency	%
White British	90	48.4
Other White	9	4.8
Mixed-White and Asian	2	1.1
Asian-Indian	32	17.2
Asian-Pakistani	4	2.2
Asian-Bangladeshi	4	2.2
Chinese	1	0.5
Asian-other Asian	10	5.4
Black-Caribbean	1	0.5
Black-African	2	1.1
Black-other Black	1	0.5
Other ethnic group	11	5.9
Unknown	19	10.2
Total	186	100

Table 2.7 Referral pattern of oral lichen planus patients

Source of referral	Frequency	%
General dental practitioners	103	55.4
Oral maxillofacial/oral surgeons	35	18.8
General medical practitioners	12	6.5
Dermatology	6	3.2
Periodontology	8	4.3
Restorative dentistry	2	1.1
Prosthodontics	2	1.1
Otolaryngology	2	1.1
Others	7	3.7
Unknown	9	4.8
Total	186	100

Table 2.8 Past medical history at first visit to oral medicine clinic of 186 patients with oral lichen planus

Condition		No.	%
Allergy	Penicillin	18	9.7
	Aspirin	2	1.1
	Hay fever	9	4.8
	Others	19	10.2
Cardiovascular	Hypertension	42	22.6
	Angina	3	1.6
	Others	9	4.8
Respiratory	Asthma	16	8.6
	Bronchietasis	1	0.5
	Chronic obstructive pulmonary disease	2	1.1
	Pneumonia	3	1.6
	Sinus problems	3	1.6
Haematological	Anaemia	10	5.4
	Thalassemia	3	1.6
	Thrombocytopenia	1	0.5
Endocrine	Diabetes mellitus	21	11.3
	Thyroid dysfunction	18	9.7
Gastrointestinal tract	Coeliac disease	3	1.6
	Hepatitis (type unknown)	9	4.8
	Jaundice (cause unknown)	6	3.2
	Gastric ulceration	5	2.7
	Ulcerative colitis	2	1.1
	Barrett's oesophagitis	1	0.5
	Constipation	1	0.5
	Diverticulitis	3	1.6
	Haemorrhoids	2	1.1
	Hernia (inguinal)	8	4.3
	Irritable Bowel Syndrome	4	2.2
	Duodenal ulcer	2	1.1
	Perianal irritation	1	0.5
	Gastro-oesophageal reflux disease	3	1.6
	Oesophegeal varices	1	0.5
	Others	2	1.1
Genito-urinary	Renal disease	4	2.2
	Urinary tract disease	5	2.7
Visual		13	7.0
Hearing		7	3.8
Central nervous system	Epilepsy	2	1.1
	Stroke	2	1.1
Mental health	Psychiatric problems (varies)	11	5.9
Others	Acne, acoustic neuroma, alopecia, arthritis, back pain, breast cancer, carpal tunnel syndrome, cerebrovascular accident, cervical cancer, hypercholesterolemia, cystitis, dermatitis, dry skin and "skin lesions", eczema, fibroid, "frozen shoulder", gout, knee pain, lichen sclerosus, limited scleroderma (CREST syndrome), lumber spondylosis, migraine, migraine-like disease, oesophageal varices, osteoarthritis, osteoporosis, polymyalgia rhumatica, primary billary cirrhosis, prolapsed bowel, psoriasis, radiotherapy for prostate cancer, Reynaud's syndrome, rheumatoid arthritis, rheumatic fever, sarcoidosis, sciatica, Sjogren's syndrome, vasculitis, vitiligo, vulvo-vaginal dryness, wart-like lesions.		

Table 2.9 Past drug history of patients with oral lichen planus

Drug group	Drug name	No.
Cardiovascular	Calcium-channel blockers	
	Amlodipine	8
	Nifedipine	3
	Verapamil HCL	1
	Diltiazem hydrochloride	1
	Felodipine	1
	Beta-adrenoceptor blocking drugs	
	Propranolol	3
	Atenolol	13
	Sotalol	1
	Potassium-channel activators	
	Nicorandil	2
	Diuretics	
	Bendroflumethiazide	7
	Frusmide	2
	Amiloride	1
	Spironolactone	1
	Indapamide	1
	Angiotensin converting enzyme inhibitors	
	Losartan potassium	2
	Ramipril	2
	Valsartan	1
	Enalapril	5
	Others	
	Digoxin (cardiac glycosides)	1
	Co-amilofruse	1
	Simvastatin	11
	Atorvastatin	5
	Pravastatin	1
	Isosorbide mononitrate	2
	Isosorbide dinitrate	2
	Glyceryl trinitrate	3
	Valsartan	1
	Salmeterol (long-acting beta 2 adrenergic receptor agonist)	1
	Candesartan cilexetil (angiotensin-II receptor antagonists)	1
	Irbesartan (angiotensin-II receptor antagonists)	1
	Navispare® (amiloride with thiazides)	1
	Clopidogrel (antiplatelet)	1
	Candesartan (angiotensin-II receptor antagonists) a	1
	Prazosin (alpha-adrenoceptor blocking)	1
Respiratory	Beclomethasone dipropionate (corticosteroids)	1
	Salbutamol (selective beta 2 agonists)	10
	Salmeterol (selective beta 2 agonists)	1
	Terbutaline sulphate	1
	Ipratropium (anticholinergic drug)	3

Table 2.9 (Cont.) Past drug history of patients with oral lichen planus

Drug group	Drug name	No.
Endocrine	Thyroid hormones	
	Thyroxin	18
	Levothyroxine sodium	1
	Antidiabetic	
	Insulin	6
	Metformin	10
	Glibenclamide	2
	Gliclaside	3
	Glipizide	1
	Rosiglitazone	2
	Vitamin D	
	Adcal-D3	2
	Calcichew	3
	Other	14
	Hormone replacement therapy	
Gastrointestinal	Rantidine (H2-receptor antagonists)	5
	Cimetidine (H2-receptor antagonists)	2
	Sulfasalazine (aminosalicylates)	1
	Lansoprazole (proton pump inhibitors)	4
	Omeprazole (proton pump inhibitors)	10
	Salazopyrin (aminosalicylates)	1
	Mesalazine	1
	Loperamide hydrochloride	2
	Gaviscon (compound alginates)	2
	Ursodeoxycholic acid (drugs affecting biliary composition and flow)	1
Central nervous system	Temazepam (benzodiazepines)	1
	Flurazepam (benzodiazepines)	1
	Diazepam (benzodiazepines)	1
	Prothiaden (tricyclic antidepressants)	1
	Fluoxetine (antidepressant)	1
	Carbamazepine (antiepileptic drugs)	2
	Phenytoin (antiepileptic drugs)	1
	Nortriptyline (tricyclic antidepressants)	1
	Amitriptyline (tricyclic antidepressants)	3
	Venlafaxin (antidepressants)	1
	Clomipramine hydrochloride (tricyclic antidepressants)	1
Corticosteroids	Topical	
	Betamethasone	1
	Clobetasol propionate	1
	Fluticansone propionate (flixonase spray)	3
	Betamethasone esters	3
	Mometasone furoate	1
	Fluocinolone acetonide	1
	Systemic	
	Prednisolone	4
Vitamins, nutrition and blood	Ferrous sulphate	3
	Folic Acid	1
	Iron supplements	11
	Ferrous gluconate	1
	Vitamin B-12	1
	Vitamin E	1
	Vitamin K	1
	Pharmaton (multivitamins and minerals)	1

Table 2.9 (Cont.) Past drug history of patients with oral lichen planus

Drug group	Drug name	No.
Bone metabolism	Alendronic acid	4
	Etidronate disodium	1
Others	Aspirin	17
	Feverfew (migraine)	1
	Co-codamol (headache)	1
	Acetaminophen (paracetamol)	6
	Coproxamol (paracetamol and dextropropoxythene)	1
	Co-dydramol (paracetamol and dihydrocodeine tartrate)	1
	Diclofenac sodium (NSAIDs)	2
	Napratec (NSAIDs)	1
	Ibuprofen (NSAIDs)	5
	Etoricoxib (NSAIDs)	1
	Arthrotec® (diclofenac with misoprostol, NSAIDs)	2
	Voltarol gel patch® (topical NSAIDs)	1
	Coproxamol (compound analgesic preparations)	1
	Tramadol hydrochloride (opioid analgesics)	1
	Hydroxychloroquine (antimalarials)	1
	Terbinafine hydrochloride (antifungal)	1
	Aciclovir (antiviral drugs)	1
	Oxytetracycline (antibacterial)	1
	Clotrimazole (antifungal)	1
	Biotène Oralbalance® (dry mouth treatment)	1
	SST tablets (dry mouth treatment)	1
	Salivix® (dry mouth treatment)	1
	Betahistine dihydrochloride (used in nausea and vertigo)	1
	Allopurinol (anti-gout)	2
	Premique® (conjugated oestrogens with progestogen)	1
	Hypromellose (ocular lubricants)	1
	Cosopt® Eyedrops (treatment of glaucoma)	1
	Lacrilube ointment	1
	Hydroxyzine hydrochloride (antihistamines)	1
	Oxybutynin (anticholinergic agent for urinary and bladder)	1

Table 2.10 Different therapeutic agents prescribed to patients to manage OLP lesions before attending the Oral Medicine clinics

Drug group	Drug name	No of patients
Corticosteroids	Topical	
	Triamcinolone acetonide in 0.1% carmellose paste (Adcortyl in Orabase)	28
	Hydrocortisone sodium succinate (Corlan pellets)	24
	Betamethasone sodium phosphate (Betnesol)	19
	Beclomethasone (Bectoid)	11
	Fluticasone propionate (Flixonase spray)	9
	Clobetasol propionate (Dermovate)	1
	Tri-adcortyl (Triamcinolone, nystatin, neomycin, gramicidin)	1
	Prednisol mouthwash	1
	Other topical corticosteroids	7
	Systemic	
	Prednisolone	9
	Intralesional corticosteroids	1
Anti-infective agents	Anti-viral	
	Aciclovir	1
	Antibiotics	
	Metronidazole	5
	Others (not specified)	5
	Anti-fungal	
	Miconazole	4
	Nystatin	5
	Amphotericin B	1
	Fluconazole	5
	Others (not specified)	6
Calcinurin inhibitors	Ciclosporin (mouthwash)	2
	Topical tacrolimus (protopic)	1
Others	Azathioprine	2
	Bonjela®	2
	Chlorhexidine gluconate	24
	Benzydamine hydrochloride (Difflam)	16
	Hydrogen peroxide	1
	Laser ablation	1

Table 2.11 Histopathological features of 158 biopsies of patients with oral lichen planus

Histopathological features	Total
Thickening of basement membrane	29
Irregular/hyperplasia of rete ridges	13
Pigmentary incontinence	11
Positive direct immunofluorescent (fibinogen)	17
Positive direct immunofluorescent (C3)	2
Apoptosis	18
Cytoid bodies	6
Civatte (colloid) bodies	12
Increase mitosis	1
Cell atypia	4
Dysplasia (mild)	2
Fungal infection	13
Bacterial infection	1

Table 2.12 Distribution of oral lichen planus lesions

Site	Frequency	%
General distribution		
Bilateral	132	71.0
Right	9	4.8
Left	11	6.0
Unknown	34	18.3
Buccal mucosa	127	68.3
Right	114	61.3
Left	109	58.6
Labial mucosa	6	3.2
Upper	3	1.6
Lower	5	2.7
Tongue	71	38.2
Dorsum	24	13.0
Lateral border	49	26.3
Ventral surface	13	7.0
Gingivae/desquamative gingivitis	95	51.1
Soft Palate	3	1.6
Hard Palate	8	4.3
Floor of the mouth	5	2.7

Table 2.13 Different therapeutic agents used to control oral mucosal lesions in group A (patients not prescribed topical tacrolimus)

Agent	Frequency	%
Topical agent		
Fluticasone propionate- 0.05% cream (Cutivate)	23	23
Clobetasol propionate- 0.05% cream (Dermovate)	8	8
Fluticasone propionate,400 mcg in 15 mL of water as mouthwash	6	6
Fluticasone propionate,50 mcg per puff-(Flixonase)	61	61
Fluticasone propionate- 125 mcg per puff-(Flixotide Evohaler)	7	7
Prednsole mouthwash	3	3
Betamethasone mouthwash	58	58
Beclomethasone dipropionate 50, 100 or 250mcg per puff-(Bectoide)	2	2
Triamcinolone acetonide in 0.1% carmellose paste	32	32
Hydrocortisone hemisuccinate pellets	5	5
Mometasone furoate 0.1% cream	1	1
Intralesional triamcinolone acetonide	1	1
Ciclosporin mouthwash	3	3
Systemic agent		
Prednisolone	2	2
Azathioprine	1	1
Mycophenolate Mofetil	1	1
Pentoxifylline	1	1

Table 2.14 Different therapeutic agents used to control oral mucosal lesions in group B (patients prescribed topical tacrolimus)

Agent	Frequency	%
Topical agent		
Fluticasone propionate- 0.05% cream (Cutivate)	54	62.8
Clobetasol propionate- 0.05% cream (Dermovate)	26	30.2
Fluticasone propionate,400 mcg in 15 mL of water as mouthwash	18	21.0
Fluticasone propionate,50 mcg per puff-(Flixonase)	54	62.8
Fluticasone propionate- 125 mcg per puff-(Flixotide Evohaler)	6	7.0
Betamethasone mouthwash	59	68.6
Beclomethasone dipropionate 50, 100 and 250 mcg per puff-(Bectoide)	3	3.5
Triamcinolone acetonide in 0.1% carmellose paste	25	29.1
Hydrocortisone hemisuccinate pellets	7	8.1
Intralesional triamcinolone acetonide	1	1.2
Tacrolimus 0.03%	38	44.2
Tacrolimus 0.1%	75	87.2
Ciclosporin mouthwash	7	8.1
Systemic agent		
Prednisolone	8	9.3
Deflazacort	10	11.6
Azathioprine	6	7.0
Mycophenolate Mofetil	3	3.5
Isotretinoin	1	1.2
Tacrolimus	1	1.2

Table 2.15 Clinical features of group A (patients not prescribed topical tacrolimus) at initial and last visit to Oral Medicine

Before therapy	After therapy
43 patients with oral mucosal ulceration/erosion	14 (32.6%) with oral mucosal ulceration/erosion 29 (67.4%) without oral mucosal ulceration/erosion
44 patients with desquamative gingivitis	33 (75.0%) with desquamative gingivitis 11 (25.0%) without desquamative gingivitis

Table 2.16 Clinical features of group B (patients prescribed topical tacrolimus) at initial and last visit to Oral Medicine clinic

Before therapy	After therapy
52 patients with oral mucosal ulceration/erosion	23 (44.2%) with oral mucosal ulceration/erosion 29 (55.8%) without oral mucosal ulceration/erosion
41 patients with desquamative gingivitis	20 (48.8%) with desquamative gingivitis 21 (51.2%) without desquamative gingivitis

Table 2.17 Clinically apparent and patient-reported drugs reactions

Drugs involved	Adverse Drug Reaction	Frequency
Systemic agents		
Mycophenolate mofetil	Bladder irritation and haematuria	1
Azathioprine	Nausea	2
	Vomiting	3
	Rash	1
	Fever	1
	Headache	1
	Dizziness	1
	Malaise	1
Systemic tacrolimus	Diarrhoea	1
Topical agents		
Betamethasone (Betnesol)	Nausea	1
	Worsening gastric reflux	1
Clobetasol propionate (Dermovate)	Burning sensation	1
Fluticasone propionate (Cutivate)	Rash	1
	Pseudomembranous candidosis	1
	Nausea	1
	Burning and local stinging	1
Prednesol mouthwash	Mouth dryness	1
Topical tacrolimus	Local tingling	6
	Burning sensation	3
	Peppery taste	3
	Stinging sensation	2
	Taste disturbance	2
	Local irritation	2
	Indigestion	2
	Nausea and vomiting	1
	Tiredness and anxiety	1

CHAPTER 3
OROFACIAL GRANULOMATOSIS

3.1 INTRODUCTION

Orofacial granulomatosis (OFG) is an uncommon disorder characterised by recurrent or persistent swelling of the orofacial tissues. In addition, ulceration and a variety of other oral mucosal and facial anomalies can occur. The term granulomatosis reflects the chronic inflammatory nature of OFG which is often characterized by the presence of granulomas in sub-epithelial stroma (Wiesenfeld et al., 1985; Leao et al., 2004). The concept of OFG was initially introduced by Wiesenfeld and co-workers in 1985, with the aim of encompassing into a single entity those patients whose oro-facial clinicopathological features resembled Crohn's disease but who did not have characteristic gastrointestinal findings of the inflammatory bowel disease (Wiesenfeld et al., 1985). However, further to Crohn's disease, OFG shows several similarities also with other inflammatory and granulomatous disorders that can affect the head and neck area. Chronic orofacial swelling, with or without ulceration and inflammation of intraoral tissues can be found in sarcoidosis. Orofacial granulomatosis is believed to be aetiopathologically distinct from these disorders as their major distinctive clinical signs, symptoms and/or laboratory changes are typically lacking in patients with OFG. Diagnosis of OFG should be considered only when laboratory, histopathological, clinical and radiological investigations have ruled out the presence of the aforementioned disorders.

When the swelling/inflammatory process akin to OFG only involves the lips the term cheilitis granulomatosa (Miescher's cheilitis) has been applied (Miescher, 1945). However, this is more likely to be a paucisymptomatic form of OFG rather than a separate entity. In addition, relapsing craniofacial neurological and neuro-vegetative manifestations have been described in patients with OFG (Greene and Rogers, 1989). These occur more commonly, but not exclusively, when chronic orofacial swelling is associated with lingua plicata. This triad of signs has been labelled as Melkersson-Rosenthal syndrome. Historically, Melkersson (1928) described a 35 years old patient presented with facial palsy and orofacial swelling. Later, Rosenthal (1932) reported a patient with same clinical features in addition to

fissured tongue which known later as Melkersson-Rosenthal syndrome (MRS). However, MRS may simply represent a subtype of OFG, where orofacial swelling and intraoral mucosal changes are associated with neurological manifestations and frequently, but not always, tongue fissuring.

Orofacial granulomatosis has the potential to cause significant adverse effects upon patient well-being. The swelling of the lips and/or face may be cosmetically unacceptable and may rarely cause difficulties of speech and drooling. The intra-oral ulceration is painful, giving rise to dysphagia and dysarthria and poor dietary intake (Leao et al., 2004).

There is still confusion about OFG, as some authors use the term to describe a spectrum of OFG-like disorders including Melkersson-Rosenthal syndrome, cheilitis granulomatosa, oral Crohn's disease, and sarcoidosis (Pryce and King, 1990; Rogers, 1996; Kolokotronis et al., 1997); however, others restricted it to patients without systemic disease (i.e. Crohn's and sarcoidosis) (Grave et al., 2009; Al Johani et al., 2010). Recently (Tilakaratne et al., 2008) coined the term idiopathic OFG to exclude those patients with systemic disease and recommended re-diagnosing patients who subsequently develop intestinal involvement.

Both OFG and the oral manifestations of Crohn's disease are similar and the histopathological features are indistinguishable. The exact relationship between the two conditions remains unclear. However, Sanderson and co-workers (2005) suggested that OFG is different from Crohn's disease as the aetiology for OFG is most likely related to dietary habits and diet modification is more likely to benefit children with OFG than those with Crohn's. In addition, the inflammatory response in the intestinal mucosa differs between the two disease processes as the intestinal mucosa of OFG patients seems to have more granulomas than that from Crohn's disease (Sanderson et al., 2005).

3.1.1 Epidemiology

As OFG is an uncommon disorder, epidemiological data are sparse. However, clinical experience from centres where OFG patients are more frequently referred suggests that the incidence of OFG is increasing (Rees, 1999; Leao et al., 2004). OFG may develop at any age and there is no gender or racial predilection (Alawi, 2005; Lourenco et al., 2008) (Table 3.1). However the clinical experience of colleagues in London (SR Porter, C Scully and T Hodgson) suggests that OFG tends to arise in early adulthood. Nevertheless, as OFG is uncommon in childhood, children with features of possible OFG should be investigated for intestinal Crohn's disease (Khouri et al., 2005).

3.1.2 Clinical features

The clinical manifestations of OFG are similar to those of the orofacial features of Crohn's disease and other granulomatous disorders. The clinical features and differential diagnosis of OFG is summarized in Tables 3.2 and 3.3. The clinical features of OFG can be divided into intra-oral and facial/extra-oral.

Intra-oral manifestations

Oral mucosal ulceration, cobblestoning, gingival enlargement (granulomatous gingivitis) and mucosal tags are the most frequent intra-oral manifestations of OFG. Other features may also present including lip fissures (midline and/or angular), labial dryness and erythema. Recently Shakeel et al (2009) reported a patient with tonsillar enlargement as a result of OFG.

Two types of oral ulcers can arise, both of which are recurrent: linear and deep with surrounding raised borders, commonly affecting buccal and/or labial vestibule, and aphthous-like flat round-shaped ulcers that can arise on any non-keratinised surface. Intra-oral ulceration can be associated with painful symptoms and significantly impair quality of life of patients (Somech et al., 2001).

Oral mucosal swelling typically affects the buccal mucosa give rise to notable thickening and folds, sometimes termed cobblestoning. The labial mucosa may occasional be similarly affected.

Gingival enlargement in OFG is not uncommon and indeed the most common affected site in a cohort of 12 cinnamon induced OFG patients (Endo and Rees, 2007). In another study (Lourenco et al., 2008), five of the 29 (17%) patients had gingival involvement. This presented clinically as erythema, oedema of interdental papillae, diffuse gingival infiltration, granular hyperplasia, or gingival enlargement which may associated with bleeding, periodontal fistulae or tooth mobility (Endo and Rees, 2007; Lourenco et al., 2008). Gingival involvement may be localized or generalized, but is commonly affect the anterior mandibular and/or maxillary gingivae which may extend from the free gingival margin on to the non-keratinised mucosa (Wiesenfeld et al. 1985; Lourenco et al., 2008). The gingival inflammation is different from plaque-induced or non-specific gingivitis as it clinically appears more granular.

Tongue fissuring can be present and this sometimes, but not always, associated with increases in the risk of neurological manifestations (Greene and Rogers, 1989). Fissures may be large with multiple grooves or single and central (Worsaae et al., 1982; Greene and Rogers, 1989). The fissures may be deep and can occasionally result in an accumulation of food debris, which may lead to bad taste (dysgeusia), malodour, and burning sensation.

Facial/extra-oral manifestations

Labial/facial swelling represents possibly the major clinical feature OFG and can affect any soft tissues of the head and neck area. Although enlargement of the lip(s) is described to be the most common finding (Wiesenfeld et al., 1985; Sanderson et al., 2005), swelling of the periorbital, zygomatic and mental areas, as well as the maxillary site, can occur (Mignogna et al., 2003). A few case reports have described isolated eyelid involvement (Pierre-Filho Pde et al., 2004; Cocuroccia et al., 2005; Akarsu et al., 2005).

Cervical lymph node enlargements can occasionally occur (James and Ferguson, 1986).

Facial swelling can be widely variable, multiform, and temporary, making early diagnosis of OFG difficult. The swelling can progress through different stages (i) initially, it is soft, non-pitting and recurrent, resembling angioedema, with involved tissues returning to their original size between acute episodes; (ii) eventually, recurrences are followed by a mild, soft permanent increase in size; (iii) finally, the swelling becomes persistent firm, rubbery and/or fibrous (Kauzman et al., 2006). The labial enlargement can affect upper and/or lower lips (Odukoya, 1994; Mignogna et al., 2003). The lips may become dry, and median cheilitis and/or angular cheilitis may develop leading to development of deep vertical cracks which may be painful and bleed during lip movement (Leao et al., 2004). Angular/median cheilitis can be secondarily infected by fungi (candida) and/or bacteria (Leao et al., 2004).

Several neurological manifestations have been described in patients with OFG. A lower motor neurone palsy of the facial nerve can arise in 20-33% of the affected individuals (Zimmer et al., 1992; Worsaae et al., 1982). This may arise months to years before or after tissue swelling (Vistnes and Karnahan, 1971) and can be unilateral or bilateral and partial or complete. Palsy usually resolves with complete recovery; although, some patients may have residual facial weakness (Alexander and James, 1972; Pino Rivero et al., 2005; Khandpur et al., 2006).

The facial palsy may be accompanied by changes in taste, hearing, or earache (Cockerham et al., 2000). The glossopharyngeal and vagus nerves have occasionally been affected (Khandpur et al., 2006). Other reported neurological manifestations include hyperhidrosis, hypogeusia, glossodynia, acroparesthesia, hyperacusia, lacrimation, sweating, migraine-like headache, and blepharospasm (Hornstein, 1973; Stosiek et al., 1992).

Gastrointestinal

The inclusion of gastrointestinal features as part of OFG is controversial. Some clinicians consider the absence of symptoms and signs of gastrointestinal (usually lower bowel) disease to be a key factor of the diagnosis of OFG, although others seem to have a contrasting view. As a consequence the exact relationship between OFG and inflammatory bowel disease is unclear.

There are contradicting results of the frequency of gastrointestinal (GI) involvement in OFG patients as different reports used different methods to investigate the intestinal involvement and there are few detailed studies that have formally investigated GI involvement. However, GI symptoms may not be uncommon in OFG patients. A recent prospective study from Sweden with a follow-up period of 6 to 8 years highlighted the risk of intestinal Crohn's development in younger (9 to 16 years old) OFG patients, as four of the eight patients later developed the condition (Saalman et al., 2009). All affected patients developed GI symptoms within 6 months of the diagnosis of OFG.

Most of published papers on OFG reported no intestinal involvement, and historically OFG was not thought to have any GI involvement and if patients developed GI symptoms they were rediagnosed as having Crohn's disease even before intestinal biopsy. However, some patients may develop asymptomatic intestinal inflammation that differs from that of Crohn's disease (Sanderson et al., 2005). Intestinal involvement in OFG patients who present without gut symptoms ranges between 37% (using rigid sigmoidoscopy and barium studies) to 54% (using ileocolonoscopy and histopathological studies) (Scully et al., 1982; Sanderson et al., 2005). In a detailed study of gastrointestinal involvement in OFG without GI symptoms, histopathological intestinal abnormalities were evident in 19 of 35 OFG patients. Non-caseating granulomas were found in 68.4% of those patients with intestinal abnormalities in the colon, ileum, or both (Sanderson et al., 2005).

The risk of developing intestinal involvement in OFG may be greater in children and younger adults (Sanderson et al., 2005). In a study by van der Waal and co-workers (2002) only two of 13 patients with cheilitis granulomatosa (mean age; 32.8 years) developed Crohn's disease within 5 years. Gastrointestinal examinations are not presently recommended unless there is likely GI disease as suggested by the development of diarrhoea, cramps, perianal fissures or abscesses, poor childhood growth and/or weight loss (Khouri et al., 2005; Ojha et al., 2007).

3.1.3 Aetiopathogenesis

The cause of OFG is unknown and some groups have labelled OFG an idiopathic disorder (Tilakaratne et al., 2008). Current evidence indicates that, after the exclusion of individuals presenting chronic/recurrent orofacial swelling as a result of systemic granulomatous disorders, deep fungal infections, C1 esterase inhibitor deficiency, foreign body, contact, or delayed hypersensitivity reaction, no specific aetiologic agent for OFG has presently been established.

OFG is presently thought to be multifactorial disorder. Several mechanisms have been suggested, such as immunity, infection, and genetic predisposition (Patton et al., 1985; Lim et al., 1997; Sciubba and Said-Al-Naief, 2003).

3.1.3.1 Genetic

The role of genetic factors has been suggested by reports of hereditary cases of OFG associated with neurological manifestations. A potential “susceptibility gene” located at 9p11 has been proposed. An increased frequency of HLA-B16 and HLA-Cw3 in OFG patients and their first kin has also been found (Ronnblom et al., 1986; Goto et al., 1999; Cabrera-Gomez et al., 2005) while another observed a significant increase in A3, B7 and DR2 alleles in OFG patients compared with the general population in Scotland (Gibson and Wray, 2000).

3.1.3.2 Hypersensitivity

It has been suggested that some OFG patients are atopic and allergic to food or other antigens (James et al., 1986). Food additives such as benzoic acid, cinnamonaldehyde, carmoisine, sunset yellow, chocolates and monosodium glutamate (Sweatman et al., 1986; Oliver et al., 1991; Wray et al., 2000; Taibjee et al., 2004; Saalman et al., 2009); metals such as gold (Lazarov et al., 2003), cobalt (Pryce and King , 1990) and amalgam/ mercury restorations (Guttman-Yassky et al., 2003; Lazarov et al., 2003; Khamaysi et al., 2006) have been reported as causative agents in OFG patients.

OFG may thus represent a delayed hypersensitivity-type response with granulomas forming as a consequence of cytokine release in the response to these unknown antigens (Lim et al., 1997).

However there are no detailed studies of the precise long-term effectiveness of diets or lifestyles that exclude these aforementioned agents and indeed not all patients with OFG have demonstrable hypersensitivity to these, or other agents.

3.1.3.3 Infection

The role of mycobacterial species (*Mycobacterium tuberculosis and paratuberculosis*) and other infectious agents (*Saccharomyces cerevisiae*, Candida albicans, *Borrelia burgdorferi*, Toxoplasma, Treponema, herpes simplex virus, and *Streptococcus mutans*) has been investigated but remain no consistent findings (Riggio et al., 1997; Gibson et al., 2000; Muellegger et al., 2000; Handa et al., 2003; Savage et al., 2004).

3.1.3.4 Immunity

OFG certainly represents a granulomatous inflammatory response to an unknown antigen (Sanderson et al., 2005). There are strong parallels with gastrointestinal Crohn's disease as levels of CD4-T cells, IFN-γ, IL-10, and IL-12 are raised in the OFG patients. In addition, chemokines; RANTES and

MIP-1α and chemokine receptors; CCR5 and CXCR3 expression levels are elevated in OFG patients, suggesting a Th1 immune response, as observed in intestinal Crohn's disease (Freysdottir et al., 2007). While these findings may point towards a commonality of aetiopathogenesis between OFG and Crohn's disease these do not explain the different clinical presentations of each disorder.

3.1.4 Histopathology

Histopathological examination of early OFG lesions usually shows oedema, lymphoedema, and paravascular and perivascular mononuclear infiltrates. Non-caseating granulomas are usually evident when clinical disease is well established. The granulomas are scattered throughout the lesion and within the lymphatic vessels. The granuloma is composed of lymphocytes and epithelioid histiocytes, dilated lymphatic vessels, and fibrosis may be found late in the disease process (Hornstein, 1973; Allen et al., 1990; Hornstein, 1997; van der Waal et al., 2001; El-Hakim and Chauvin, 2004; Kruse-Losler et al., 2005; Cockerham et al., 2005; Sanderson et al., 2005; Lourenco et al., 2008). The presence of perilymphatic granulomas, granulomatous lymphangitis, and lymphedema has been considered to be pathognomonic of this disease (Cockerham et al., 2000). However in the early stages of OFG, typical granulomas may not be present (Lourenco et al., 2008), and even in the late disease process some patients may not have granulomas (Wiesenfeld et al., 1985; Hegarty et al., 2003; Endo and Rees, 2007). This lack of reliable presence of granulomas can thus complicate definitive diagnosis of OFG.

3.1.5 Management

Patients with OFG may consult several groups of clinicians and undergo a number of testing procedures before the appropriate diagnosis is made. Furthermore, patients may be followed for long periods to facilitate early diagnosis and management of other systemic involvement, such as intestinal

Crohn's disease, that may develop (Mignogna et al., 2001; Shakeel et al., 2009).

In general, management of orofacial manifestations in OFG and Crohn's disease is the same. However, the status of oral mucosa in Crohn's disease may correlate with the activity of intestinal disease (Ojha et al., 2007; William et al., 2007) and may respond to systemic treatment of intestinal Crohn's. For example, Bogenrieder et al. (2003) described a patient with oral manifestations of Crohn's who responded well to treatment of intestinal symptoms with mesalazine (3 g daily) and oral prednisolone (initial dose, 60 mg/day).

In general, although OFG and Crohn's are considered to be different disorders; there is overlap in the management of the orofacial features of both.

3.1.5.1 Therapeutic agents

The management of OFG generally remains symptomatic and is directed towards lessening or resolving the facial swelling and associated intra-oral ulceration. However, this typically remains difficult and is often unsatisfactory (Sciubba and Said-Al-Naief, 2003). As there are no systematic reviews nor large-scale, well-planned randomised control studies, treatment is mainly based upon data from case reports, case series studies and clinician experience. At the present no single therapy has proven to be universally effective for OFG and the possible potential of novel therapeutic strategies, such as specific anti-TNF-α agents, remains unknown. Different approaches, utilizing a wide range of topical and/or systemic agents have been used on the basis of disease extent, severity and typology of lesions. These therapeutic strategies include elimination diet, antiseptics, non-steroidal anti-inflammatory drugs, antibiotics (Stein and Mancini, 1999) antihistamines (Allen et al., 1990) topical, intralesional and systemic corticosteroids, (Tyldesley, 1979; Wiesenfeld et al., 1985; Kolokotronis et al., 1997),

antilepromatous agents (Ridder et al., 2001) and anti-TNF-α agents (Tables 3.4, 3.5 and 3.6).

As indicated previously some patients may have an identifiable precipitant such as a food stuff in particular food additives. Perhaps just under 40% of patients have clinical benefit following avoidance of a likely precipitant alone (Sweatman et al., 1986; Oliver et al., 1991; Wray et al., 2000). Labial swelling and other signs may subside within about 5 months (Lazarov et al., 2003). Resolution of OFG following removal of amalgam restorations has been reported (Guttman-Yassky et al., 2003).

Cutaneous patch testing has been suggested to aid the identification of patients who may respond to an elimination diet (Armstrong et al., 1997) but there can be considerable variation in the ability to identify a likely precipitant as the clinical skills of the attending clinicians may vary. Such investigations are also labour-intensive, time consuming and ultimately expensive.

If the causative agent(s) cannot be identified or any elimination protocol has failed then the use of therapeutic agents is inevitable.

Management of intraoral lesions

Many topical regimens (such as antibacterials, topical corticosteroids and tacrolimus) have been used for the management of intraoral manifestations of OFG. Good oral hygiene has been reported to potentially lessen the severity of ulceration of OFG and hence topical anti-microbial agents such as chlorhexidine gluconate may be of some benefit in mild disease (Sciubba and Said-Al-Naief, 2003).

The mucosal ulceration may lessen with a range of topical corticosteroids and topical calcineurin inhibitors (e.g. tacrolimus). Mignogna and co-workers (2003) reported good response of intraoral lesions to topical clobetasol (0.05% ointment) with orabase. Mucosal tags and gingival lesions disappeared after use of 0.05% topical clobetasol ointment mixed with

orabase (1:1) (twice/day, 2-4 weeks) (Mignogna et al., 2001), employing custom-made trays for the gingival lesions.

However, hydrocortisone hemisuccinate pellets, triamcinolone acetonide, betamethasone sodium phosphate, dexamethasone mouth rinses and fluticasone propionate aqueous spray have been suggested to be ineffective or of transient benefit in lessening oral ulceration of some patients (Hegarty et al., 2003). In general intraoral lesions rarely necessitate systemic therapy with systemic corticosteroids, immunosuppressants or anti-TNF-α agents.

Management of orofacial swelling

The labial swelling of OFG is difficult to resolve (Fdez-Freire et al., 2005). In particular if there has been a considerable time lag from initial onset to presenting at specialty clinic, the lip swelling can be rubbery or fibrous in consistency and difficult to resolve.

Mild labial swelling may be managed with topical corticosteroids while moderate to severe swelling respond to intralesional corticosteroids. Other management modalities include immunosuppressive therapies, surgery, and psychological support.

Topical agents

Topical corticosteroids and tacrolimus applied onto the involved lip(s) have been reported to be effective in reducing swelling and lip fissuration (Casson et al., 2000). However, this approach is likely to be effective only in patients with mild disease (Hegarty et al., 2003). The precise efficacy and safety of facial application of such agents have not been detailed.

Topical tacrolimus has been suggested to have a role in lessening the labial swelling of granulomatous cheilitis, OFG and Crohn's disease (Hegarty et al., 2003; Kovich and Cohen, 2004) and as with topical corticosteroids are likely to only be useful when lip swelling is mild. Topical tacrolimus has been used successfully, without any systemic absorption, in three young patients

with Crohn's disease (Casson et al., 2000). It resulted in lessening of labial swelling and fissures following 4 to 6 weeks of application (0.5 mg/g in Orabase). However, there is a need for additional studies to determine whether topical tacrolimus is consistently effective in lessening other lesions of OFG.

Intralesional corticosteroids

Intralesional injections of corticosteroids have been long advocated for lessening or resolving the oro-facial swelling of OFG (Sakuntabhai et al., 1993; Kolokotronis et al., 1997; Camacho-Alonsoet et al., 2004), particularly if the disease is recognized in its early stage and the tissues are not fibrotic. In a recent study (Lourenco et al., 2008), intralesional corticosteroids with dapsone (100 mg/day) with/without systemic corticosteroids were used in the management of 5 patients with lip and gingival swelling. All patients had either partial or complete resolution of their lesions. In another study, intralesional triamcinolone (1 cm^3 every other week for 6 weeks) has been found to be effective either alone or in combination with clofazimine (100 mg/ every 2 days) or with systemic betamethasone (4 mg/day) (Camacho-Alonsoet et al., 2004).

Aside from resolving tissue swelling within 2-4 weeks intralesional therapy may decrease the rate of recurrence and increase the disease-free period in upto 80% of patients (Sakuntabhai et al., 1993). Nevertheless, there are no studies of the long-term efficacy of this therapeutic approach.

Two different techniques of intralesional therapy have been described on the basis of different corticosteroid formulation. Sakuntabhai and co-workers (1993) performed intralesional therapy using the 10 mg/ml formulation of triamcinolone acetonide. This was effective in reversing existing swelling or reducing further lip enlargement for about 10 months. In instances of recurrence, the regimen was repeated. However, the low concentration of medication necessiate the injection of high volume of triamcinolone (3 to 10 ml) giving rise to pain and a transient increase in swelling. As a

consequence, regional nerve block anesthesia is required. Other group has used high concentration triamcinolone (10 mg/ml) injected via a tuberculin syringe on a weekly basis for 2-3 weeks (each session consisting of topical anesthetic application then 0.1 ml of triamcinolone to be injected in each of 3-4 sites of each swollen lip) (El-Hakim and Chauvin, 2004). This protocol led to good long-term results (up to 5 years in some instances) and was generally painless.

As an alternative to trimacinolone 10 mg/ml, a small volume of a delayed-release high-concentrated triamcinolone formulation (40 mg/ml) was recently used in a cohort of 7 patients and found to be an effective means of decreasing labial swelling of OFG for 8 to 30 months following one cycle of therapy (Mignogna et al., 2004). In addition this strategy may be useful for the treatment of orofacial manifestations of Crohn's disease (Mignogna et al., 2008).

Systemic corticosteroids

There are several reports upon the effectiveness of moderate doses (0.5-1 mg/kg/day) of systemic corticosteroid therapy (usually oral prednisolone or deflazacort) in the treatment of swelling of OFG (Sciubba and Said-Al-Naief, 2003; El-Hakim and Chauvin, 2004; Mergulhao et al., 2005; Kauzman et al., 2006; Lourenco et al., 2008). However, because of the recurrent/chronic nature of OFG, extended periods of therapy are inevitable thus increasing the risk of corticosteroid-induced adverse side effects. Intravenous methylprednisolone (1000 mg/day) alone (Kesler et al., 1998) or in combination with systemic prednisolone (Saito et al., 1994) has been effectively used to control synchronous neurological manifestations (e.g. facial palsy) and facial swelling in some OFG patients.

Clofazimine

The anti-leprotic clofazimine has been used in combination with, or as an alternative to, systemic corticosteroids for the treatment of OFG (Podmore and Burrows, 1986; van der Waal et al., 2002; Sciubba and Said-Al-Naief,

2003; Camacho-Alonso et al., 2004; Fdez-Freire et al., 2005; Shakeel et al., 2009). However, the duration of clofazimine therapy to induce and maintain clinical remission/improvement is unknown. Mahler and co-workers reported resolution of peri-oral and lingual swelling after two weeks of treatment with clofazimine (Mahler et al., 1995). Sussman and co-workers used clofazimine (100 mg 4 times weekly) for 3-11 months in 10 OFG patients and obtained complete and partial remission in five (50%) and three (33%) patients respectively. Two patients did not respond to treatment. Histopathological studies of lesional tissue after treatment with clofazimine have demonstrated a decrease or disappearance of granulomas (Sussman et al., 1992).

Anti-TNF-α strategies

As TNF-α is considered a major determinant of granuloma formation in several disorders, anti-TNF-α therapies have been tested as potential therapeutic agents. Medications with anti-TNF-α activity include thalidomide and novel monoclonal antibodies such as infliximab and adalimumab. The largest experience comes from the treatment of Crohn's disease but also patients with idiopathic OFG have been recently studied. Low-dose thalidomide (25-100 mg/day) has been found to lessen the labial and facial swelling of OFG (Safa et al., 1995; Odeka and Miller, 1997; Weinstein et al., 1999; Medeiros et al., 2002; Hegarty et al., 2003). Clinical benefits seem to be rapid, leading to a quick reduction or remission of labial swelling within weeks (Hegarty et al., 2003). Nevertheless, in view of the significant risk of teratogenesis, sensory (and motor) neuropathies and occasional cutaneous adverse effects, the use of thalidomide must be carefully considered. Regular clinical monitoring is essential (particularly a 6-month assessment of sensory nerve action potentials) (Odeka and Miller, 1997; Hegarty et al., 2003; Thomas et al., 2003) and patients receiving thalidomide must always be informed and instructed to follow strict contraceptive measures. Although thalidomide itself is a low cost agent, the clinical monitoring is complex and expensive, and patients must be reminded of the significant adverse effects of therapy.

The murine/human anti-TNF-α monoclonal antibody infliximab is an effective therapy for intestinal Crohn's disease (Targan et al., 1997; Baert et al., 1999) and has been reported to lessen the orofacial lesions of Crohn's disease (with/without azathioprine) (Mahadevan and Sandborn, 2001; Ottaviani et al., 2003; Cardoso et al., 2006). There have been a small number of reports that infliximab may be effective for the treatment of OFG (Barry et al., 2005; Peitsch et al., 2007). Adalimumab, a recombinant human anti-TNF-α antibody, has been reported to be of potential benefit for the treatment of OFG (Gaya et al., 2006) but such agents are costly and not without risk of significant adverse side effects.

Other agents

A wide variety of other agents (alone or in combination with others) have been proposed in the management of OFG. These include methotrexate (Tonkovic-Capin et al., 2006), sulphasalazine (500 mg/day) (Clayden et al., 1997), lymecycline (Pigozzi et al., 2004), dapsone (van der Kooi et al., 2005; Thomas et al., 2003; Lourenco et al., 2008), prednisolone with diclofenac (Gerressen et al., 2005), minocycline (Stein and Mancini, 1999) or 5-aminosalicylic acid (Girlich et al., 2002; Saalman et al., 2009), metronidazole (Miralles et al., 1995; Coskun et al., 2004), hydroxychloroquine (van der Waal et al., 2002), and combination of metronidazole, methylprednisolone and mesalamine (Dummer et al., 1999).

3.1.5.2 Surgery

Surgery for persistent or recalcitrant disease has been proposed but there are few reports of outcomes. Cheiloplasty, alone (Glickman et al., 1992; Ellitsgaard et al., 1993; Kruse-Losler et al., 2005) or in combination with corticosteroids (intralesional triamcinolone acetonide) (Krutchkoff and James, 1978; van der Waal et al., 2002), has been suggested to correct facial swelling and maintain clinical remission. The basic surgical procedure consists of excising transversely a variable amount of labial mucosa, submucosa and orbicularis oris muscle on the basis of the degree of lip swelling (also known as Conway method) (Kruse-Losler et al., 2005). More

rarely, when severe gigantic macrocheilia is present, lip reduction can be performed combining the transversal Conway method with a central sagittal wedge excision (Kruse-Losler et al., 2005). In instances of severe facial swelling and asymmetry, facial liposuction (suction lipectomy) has been undertaken (Tan et al., 2006). Surgery is likely to be of greatest benefit if performed when the swelling is quiescent or stable (Worsaae et al., 1982; van der Waal et al., 2002) as post-surgical inflammation process may cause a further increase or recurrence of swelling. It has been suggested surgical treatment to be deferred until a patient has been free of active disease for about 8 to 12 months (Kruse-Losler et al., 2005). Temporary post-operative lip swelling and paraesthesia commonly arise following cheiloplasty but these may settle 4 to 6 weeks (Oliver and Scott, 2002). Although labial swelling may recur or persist long-term benefit for up to 8 years has been reported (Ellitsgaard et al., 1993; Oliver and Scott, 2002). Some clinicians have suggested surgery be combined with intralesional corticosteroids and long-term systemic tetracycline therapy (Camacho et al., 2001). Four patients with gingival enlargement as part of OFG process had gingivoplasty with dapsone, intralesional corticosteroids with/without systemic corticosteroids and achieved either partial or complete resolution of gingival and lip(s) swelling (Lourenco et al., 2008).

3.1.5.3 Psychological support

The labial and facial swelling of OFG can be distressing to patients, particularly when they are children or young adults. Affected individuals can be embarrassed and can become socially isolated. Accordingly, social support and psychological counselling are important, particularly short-term, in management of individuals distressed by their disease (Clayden et al., 1997).

3.1.6 Clinical outcome and prognosis

The precise clinical outcome of patients with OFG is not known. Gradual improvement (Mignogna et al., 2001) and spontaneous resolution have been rarely reported but this may take many years (Lourenco et al., 2008). The majority of patients seem to have chronic relapsing clinical picture which is variably controlled by medical therapy. In general however the treatment remains usually satisfactory and recurrence of labial swelling may occur (van der Waal et al., 2002).

While there is considerable increase in the published reports concerning the clinical presentation and management of OFG in the last few years, the long-term outcomes of OFG remain largely unknown. Hence the aim of this chapter is to describe the long-term outcomes of therapy in a large homogeneous cohort of OFG patients attending a single Oral Medicine unit.

3.2 AIMS

The aims of this chapter were to:

1. Detail description of the early and late clinical features and other clinical characteristics of a substantial cohort of patients with orofacial granulomatosis resident in England, UK.
2. The clinical outcomes of long-term therapy of orofacial granulomatosis.
3. The frequency and nature of adverse side effects of therapy of orofacial granulomatosis.

3.3 PATIENTS AND METHODS

3.3.1 Patients group

The study group comprised 49 patients managed by the Oral Medicine Unit of UCL Eastman Dental Institute and UCLH Eastman Dental Hospital, with clinical and usually histopathological features consistent with the diagnosis of orofacial granulomatosis (OFG). The patients had been under the care of the clinicians of the unit between 1985 and 2007.

3.3.2 Methods

The case record of each patient was examined using multiple data extraction forms for details of demographics, past medical and drug histories, extra- and intra-oral clinical features and clinical progress data. Incisional biopsy was performed wherever possible and relevant histopathology obtained. Haematology and serology data were evaluated in some of the studied patients as they were required for (i) diagnostic purposes, (ii) to evaluate potential gastrointestinal involvement and (iii) to monitor therapy. These include full blood cell count, differential white cell count, hepatic and renal biochemistry, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum angiotensin converting enzyme (SACE) levels. The number of patients tested varied from 16 to 34 on the basis of which types of investigations were undertaken. The details of diagnostic and monitoring investigations were systematically extracted using a preformed data extraction sheets (Appendices 1-5). Analyses were performed with regard to the total number of investigations, the total number of patients tested, and any association with pharmacological therapies.

Inclusion criteria:

1. Intra-oral and/or extra-oral clinical features suggestive of OFG.
2. Histopathological evidence of non-caseating granulomas.
3. Exclusion of other granulomatous disease on the basis of clinical, histopathological and laboratory investigations (Mignogna et al., 2003; Leao et al., 2004).

All patients met at least criteria (i) and (iii). Patients who developed intestinal inflammation of Crohn's disease after the onset of orofacial manifestations were re-categorized as having oral Crohn's disease and were thus excluded from the study.

Clinical outcome

Disease onset was evaluated on the basis of patients' history, referral letter and/or first clinical examination at the Oral Medicine clinic. Long-term clinical manifestations occurring during the course of the disease were evaluated on the basis of clinicians' descriptions in the clinical notes and photographs taken during clinical reviews. The impact of therapies on the behavior of clinical manifestations was not considered.

The outcome of therapy was evaluated separately for both intra-oral ulceration and soft tissue (labial) swelling on the basis of observation at 6 monthly reviews recorded in clinical notes. The therapeutic effectiveness was estimated using a 4-point scoring system: 0 (initial status), -1 (worsening), +1 (partial resolution), +2 (complete resolution). Initial status defined the size of oro-facial swelling and number/size of intra-oral ulceration at pre-therapy stage. Partial resolution was defined as partial dimensional reduction of swelling in case of facial manifestations and partial resolution of intra-oral ulcerative disease. Complete resolution was defined as complete return to normal dimension/shape of affected facial tissues and complete resolution of intra-oral ulcerative disease. Worsening was defined as dimensional increase of any facial swelling and/or an increase in number and/or size of intra-oral ulcerative disease. Evaluation of response was based on clinicians' judgments during clinical examination, upon clinical photographs, and the patients' opinions as reported in clinical notes.

Analysis of treatment outcome was based on (i) the comparison between disease status before therapy and last review in 2007, and (ii) the serial measurements of disease status at 6-month reviews. The Kaplan Meier

cumulative incidence curve was constructed to assess the proportions of patients having a complete resolution of labial swelling over time.

Statistical analyses

Descriptive and analytical statistics were undertaken using the SPSS program (SPSS for Windows: (Statistical Package for the Social Sciences) software, version 12.0.

3.4 RESULTS

3.4.1 Patient demographics

Age and gender

The mean age of the patients at the time of diagnosis or referral to the oral medicine unit was 32.4 years (SD 19.1), with age range of 7.4 to 72.1 years. The mean age at OFG diagnosis was statistically significant lower in males (23.3 years) than females (43.6 years) (P=0.00). The onset of the clinical features of disease was thus usually in the second decade of life. There were a slightly higher number of males (27; 55.0%) than females (22; 45.0%), with a male to female ratio of 1.2:1 (Table 3.7).

Ethnic group

The majority of patients were white British (36; 73.5%) (self-reported, according to 2001 UK Census) (Office for National Statistics, 2003). In present cohort there were 6 (12.2%) white other than British, 4 (8.2%) Black African and 3 (6.1%) Asian.

Marital status

Marital status was stated under four categories; married which included married patients and patients in a civil partnership; single, divorced and widowed patients. 29 (59.2%) were single, 17 (34.7%) were married or living with a partner, 1(2.0%) was widowed, 1 (2.0%) was divorced and the marital status was not reported in the case note of one patient.

Tobacco use and alcohol consumption

Nine (18.4%) of the patients were previous tobacco users and 8 (16.3%) were current users of tobacco. The mean number of self- reported cigarettes per day by the present tobacco users was 8.6. Twenty five (51.0%) of the group currently drank alcohol. The mean total weekly consumption by the present alcohol users was 9.9 units.

Sources of referral to oral medicine

Twenty three (46.9 %) of the patients had been referred to the Oral Medicine unit by specialists in Oral and Maxillofacial Surgery (OMFS) from within and outside London. Fifteen (30.6%) patients were referred by general dental practitioners. Four (8.2%) patients were referred by periodontist and the remaining patients were referred by their general medical practitioner, medical or a dental specialist (Table 3.8). The patients had been referred to Oral Medicine clinics for the diagnosis and/or management of variety of orofacial lesions such as labial swelling or intra-oral mucosal ulcers.

3.4.2 Past medical history

The patients had a history of a wide variety of common medical conditions, the most common of which were: allergies, respiratory, and gastrointestinal diseases. A variety of allergic diseases were reported by the 14 (28.6%) patients of whom 2 (4.0%) were allergic to penicillin, one to plaster (sticky-plaster, e.g. band-aid) and 11 were allergic to a variety of other allergens. Eight (16.0%) patients had a history of asthma and 10 (20.4%) had central nervous system diseases. Gastrointestinal symptoms and/or serological abnormalities necessitated referral to a gastroenterology unit where endoscopic investigations failed to show any intestinal Crohn's disease. More details about the past medical history of this cohort of OFG patients in table 3.19.

3.4.3 Clinical signs and symptoms at presentation and at disease onset

3.4.3.1 Duration of oral symptoms at first visit

The duration of oral symptoms before clinical diagnosis varied from 4 to 192 months, with a mean of 44 months (SD 44.6).

3.4.3.2 Clinical signs and symptoms at presentation

Thirty seven patients (37/49; 75.5%) had labial swelling at the time of initial specialist examination. Both lips were affected in 9 (18.4%) patients while 9

and 19 patients had swelling of upper and lower lips respectively. Eighteen patients (36.7%) had oral ulcer at time of initial examination. Seventeen of the 18 patients (94.4%) had superficial aphthous-like ulcers while 2 patients (4.1%) had linear, deep ulcers of the vestibular fold areas. Ten patients (20.4%) had cervical lymphadenopathy, this usually comprising multiple small (<1 cm diameter) rubbery mobile nodes of the anterior and/or posterior triangle of the neck. Additional details about presenting clinical features are provided in Table 3.10.

3.4.3.3 Clinical features at disease onset

Five major patterns of disease onset were identified in the present cohort of patients. These include: facial swelling only (Group 1), facial swelling with other manifestations (Group 2), oral ulceration only (Group 3), other intra-oral manifestations without facial swelling (e.g. gingival hyperplasia) (Group 4), and neurological manifestations only (e.g. facial palsy) (Group 5) (see Table 3.11 and Figure 3.1). The most commonly reported abnormality at disease onset was recurrent oro-facial swelling, reported by 26 (53.1%) patients (groups 1 and 2). Twenty-five patients (51.0%) had swelling of one or both lips, and 1 patient (2.1%) reported bilateral malar swelling. Fifteen (Group 1) of these 26 patients, reported oro-facial swelling to be their only initial manifestation (upper and/or lower lip in 14 and malar area in 1) while in the other 11 patients (Group 2) the swelling of the lips co-existed with other extra- and/or intra-oral manifestations including angular cheilitis (1 patient), perioral erythema (1), fissuring plus angular cheilitis plus mucosal cobblestoning and tags (1), swelling of the cheek (1), mucosal cobblestoning and gingival enlargement (1), intra-oral ulceration (4), gingival enlargement (1) and lip fissuring (1). Lymph node swelling was never found to be the only presenting manifestation of OFG.

Oral mucosal ulceration as the only presenting sign were reported by 14 patients (28.6%) (Group 3) consisting of either superficial aphthous-like ulcers or linear, deep ulcers of the vestibular fold areas. However, intra-oral

ulcers were associated with other oro-facial and/or intra-oral manifestations at disease onset in a further 4 patients.

In patients with other intra-oral manifestations (Group 4), gingival enlargement was the presenting sign of OFG in four patients (8.2%), one of whom had also cobblestoning while the other had cervical lymph nodes swelling. One patient (2.1%) reported swelling of the tongue as the probable initial feature of OFG.

Mucosal cobblestoning was never reported as the only presenting sign of OFG. However it was associated with gingival enlargement (probably unrelated to plaque) in 1 patient (2.1%) and with multiple orofacial and intra-oral manifestations in 2 patients (4.1%).

Mucosal tags were never the sole presenting sign of disease but were associated with oro-facial swelling and other intra-oral manifestations in one patient (1/49; 2.1%).

One or more episodes of facial nerve palsy, at disease onset, were reported by three patients (6.1%) and one (2.1%) patient had chronic paroxysmal haemicrania as presenting manifestation of OFG (Group 5).

3.4.4 Histopathology

Details of histopathological examination of lesional tissue were available for 37 patients (75.5%). In the remaining cases (12; 24.5%) biopsy was refused by the patient, undertaken in other hospitals/units (and the results unavailable for review) or considered not necessary by the attending specialist. Non-caseating granulomas were observed in only 43.2% of the examined specimens (16/37). The granulomas were usually small, loose and poorly defined consisting of epithelioid histiocytes surrounded usually by lymphocytes. Moreover, multinucleate giant cells were present and were sometimes of the Langhans's type.

Features of oedema of the corion with dilated lymphatic and blood vessels and unspecific inflammatory infiltrate were observed in all specimens, regardless of the presence or absence of granulomas.

3.4.5 Haematological and serological assessments

Table 3.12 shows the abnormal findings with regards to the total number of investigations and the type of therapy (topical or combined therapy). Overall 12.2% (mean value; range 0-41.4%) of the total number of investigations showed abnormal results and these were mainly associated with combined therapy.

Table 3.13 shows the abnormal findings with regards to the total number of patients and the type of therapy (topical or combined therapy). Overall 20% (mean value; range 0.0-42.1%) of the total number of patients showed abnormal results and these were mainly associated with combined therapy.
Most of the abnormal results consisted of mild reduction/elevation with respect to normal values and were thus considered of little clinical significance.

3.4.6 Long-term clinical features

The majority of patients (42/49; 85.7%) developed a variety of different additional features of OFG following its initial manifestation (Table 3.11 and Figure 3.1).

Ten out of the 15 patients (66.7%) with OFG who initially presented with facial swelling only (Group 1), developed other manifestations during the course of the disease including intra-oral ulceration only (1 patient), intra-oral ulceration and cobblestoning (2), labial swelling (2), labial swelling and ulceration (1), labial swelling with cobblestoning and tags (1), perioral erythema (1), cervical lymph node swelling (1) and cervical lymphadenopathy with cobblestoning and mucosal ulceration (1).

Eight of the 11 patients (72.7%) who initially had facial swelling co-existing with other clinical features (group 2) developed further signs of OFG including labial/buccal swelling (3 patients), labial swelling with cobblestoning and cervical lymphadenopathy (1), intra-oral erythema, tags and cobblestoning, hyperplasia of palatal mucosa and cervical lymphadenopathy (1), perioral erythema plus gingival hyperplasia or cobblestoning (2) or gingival enlargement only (1).

Thirteen of the 14 (92.9%) patients who had only intra-oral ulceration at disease onset (group 3) eventually developed facial swelling only (4), or swelling associated with cobblestoning (3), angular cheilitis (1), lymphadenopathy with or without tags (2), cobblestoning with tags (1), tags with perioral erythema and lymphadenopathy (1) or with angular cheilitis and lymphadenopathy, labial abscess and tags (1). In only one patient, intra-oral ulceration was followed by cobblestoning without any labial/facial swelling.

Within group 4, the patient with tongue swelling at disease onset eventually developed gingival enlargement. The patients presenting initially with gingival enlargement at disease onset without facial swelling (4/49) developed intra-oral erythema and tags (1 patient), or labial swelling (1) and labial swelling plus cobblestoning (2).

All four patients with neurological manifestations only at disease onset (Group 5), later developed labial swelling alone (1 patient), labial swelling plus mucosal cobblestoning (1), labial swelling with gingival hyperplasia, cobblestoning and tags (1) and labial and buccal swelling plus perioral erythema (1).

Twenty of the 23 (87%) patients who had intra-oral (groups 3 and 4) or neurological (group 5) manifestations only at disease onset (individuals presenting without facial swelling) had swelling of one or more facial areas during the following years of clinical monitoring. Similarly, among those

patients who only had facial swelling at disease onset (15 patients), the majority (10/15; 66.7%) eventually developed intra-oral manifestations.

In total, 47 of the 49 patients (95.9%) developed facial swelling along the course of their disease whilst mucosal ulceration occurred only in 24 (49%). The lips were affected in 46 of the 47 patients with facial swelling (98%). Labial enlargement affected lips in 20 patients (43.4%), the lower lip only in 19 (41.3%) cases, and the upper lip in 7 (15.2%) patients. Full-blown symptomatic OFG (intra-oral ulceration and facial swelling) occurred in 23 patients (46.9%) during the disease course.

3.4.7 Therapies provided

A wide variety of different topical and systemic agents had been provided in an attempt to control the extra-and intra-oral manifestations in this group of OFG patients (Table 3.14 and Figure 3-2). Patients with oral lesions alone were almost always managed initially with topical corticosteroids and/or tacrolimus. However, if the signs failed to reduce with topical agents alone intralesional corticosteroids with/without systemic agents were prescribed.

Overall 45 of 49 (91.8%) needed medical treatment whilst 4 experienced spontaneous remission. Twenty four patients out of 45 (53.3%) were managed with topical therapy only, while 21 (46.7%) received combined therapy (topical plus systemic and/or intra-lesional). Different topical and/or systemic agents were used during the long-term management of OFG because of (i) development of new manifestations, (ii) lack of response, or (iii) adverse side effects. Further details about the total number of topical and systemic agents employed in the management of this cohort of patients can be found in Table 3.15.

The duration of treatment of OFG (from commencement of therapy until end of data collection) differed greatly among patients (1 to 15 years; median 1.8).

Details of treatment outcome after a minimum of 3, 5 and 10 years of therapy were available for 38 (77.6%), 26 (53.1%), and 9 patients (18.4%) respectively.

3.4.8 Clinical outcome

3.4.8.1 Clinical outcome of oro-facial swelling

i Disease status before therapy and at last clinical consultation

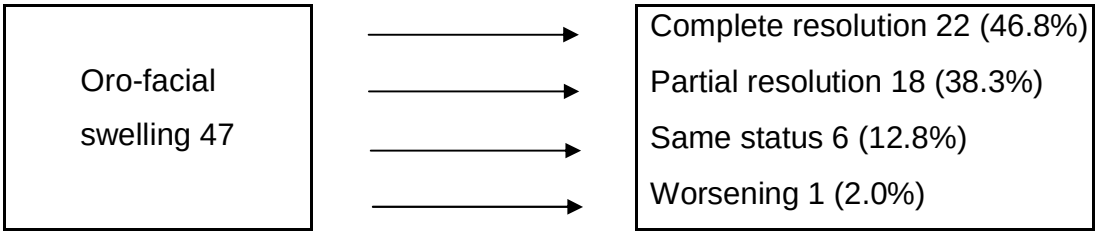

Figure 3.3 Status of patients with regards to oro-facial swelling before (left side) and after therapy (right side).

Forty seven of the 49 (95.9%) OFG patients in this cohort had orofacial swelling and 44 needed medical therapy to control their disease. Analysis of the overall outcome (based on the comparison between disease status before therapy and last review in 2007) indicated 19 (40.4%) patients had complete resolution of disease while 18 (38.3%) had partial resolution. The disease status on last review was the same as that observed at the commencement of treatment of only 6 (12.8%) patients. Only one patient (2.1%) had a worsening of disease. Three patients (6.4%) presented with complete resolution at their last review but were classified as being spontaneous remission cases as resolution was not associated with any ongoing therapy.

The 19 patients with complete resolution of the swelling were managed with topical agents only in 8 cases and with combined therapy (topical and systemic/intralesional therapy) in 11 cases. The 18 patients with partial resolution of the swelling were managed with topical agents only in 4 cases and with combined therapy in 14 cases. The 6 patients whose disease status

on last review was the same as that observed at the commencement of treatment were managed with topical agents only in 5 cases and with combined therapy in 1 case. The patient who had worsening of the disease was managed with topical therapy only.

ii Serial measurement of disease status

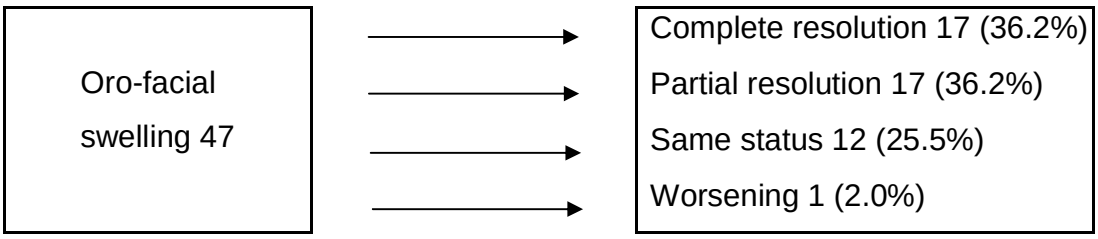

Figure 3.4 Serial measurement of oro-facial swelling before (left side) and during therapy (right side).

Analysis of the typical progress during the treatment (calculated upon serial measurements of disease status during 6-month reviews) showed a typical remitting behaviour. It permitted classification of patients into distinct 4 groups on the basis of the most common (>50%) disease status during reviews: complete resolution (17 patients; 36.2%), partial resolution (17 patients; 36.2%), worsening (1 patient; 2.0%), and same disease status as that before therapy (12 patients; 25.5%).

The 17 patients who showed complete resolution in the majority (50%) of reviews had been treated with combined therapy in 9 cases, and with topical agents only 5 cases. Three patients had spontaneous resolution.
The 17 patients who showed partial resolution in the majority (>50%) of reviews during therapy were managed with topical agents only in 5 cases and with combined topical/systemic agents in 12 cases.

The 12 patients whose disease status was mainly the same as that at initial pre-therapy were managed with topical therapy (8 patients) or combined

topical and systemic agents (4 patients). The patient with worsening disease status was managed with topical agents only.

A sub-analysis of three patients treated with systemic thalidomide showed that the most frequent disease status during therapy was equally distributed between complete resolution (1 patient), partial resolution (1 patient), and initial status (1 patient).

Kaplan Meier plot analysis of 46 patients with labial swelling showed that 23 (50%) of them had complete resolution of the swelling within 3 years of treatment (median time to complete resolution was 36 months). Also, about 25% of patients had complete resolution of swelling within the first year of therapy. However, there were still 6 patients who did not have complete resolution of swelling during the follow-up period (Figure 3.5).

3.4.8.2 Clinical outcome of intra-oral mucosal ulceration

i Disease status before therapy and at last clinical consultation

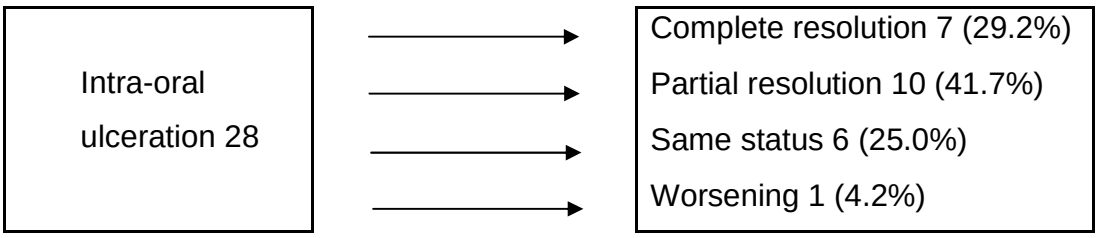

Figure 3.6 Status of patients with regards to intra-oral ulceration before (left side) and after therapy (right side).

Twenty four (24/49; 49%) patients had symptomatic intra-oral ulceration which required medical therapy. Analysis of the overall outcome (based on the comparison between disease status before therapy and the last review in 2007) demonstrated that complete resolution occur in 7 patients (29.2%), while partial resolution in 10 (41.7%). The disease status on last review was the same as that observed at treatment start in 6 (25%) patients, and in only one patient (4.2%) had the disease worsened.

The 7 patients who showed complete resolution of intra-oral ulceration were managed with topical agents only in 5 cases and combined topical/systemic agents in 2 instances.

The 10 patients who showed partial resolution of intra-oral ulceration were managed with topical agents only in 4 cases and combined therapies in 6 cases.

The 6 patients whose disease status on last review was the same as that observed at the commencement of treatment were managed with topical agents only in 4 cases and with combined therapy in 2 cases. The patient who had worsening of the disease was managed with topical therapy only.

ii Serial measurement of disease status

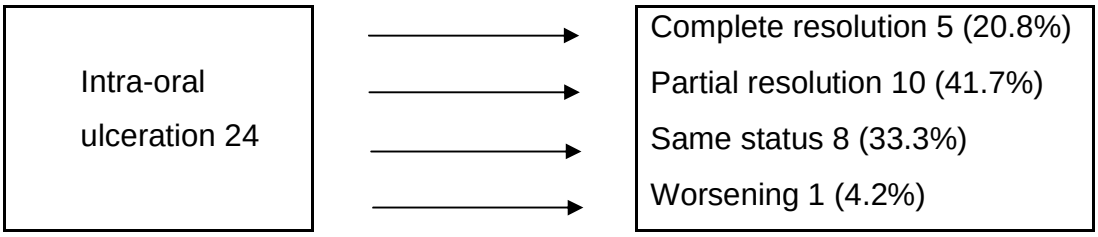

Figure 3.7 Serial measurement of intra-oral ulceration before (left side) and during therapy (right side).

Analysis of the typical progress during the treatment (calculated upon serial measurement of disease status during 6-month reviews) was undertaken based on the aforementioned classification. One group of 5 patients (20.8%) had complete resolution of intra-oral ulceration in the majority (>50%) of reviews. Another 10 (41.7%) patients showed partial resolution in the majority of reviews. Disease status was the same as the initial pre-therapy status during >50% of the reviews in a third group of 8 patients (33.3%). Only one patient (4.2%) showed a worsening of disease status in the majority of reviews.

The 5 patients who presented complete resolution in the majority (>50%) of reviews were managed with topical agents only (3 patients) and topical and systemic therapies (2 patients). The 10 patients who showed partial resolution in the majority (>50%) of reviews during therapy were managed with topical agents only in (5 patients) and combined topical/systemic agents in 5 cases. The 8 patients whose disease status was mainly the same as initial pre-therapy status were managed with topical therapy only in 5 cases and combined topical and systemic agents in the remaining 3 cases. The patient with worsening disease status was managed with topical agents only.

3.4.9 Adverse drug reactions

Six patients had adverse side effects (ASEs) such as gastrointestinal upset, nausea, vomiting, diarrhoea, cutaneous rash or sensory neuropathy. Five patients had one ASE and one had three ASEs. All patients who developed an ASE were on systemic agents, mainly long-term azathioprine or thalidomide.

Azathioprine was prescribed to 7 patients; adverse side effects developed in 3 patients and included skin rash (1 patient), nausea and headache (1), and cardiac arrhythmia (1).

Thalidomide was prescribed to 7 patients; adverse effects developed in 4 patients and included skin rash (3 patients) and fatigue (1).

Systemic prednisolone was prescribed to 13 patients; it caused gastrointestinal upset in one patient. Gastrointestinal upset developed in the only patient was on systemic tacrolimus. Oral candidosis was the most common adverse side effect from topical therapy.

3.5 DISCUSSION

Oro-facial granulomatosis (OFG) is a chronic inflammatory disease with the potential to adversely affect the quality of life of patients by virtue of persistent labial and/or facial swelling, painful oral ulcerations, and in occasionally neurological manifestations (Somech et al., 2001).

There are few detailed studies with large groups of patients on the clinical onset and long-term behaviour of this disorder and little is known regarding the long-term effects of different therapies. The present chapter attempted to clarify these issues by virtue of a retrospective analysis of a group of patients with OFG who were managed at a single centre over more than 20 years. The study represents the largest homogenous group of individuals diagnosed with only OFG reported in the past two decades, as individuals with likely Crohn's and sarcoidosis were excluded. As the majority of previous clinical studies (Wiesenfeld et al., 1985; Patton et al., 1985; James et al., 1986; Williams et al., 1991) of OFG-like diseases included patients with Crohn's disease and those with hypersensitivity reactions and their findings should be interpreted with caution as these disorders may behave and respond to therapy differently from OFG.

With regards to epidemiological findings, our cohort had a ratio of males to females of 1.2:1, which agrees with the majority of previous reports (Wiesenfeld et al., 1985; Plauth et al., 1991; Williams et al., 1991; Sanderson et al., 2005; White et al., 2006). These studies also suggest that OFG may develop at any age and only one study reported that young individuals are more frequently affected than adults (James et al., 1986). Our results are in accordance with the latter as we found that more than half of patients (26/49; 53.1%) in our cohort were younger than 30 years of age and about two-thirds (32/49; 65.3%) were ≤ than 40 at diagnosis. These were mainly males, which is difficult to explain as there was no significant difference in the symptoms or signs of OFG between genders (data not shown).

Caucasians were the most common reported ethnic group (85.7%) with Asian, and Black-Africans representing 14.3% of our patients. This ethnical distribution parallels that of general population of London as indicated by the 2001 consensus (Office for National Statistics, 2003) and indeed OFG had been reported in patients from many parts of the world (Odukoya, 1994; Mignogna et al., 2003; Guttman-Yassky et al., 2003 ; van de Scheur et al., 2003; Sciubba and Said-Al-Naief, 2003; Lazarov et al., 2003; Khouri et al., 2005; Gaya et al., 2006; Kauzman et al., 2006; Endo and Rees, 2007; Shams et al., 2007).

Labial swelling is traditionally indicated as the most common clinical feature of OFG. It is also reported as being the most frequent manifestation at disease presentation (Alawi, 2005) and with agreement with previous reports (Wiesenfeld et al., 1985; Plauth et al., 1991; Mignogna et al., 2003; Sanderson et al., 2005) OFG in the present cohort of patients typically gave rise to recurrent/persistent painless facial (mainly of the lips) swelling (95.9%) and long-standing painful ulceration (49%) during the course of the disease.

However, few authors have reported that clinicians should not focus solely on labial swelling as patients with OFG can in fact present with multiple, temporary and multi-focal clinical features affecting intra-oral mucosa, gingivae, facial tissues and the craniofacial nervous system (Wiesenfeld et al., 1985; Mignogna et al, 2003). Moreover they have been reported to develop at different time points in the duration of disease (Mignogna et al., 2003). Little is known about clinical onset and early manifestations of OFG. The few data available suggest that early OFG can cause clinical manifestations other than lip swelling (e.g. atypical onset) that can include gingival hyperplasia, transient facial palsy or daily persistent headache and swelling of other areas of the face (Rozen, 2001; Mignogna et al., 2003).

Mignogna et al (2003) reported that about half of their 19 OFG patients (9/19) had a disease onset characterized by the absence of labial swelling

and occurrence of facial palsy, intra-oral manifestations and swelling of facial areas other than the lips. However 7 of these 9 patients eventually developed labial swelling. Zimmer et al (1992) reported that labial swelling was the initial disease manifestation in only 43% of their 42 patients but this percentage increased to 74% during the course of the disease. Moreover, the overall number of clinical manifestations increased during the years as the percentage of patients with facial swelling increased from 26% to 50% and those with facial palsy from 19% to 33% (Zimmer et al., 1992). In partial agreement with these findings, the present study identified five patterns of disease onset (Figure 3.1) with orofacial swelling (53.1%) and oral ulceration (28.6%) being the most common initial manifestations. Most patients (85.7%) developed further facial and/or intra-oral manifestations over the years. This confirms the concept that the clinical behaviour of OFG is multiform, progressive and highly variable, and that perhaps each patient's disease has a unique pattern of duration and presentation (Mignogna et al, 2003).

Gingival inflammation and/or enlargement unrelated to plaque or a drug were observed in 26.5% of the present group of patients and is generally similar to that reported in previous group of UK residents (Wiesenfeld et al., 1985) but twice as common as that reported in a group of patients' residents in Italy (Mignogna et al., 2003).

Cervical lymphadenopathy has not been frequently described in association with OFG, but was found in 10 (20.4%) of the present patients. It can cause facial/submandibular swelling and may reflect, at least in some individuals, granulomatous lymphadenitis, as observed in the mesenteric lymph node of Crohn's disease (Geboes et al., 1986).

Neurologic manifestations are reported to affect up to 33% of patients with OFG (Wiesenfeld et al., 1985; Zimmer et al., 1992; Mignogna et al., 2003; Kanerva et al., 2008) and were observed in 4 patients of present cohort (8.2%). They all occurred at early stage of disease and never as subsequent

clinical manifestation, suggesting that patients who do not present neurologic involvement at early stage are unlikely to develop it afterward.

OFG does not seem to be associated with any significant haematological abnormalities or serological evidence of systemic inflammation (CRP, ESR), other granulomatous disorders (e.g. SACE) or gastroenterological involvement (e.g., iron or folic acid anaemia). All these parameters were normal in this group of patients which in part reflects inclusion criteria applied. These findings appear consistent with previous report (Sanderson et al., 2005) which found no consistent haematological and/or serological abnormalities in OFG patients.

OFG is considered to be a granulomatous disorder (Wiesenfeld et al., 1985); however, few studies have determined the exact frequency of granulomas in a large cohort of homogenous OFG patients (Sanderson et al., 2005). In the present study, histopathological results were available for 37 patients (75.5%). In general, the reports revealed a range of features and typical non-caseating granulomas were observed in only 43.2% of the specimens, which is similar to the prevalence (46.4%) reported before by Williams et al (1991). Other studies reported that granulomas were found in 81% to 100 % of affected patients (Wiesenfeld et al., 1985; Harty et al., 2005; Sanderson et al., 2005). It should be noted that two of them included patients with oral Crohn's disease (Wiesenfeld et al., 1985; Harty et al., 2005). As reported earlier, (Wiesenfeld et al., 1985; Sanderson et al., 2005), other histopathological features such as oedema of the corium with dilated lymphatic and blood vessels and unspecific inflammatory infiltrate can characterize OFG and these were found in the histopathological lesional tissues examined in present study.

The analysis of OFG treatment described in the present study showed that combined therapy (topical and intra-lesional corticosteroids or systemic agents) was more frequently associated with partial/complete control of the facial manifestations of OFG than topical therapy alone. Even though the

behaviour of OFG was typically remittent, almost half of the patients showed complete resolution of facial swelling at last review. About one-third of the patients responded only partially to therapy and in 12.8 % of cases the treatment could only prevent further increase in facial swelling. Resistance to therapy with worsening of the disease was extremely uncommon (1/49; 2.0%).

Comparison of long-term clinical outcomes (as recorded at last review) with serial outcomes recorded during 6-month reviews demonstrated that facial swelling of OFG tends to improve slowly over time as long as therapy is provided. The percentage of patients with complete resolution of swelling increased from 36.2% during the course of therapy to 46.8% at last review where as the percentage of patients with no significant improvement decreased from 25.5% to 12.8%. This means that a considerable number of patients who had not benefited from treatment in the short to medium term eventually showed partial or complete resolution in the long-term.

With regards to the time needed to achieve clinical effectiveness, the results of the present study suggest that OFG responds slowly to treatment with 50% of the patients achieving complete resolution of the orofacial swelling within 3 years of treatment and only 25% of them doing so within the first year of therapy (Figure 3.5). However a sub-analysis of clinical outcome data suggests that intra-lesional corticosteroids are usually effective in the first weeks of treatment (data not shown). Intra-oral ulceration was typically less responsive to treatment than facial swelling. Only one-third of patients achieved complete resolution of intra-oral ulceration whilst in the majority of cases treatment led to obtain partial resolution only (41.7%) or prevent further worsening (25%) of the mucosal disease.

The aims of OFG management were to lessen and hopefully resolve intra-oral painful lesions, oro-facial swelling and other features of the diseases (e.g. lip fissures, angular cheilitis, etc). Ulceration of the oral mucosa, mucosal tags and cobblestoning were usually managed with topical

corticosteroids (Mignogna et al., 2003) and only rarely were they severe enough to require systemic therapies. Mild oro-facial swelling was managed with topical corticosteroid (e.g. Fluticasone propionate 0.05% cream prescribed to 23 patients) and/or tacrolimus (Tacrolimus 0.1% prescribed to 22 patients). Mild swellings that were non-responsive to topical agents and moderate to severe swellings were usually managed with short courses (1-2 weeks) of moderate doses of systemic corticosteroids (25-50 mg of prednisolone) and, when required, with intra-lesional corticosteroids injections, long-term systemic immunosuppressants (e.g. azathioprine), or anti-TNF-α agents (e.g. thalidomide).

Despite the wide range and long-time use of topical and/or systemic therapies employed in the management of this cohort of OFG patients, no consistent haematological and/or serological abnormalities were observed. A few patients undergoing long-term topical therapy developed oral candidosis which was managed by appropriate antimycotic agents such as nystatin. The other clinical adverse drug reactions were minor and were mostly observed in patients on systemic therapy.

3.6 CONCLUSION

The results of this study show that OFG is a rare disease of young adults whose ethnicity reflects that of the general population living in the same area. Onset of OFG is characterised by facial swelling in only half of the patients whilst in the other half early disease causes intra-oral or neurological manifestations only. Lip/facial swelling is the most common clinical manifestation of OFG leading the patients to seek medical attention. Among intra-oral manifestations, the prevalence of cobblestoning, gingival enlargement and mucosal changes exceeds that of oral ulceration. The long-term behaviour of OFG is subsequently characterised by development of further clinical manifestations with most patients (95.9%) developing, at any time during the course of the disease, orofacial swelling and, less frequently (49 %), intra-oral ulceration. A careful differential diagnosis is mandatory as OFG and related disorders have different aetiologies and different treatments and clinicians should consider the variable, progressive and multiform nature of OFG when they attempt early diagnosis and long-term management.

A wide range of topical, intralesional, and systemic agents can be used to control signs and symptoms. The response of OFG to therapy is typically remitting but some improvement of tissue swelling and oral ulceration can be achieved in 78.8% and 70% of patients respectively. Complete remission of facial swelling is possible in about 50% of patients within 3 years of therapy but may be achieved quicker when intra-lesional corticosteroids are used. Intra-oral ulceration is usually less responsive. Significant adverse side effects are rarely observed and spontaneous remission may occur in few patients.

Table3.1 Demographic and clinical presentation of some of the published studies on the orofacial granulomatosis*

First author/ year	No of pts	Female	Male	Age (range)	Diagnosis	**Clinical presentation** (No. or % of patients when available)	Comment
Al Johani 2009	49	22	27	32.4 (7.4-72.1)	OFG	Oro-facial swelling, angular cheilitis, perioral erythema, fissuring, mucosal cobblestoning, tags, gingival enlargement, ulceration, lymph node swelling, facial nerve palsy, chronic paroxysmal hemicrania	-
Kanerva 2008	35	23	12	20 (3-61)	MRS	Facial palsy (20), triad of symptoms (11), edema (33), lingua plicata (13)	-
White 2006	25	11	14	30 (9-69)	OFG	NA**	9 pts had had minor changes in the gut including aphthous ulcerations and granulomas present in histopathological specimens
Sanderson 2005	35	18	17	24 (6-74)	OFG (no GI symptoms)	Lip swelling present in (95%), Buccal and gingival inflammation, Cobblestoning (49%), Fissuring (37%), Aphthous-like ulceration (15%), Deep linear-type ulcers (12%)	-
Mignogna 2003	19	NA	NA	NA	OFG	10 patients had recurrent lips swelling (6 lower; 4 upper). Transient unilateral facial nerve palsy (2), gingival hyperplasia (2), palatal erythema (1), recurrent swelling of the: peri-orbital area (2), chin (1), zygomatic area (1) and cheeks (1)	-

*Studies with more than 15 patients published between 1985 and 2009. **NA, not available.

Table 3.1 (Cont.) Demographic and clinical presentation of some of the published studies on the orofacial granulomatosis*

First author/ year	No of pts	Female	Male	Age (range)	Diagnosis	Clinical presentation (No. or % of patients when available)	Comment
Gibson 2000	16	8	8	Male; 30 female; 32 range (9-58)	OFG (excluding Crohn's and other systemic disorders)	NA**	-
Armstrong 1997	48	26	22	24 (9-70)	OFG (excluding Crohn's and sarcoidosis)	Facial swelling (12) Lip swelling (41) Mucosal oedema/ gingivitis (9) Vertical lip fissuring (7) Angular cheilitis (6) Oral ulceration (11) Facial nerve palsy (4)	Granuloma found in 41 lesional biopsies
Williams 1991	29	13	13	30 (6-78)	OFG including Crohn's disease patients	Labial swelling (19) Both lips (9) Upper lip (6) Lower lip (4) Cobblestoning (11) Linear ulceration (11) Localized swelling (5) Mucosal tags (2)	28 of the 29 biopsies were reviewed. Granuloma were present in 13 patients
James 1986	75	39	36	15 (4-64)	13 patients had Crohn's disease, 5 had abdominal symptoms and one diagnosed with sarcoidosis	NA	The clinical atopy prevalence among OFG patients alone or in association with Crohn's disease is highly significant than control group

*Studies with more than 15 patients published between 1985 and 2009. **NA, not available.

Table 3.1 (Cont.) Demographic and clinical presentation of some of the published studies on the orofacial granulomatosis*

First author/ year	No of pts	Female	Male	Age (range)	Diagnosis	**Clinical presentation** (No. or % of patients when available)	Comment
Haworth 1986	16	NA**	NA	NA	OFG without Crohn's and sarcoidosis	NA	Food or flavouring provoking the disorder.
Wiesenfeld 1985	60	30	30	20 (3-61)	OFG (including MRS and CG. Six had confirmed GI Crohn's and 9 had evidence suggestive of Crohn's disease, 2 patients had sarcoidosis	Facial swelling (28), Labial swelling (41); upper (27), lower (30), Intra-oral mucosal oedema (14), tags (12), gingival lesions (13), angular cheilitis (11), oral ulceration (19), geographic tongue (3), fissured tongue (1) Facial nerve palsy (8)	47/58 had granuloma.
Patton 1985	80	NA	NA	NA	OFG (including MRS) Oral Crohn's Urticarial rash with porridge and allergic patients	NA	14 of the 80 patients had food or flavouring intolerance to cinnamaldehyde, carvone and/or piperitone.
Scully 1982	19	10	9	15 (3-40)	OFG (Crohn'?)	Lip/facial swelling (16) Aphthous-like ulceration (6) Deep linear-type ulcers (2) Fissured tongue (1) Mucosal tags or cobblestoning (10) Angular cheilitis (7) Facial palsy (1)	Granulomas present in 14 cases. - 7 patients had nutritional deficiency and intestinal disease (on rectal biopsy).

*Studies with more than 15 patients published between 1985 and 2009. **NA, not available.

Table 3.2 Clinical features and differential diagnosis of orofacial granulomatosis

Disorder	Aetiology and pathogenesis	Extra-oral/ facial manifestations	Intra-oral manifestations	Histopathology	Comments
OFG	Largely unknown. OFG is thought to be multifactorial disorder. Several mechanisms have been suggested, such as immunity, infection, and genetic predisposition. It may represent a generalized GI inflammatory response to an unknown antigen.	- Swelling: mainly the lip but other facial areas possibly affected. Initially, soft and recurrent, then progressive and finally persistent and firm. - Erythema can accompany the swelling - Patients may have facial palsy (lower motor neuron); other cranial nerves may be involved. Other neurological manifestations (e.g. headache, lacrimation, etc) may present. - Cervical lymph nodes can be enlarged in some patients.	- Oral ulcerations (linear and/or aphthous-like ulcers) - Cobblestoning - Mucosal tags - Gingival enlargement - Tongue fissures - Angular cheilitis	Non-caseating epitheloid granulomas with/ without multi-nucleated giant cells can be found but not in all lesional biopsies (especially early stages). Oedema of the superficial corium with lymphangie-ctasia and aggregates of lymphocyte is observed (early stages).	Some patients may have intestinal inflammation that differs from that of Crohn's disease.
Crohn's disease	Largely unknown. Evidence of dysfunction of innate immune system causing inappropriate (often excessive) response to indigenous flora and other luminal antigens.	-Identical to OFG except cranial nerve involvement and other neurological manifestations	-Similar to OFG	- Similar to OFG	- Patients need to have proven intestinal involvement to be diagnosed with oral Crohn's disease. - Serology shows the typical abnormalities of CD and can help identifying patients with still undiagnosed asymptomatic gut disease (FBC, Vit. B12, iron and ferritin, CRP, ERS, albumin, ASCA).

Table 3.2 (Cont.) Clinical features and differential diagnosis of orofacial granulomatosis

Disorder	Aetiology and pathogenesis	Extra-oral/ facial manifestations	Intra-oral manifestations	Histopathology	Comments
Sarcoidosis	Unknown. Infection, environmental agents, genetic predisposition and immunological factors have been suggested.	- Lip swelling, usually progressive and persistent, followed by slow spontaneous resolution in 60% of cases. - Salivary gland swelling - Lymph nodes enlargement - Facial nerve palsy - Heerfordt syndrome (combination of fever, parotid enlargement, anterior uveitis, and facial nerve palsy). - Yellowish-brown papules and lupus pernio affecting the skin of the face.	- Submucosal diffuse swelling or focal firm nodules, papular eruptions or superficial ulceration. Usually progressive and persistent, followed by slow spontaneous resolution in 60% of cases. - Dry mouth	- Non-caseating, epithelioid-cell granulomas surrounded by lymphocytes, -Basophilic calcification (Schaumann bodies) and stellate inclusion (asteroid bodies) can be found.	Orofacial involvement is usually a manifestation of widespread multiorgan disease and can be the initial manifestations of the disease in about 50% of patients. - Serology (elevated ACE level), chest radiograph (bilateral hilar adenopathy) and Gallium 67 scanning can support diagnosis.
Tuberculo-sis (TB)	*Mycobacterium tuberculosis* or other related species (*M. bovis, M. africanum, M. microti, and M. canettii*)	- Cervical lymphadenopathy - Salivary gland swelling - Chronic progressive swelling of the lip due to submucosal nodular infiltration - Swelling of the face due to tuberculous osteomyelitis.	- Superficial non-healing, indurated ulcer with irregular borders. - Mucosal swelling due to submucosal nodular infiltration. -Bone lesion (osteomyelitis).	Caseating, granulomas with central necrosis. Ziehl-Neelsen or other acid-fast stains (e.g. Fite method) can demonstrate mycobacteria infection.	- TB can affect the head and neck area in both its primary and secondary form. - Collection of sputum for culture and DNA analysis, chest radiography, tuberculin skin testing and the new serological INF-gamma assay can support diagnosis.

Table 3.2 (Cont.) Clinical features and differential diagnosis of orofacial granulomatosis

Disorder	Aetiology and pathogenesis	Extra-oral/ facial manifestations	Intra-oral manifestations	Histopathology	Comments
Delayed hypersens-itivity reactions (DHSR)	Type IV DHSR. Antigens include food (e.g. chocolate), additives (e.g. benzoate), and dental materials (e.g. gold).	Lip and/or facial swelling. Usually recurrent but chronic permanent enlargement possible.	-Intra-oral mucosal swelling	No distinctive features	- Patch testing usually helps in diagnosing the causative agent. - Allergen removal (e.g. dietary modification) leads to improvement/ remission of clinical features.
Acquired and hereditary forms of angiodema	- C1 esterase inhibitor (C1-inh) deficiency syndrome can be hereditary or acquired. - Hereditary type is a rare autosomal dominant condition. - Acquired forms are generally triggered by autoimmune or neoplastic disorders	- Orofacial swelling: always recurrent but never progressive or permanent. - Episodes are triggered by minor trauma, drugs, emotional stress or infection.	- Recurrent intra-oral mucosal swelling.	Non-specific inflammatory changes. No granulomas.	Gastrointestinal symptoms (e.g. nausea, vomiting, or diarrhoea) are typically associated.

Table 3.3 Diagnostic investigations and criteria of orofacial granulomatosis[$]

Investigations	Results
Full blood cell count	Should be normal
Haemoglobin	Should be normal
Serum angiotensin I converting enzyme levels*	Should be normal
C-1 esterase inhibitor levels**	Should be normal
Serum iron and transferrin	Should be normal
Tuberculin skin test (when clinically justified)	Should be negative
Chest radiography (when clinically justified)	Should be normal
Gastrointestinal (GI) endoscopy/histopathology***	Should be normal. If inflammatory changes are present, Crohn's disease should be excluded
Histopathology I : dilated lymphatics, oedema of the corium, slight fibrosis, with/without multiple non-caseating granulomas with Langhan's giant cell and lymphocytes	Should be present****
Histopathology II : PAS reaction and Ziehl-Neelsen stain (when clinically justified)	Should be negative
Polarised light microscopy: identification of birefringent foreign-body material (when clinically justified)	Should be negative

$ Modified from Mignogna et al., 2003
* To be performed when there are clinical features compatible with a potential diagnosis of sarcoidosis.
** To be performed when oro-facial swelling is recurrent and oedematous without signs of persistent tissue fibrosis.
*** To be performed when clinical or laboratory features rise the suspect of GI inflammatory disease.
**** Absence of histopathological features does not exclude OFG diagnosis if clinical features are compatible.

Table 3.4 Reported therapeutic regimes for the treatment of OFG and related agents

Drug	First author	Year	Drug	Comments
Topical corticosteroids	Mignogna	2002	Clobetasol 0.05% ointment mixed 1:1 with orabase	Good response with intraoral lesions
	Hegarty	2002	Betamethasone sodium phosphate mouthrinse	Good response with intra-oral ulcers.
	Hegarty	2002	Fluticasone propionate aqueous spray Benzydamine hydrochloride mouthwash	little effect
	van der Waal	2002	Triamcinolone in orobase/ clobetasol in orobase	Moderate to good results and effective in long-term
Intralesional corticosteroids	Lourenco	2008	Intralesional triamcinolone	Good improvement in 4/5 patients
	Barry	2005	Intralesional triamcinolone (30 mg)	Some effect
	van der Kooi	2005	Intralesional corticosteroids	Partial improvement
	Mignogna	2004	Intralesional triamcinolone (40 mg/ml)	Effective with long disease-free period
	El-Hakim	2004	Intralesional triamcinolone (10 mg/ml)	Good outcome in 5 patients and moderate in one patient.
	Camacho-Alonso	2004	Triamcinolone 0.1% injection (every 2 weeks for 6 weeks)	Satisfactory improvement in lip swelling.
	Van de Scheur	2003	Intralesional (2 mL) triamcinolone acetonide (10 mg/mL) each month for 6 months	Partially effective
	Mignogna	2002	Intralesional triamcinolone (0.1 ml- 40 mg/ml) 2-4 injections, 2-3 times over 2-3 weeks	Good response in management of swelling
	van der Waal	2002	Triamcinolone 0.1%	Variable results.

Table 3.4 (Cont.) Reported therapeutic regimes for the treatment of OFG and related agents

Drug	First author	Year	Drug	Comments
Systemic corticosteroids	Lourenco	2008	Prednisone (40mg/day)	Good improvement in 4/5 patients
	Peitsch	2007	Prednisolone, hydroxychloroquine (400mg/day) and sulphasalazine (3 g/day)	Partial resoponse
	Thomas	2003	Prednisone (40 mg/day)	Lessening lip swelling but swelling recurred when stops prednisone.
	Kauzman	2006	Prednisone (50 mg/day) Intralesional triamcinolone (40 mg/mL)	Effective
	Tonkovic-Capin	2006	Systemic corticosteroids	Partial response
	Barry	2005	Prednisolone (40 mg/day)	Some effect
	Mergulhao	2005	Prednisone (60 mg/day)	Rapid response
	van der Kooi	2005	Systemic corticosteroids	Not effective
	Taibjee	2004	Systemic corticosteroids	Partial response
	Camacho-Alonso	2004	Systemic betamethasone (4 mg/day) and triamcinolone 0.1% injection (every 2 weeks for 6 weeks)	Satisfactory improvement in lip swelling.
	van de Scheur	2003	Prednisone (60 mg/day)	Decrease lip swelling
	Girlich	2002	Prednisolone (60 mg/day) 5-ASA	Rapid reduction of lip swelling
	Mignogna	2002	Prednisone (25-50 mg/day)	Partial or complete resolution of facial swelling
	Hegarty	2002	Prednisolone/deflazacort (24 mg/day)	Little improvement or no effect
	van der Waal	2002	Prednisolone/ Dexamethasone	Moderate to good results
	Ziem	2000	Prednisolone (1 mg/kg/day)	Labial swelling resolved with residual mild enlargement and persistent facial palsy

Table 3.4 (Cont.) Reported therapeutic regimes for the treatment of OFG and related agents

Drug	First author	Year	Drug	Comments
Clofazimine	Fdez-Freire	2005	Clofazimine 100 -200 mg/ daily for 3 to 6 months	Effective
	Barry	2005	Clofazimine (200 mg)	Not effective
	Camacho-Alonso	2004	Clofazimine 100 mg every other day	Satisfactory improvement in lip swelling.
	Camacho-Alonso	2004	Clofazimine 100 mg every other day Triamcinolone 0.1% injection (every 2 weeks for 6 weeks)	Satisfactory improvement in lip swelling.
	Sciubba	2003	Clofazimine (50 mg/day) Intralesional triamcinolone Systemic corticosteroids Nystatin, Fluocinonide Tetracycline Diphenhydramine Maalox suspension Chlorhexidine gluconate	Combination of clofazimine and topical preparation lessening the lip enlargement and erythema.
	van der Waal	2002	Clofazimine	Variable results.
Dapsone	Lourenco	2008	Dapsone (100mg/day)	Good improvement in 4/5 patients
	Peitsch	2007	Dapsone (100 mg/day) Oral methylprednisolone (25 mg/day), Metronidazole, Ibuprofen	Not effective
	Tonkovic-Capin	2006	Dapsone Doxycycline Intralesional triamcinolone acetonide	Partial response
	Thomas	2003	Dapsone (50 mg/day)	Not effective
	van der Kooi	2005	Dapsone	Decrease lip swelling
	Hegarty	2002	Dapsone (25 mg/day)	Not effective
Anti-TNF-α	Peitsch	2007	Infliximab (5 mg/kg)	Effective
	Barry	2005	Infliximab (3-5 mg/kg)+ IV hydrocortisone (200 mg)	Marked clinical improvement
	Mahadevan	2001	Infliximab (5 mg/kg/day) Azathioprine (2.5 mg/kg/ day), Prednisone	Effective
	Thomas	2003	Thalidomide (100-mg/ day) for 6 months then every other day for 2 months	Complete disappearance of lip swelling.
	Hegarty	2002	Thalidomide (50 mg daily)	Effective for both labial swelling and mucosal ulceration

Table 3.4 (Cont.) Reported therapeutic regimes for the treatment of OFG and related agents

Drug	First author	Year	Drug	Comments
Methotrexate	Tonkovic-Capin	2006	(5-10 mg, once weekly)	Marked improvement
Tacrolimus	Barry	2005	Topical tacrolimus	No effect
	Casson	2000	Topical tacrolimus Prednisolone	Good response to topical tacrolimus
	Hegarty	2002	Topical tacrolimus 0.1%	Improvement in oral ulceration and little effect on labial swelling
Antibiotics	Barry	2005	Minocycline hydrochloride (100 mg)	Little effect
	Barry	2005	Erythromycine (500 mg twice/day)	No effect
	El-Hakim	2004	Doxycycline	No effect
	van der Waal	2002	Metronidazole	Not effective
Amino-salicylates	Mergulhao	2005	Sulfasalazine	Not respond
	Hegarty	2002	Sulphasalazine (500 mg/twice daily)	No effect
	van de Scheur	2003	Mesalazine (500 mg) Sulfasalazine (500 mg)	Used for the treatment of intestinal Crohn's disease
	van der Waal	2002	Sulfasalazine/Mesalazine	Moderate improvement
Hydroxy-chloroquine	Mergulhao	2005	Hydroxychloroquine	Partial improvement
	van der Waal	2002	Hydroxychloroquine	Not effective
Antihistamines	van der Kooi	2005	Oral antihistamines	Not effective
Surgery (Cheiloplasty)	van der Waal	2002	Cheiloplasty	Moderate outcome
	Kruse-Losler	2005	Cheiloplasty (Conway method)	Good results with partial recurrence in 1 patient
	Oliver	2002	Cheiloplasty	Good improvement
	Camacho	2001	Cheiloplasty with 40 mg triamcinolone acetonide injection with tetracycline hdrochloride (1 g/day) for 2 months then (500 mg/day) for 3 months then (250 mg/day) for 6 months	Results were satisfactory with 9 months follow up
Restoration replacement	Guttman-Yassky	2003	Replacement of amalgam	Complete swelling disappearance within 6 months
	Lazarov	2003	Replacement of gold crowns and amalgam	Complete resolution of OFG within 5 months

Table 3.5 Summary of the reported regimes for the treatment of OFG

Therapy	Medication	Target	Effect	Adverse side effects (Reference)
Topical corticosteroids	Clobetasol ointment (in orabase) Betamethasone mouthwash Fluticasone spray Benzydamine mouthwash Triamcinolone in orabase	Intraoral lesions	Moderate to good results in controlling intra-oral lesions	
Topical immuno-suppressants	Tacrolimus ointment	Intra-oral lesions and lip swelling	Effective in controlling intra-oral lesions. Lip swelling response only in mild cases.	
Intralesional corticosteroids	Triamcinolone acetonide 10mg/ml Triamconolone acetonide 40mg/mL	Oro-facial swelling	Variable results. From partial, short-term improvement to complete, long-term remission	Hypopigmentation (Mignogna et al., 2004)
Systemic corticosteroids (short courses)	Prednisone (0.5-1 mg/Kg/day) Deflazacort (24 mg/day) Betamethasone (4 mg daily)	Orofacial swelling and severe intra-oral lesions	Rapidly effective but recurrence after therapy termination.	
Systemic anti-leprotic therapy	Clofazimine (50-100 mg/day)	Orofacial swelling and severe intra-oral lesions	Clofazimine: Effective but recurrence after therapy termination.	Hyper-pigmentation, morbilliform eruption and elevation of liver enzymes (Sciubba and Said Al-Naief, 2003;Thomas et al., 2003; Fdez-Freire et al., 2006)
	Dapsone (25-50 mg/day)		Dapsone: Partially effective	

Table 3.5 (Cont.) Summary of the reported regimes for the treatment of OFG

Therapy	Medication	Target	Effect	Adverse side effects (Reference)
Anti-TNF-α	Thalidomide (50-100 mg/day)	Orofacial swelling and severe intra-oral lesions	Effective	Pruritic rash and somnolence (Hegarty et al., 2002)
	Infliximab			
	Adalimumab			
Antibiotic therapy	Minocycline Erythromycine Doxycycline Metronidzole	Orofacial swelling	Little or no effect	
Amino-salicylates	Sulphasalazine Mesalazine	Orofacial swelling	Little or no effect	
Antimalarial	Hydroxychloroquine	Orofacial swelling	Little or no effect	
Systemic Immuno-suppressants	Azathioprine	Orofacial swelling and severe intra-oral lesions	Azathioprine: Moderately effective as maintenance therapy.	Flu-like symptoms (malaise, fever and arthralgias) (Tonkovic-Capin et al. 2006)
	Methotrexate		Methotrexate: Effective	
Surgery	Cheiloplasy +/- facial liposuction (+/- intralesional or systemic corticosteroids)	Orofacial swelling	Effective but risk of recurrence	

Table 3.6 Outcome of treatment of some of orofacial granulomatosis cohorts

First author/ year	No of pts	Intervention/ treatment	Outcome
White 2006	25	Cinnamon and benzoate free diet for 8 weeks.	-There was a significant improvement in oral inflammation in patients on the diet after 8 weeks -Significant improvement in both lip and oral site and activity involvement
Mignogna 2003	19	Intraoral lesions were treated by topical clobetasol (0.05%). Lip, cheek, and chin swellings were treated with concentrated (40 mg/ml) delayed-release intralesional triamcinolone injections. Facial (zygomatic and periorbital) swellings were treated with oral prednisone, 25 50 mg/day (0.3 0.7 mg/ kg/day) for 7–15 days.	Intraoral lesions responded well to topical clobetasol 0.05% ointment mixed 1:1 with orabase. Soft tissue swelling: intralesional and systemic corticosteroids resulted in partial or complete resolution of the swelling
Armstrong 1997	48	Elimination diet for 10 patients.	7 of the 10 who have positive reactions to the Oral Battery on standard patch testing reported improvement on elimination diet.
Williams 1991	29	12 patients received systemic corticosteroids of whom three were corticosteroid-dependent. 5 patients tried elimination diets. 8 patients required no therapy	Systemic corticosteroid was the only effective treatment. Elimination diets, ciclosporin, azathioprine sulphasalazine and/or topical corticosteroids were not effective.
Wiesenfeld 1985	60	Intralesional corticosteroid injections (10 pts), systemic corticosteroids (1 pt), anti-inflammatory agents (2 pts), co-trimoxazole and metronidazole (2 pts) and surgical reduction (2 pts)	None of the patients respond to systemic corticosteroids, anti-inflammatory agents or co-trimoxazole and metronidazole. Temporary response to intralesional corticosteroid injections and surgical reduction
Patton 1985	80	Elimination diet Systemic corticosteroids Azathioprine Salazopyrine Surgery Sodium cromoglycate	Response to elimination diet: Complete response (3 Pts) Partial response (11 Pts)

Table 3.7 Age of 49 patients with OFG

Age group	Female		Male		Total	
	No	%	No	%	No	%
1-9	0	0.0	3	6.1	3	6.1
10-19	2	4.1	13	26.5	15	30.6
20-29	3	6.1	4	8.2	7	14.3
30-39	4	8.2	3	6.1	7	14.3
40-49	2	4.1	2	4.1	4	8.2
50-59	7	14.3	1	2.0	8	16.3
60-69	3	6.1	1	2.0	4	8.2
70-79	1	2.0	0	0.0	1	2.0
Total	22	44.9	27	55.1	49	100

Table 3.8 Referral pattern of OFG patients

Source of referral	Frequency	%
Oral maxillofacial/oral surgeons	23	47
General dental practitioners	15	30.6
Periodontist	4	8.2
Ear, Nose and Throat Specialist	2	4.1
Orthodontic department	2	4.1
General medical practitioners	1	2.0
Dermatologist	1	2.0
Hospital (Paediatrician)	1	2.0
Total	49	100

Table 3.9 Past medical history of this cohort of OFG patients

Disorder		No	%
Allergy (excluding asthma and eczema)	Penicillin	2	4
	Plaster	1	2
	Other	11	22
Cardiovascular	Heart Disease	0	0
	Hypertension	2	4
	DVT	1	2
Respiratory	Asthma	8	16
	Bronchitis	1	2
	Allergic rhinitis	1	2
Haematological	Sickle cell anaemia	1	2
	Anaemia	2	4
	Haemophilia	1	2
Endocrine	Diabetes mellitus	2	4
	Thyroid (disease)	3	6
Gastrointestinal tract	Irritable bowel syndrome, constipation, diarrhoea, anal ulceration, perianal irritation, haemorrhoids, recurrent gastric complain, gastroesophageal reflux disease	7	14
Visual		5	10
Hearing		1	2
Central nervous system	Learning disability	1	2
	Lower motor neurone facial palsy	3	6
	Psychiatric problems	3	6
	Migraine	2	4
	Migranous neuralgia	1	2
Other	Eczema	13	26
	Vasculitis	1	2
	Arthritis	3	6
	Osteoarthritis	2	4

Table 3.10 Presenting clinical features of 49 patients with OFG

Signs and symptoms	No	%
Lip enlargement	**37**	**75.5**
Both lips	9	18.4
Upper lip	9	18.4
Lower lip	19	38.8
Other intra-oral	**36**	**73.5**
Cobblestoning	15	30.6
Gingival enlargement	13	26.5
Fissure tongue	7	14.3
Swelling of tongue	1	2.0
Mucosal tags	4	8.2
Other facial	**20**	**40.8**
Median lip fissure	7	14.3
Angular cheilitis and fissure of the lip	7	14.3
Facial swelling and/or erythema	6	12.2
Oral ulceration	**18**	**36.7**
Aphthous-like ulcers	17	34.7
Linear, deep ulcers	2	4.1
Cervical lymphadenopathy	**10**	**20.4**
Neurological	**2**	**4.1**
Facial nerve palsy	2	4.1

Table 3.11 Clinical features of the 49 patients with OFG at disease onset and during long-term follow-up

Patient	Manifestations at presentation	Subsequent manifestations	Patient	Manifestations at presentation	Subsequent manifestations
	Group 1 *Facial swelling only (15 Patients)*			***Group 2*** *Facial swelling with other manifestations (11 Patients)*	
1	Upper/lower lip swelling	Intra-oral ulceration, cobblestoning, cervical lymph node swelling	16	Upper/lower lip swelling , perioral erythema	Intra-oral erythema, mucosal tags and cobblestoning, hypertrophy of palatal mucosa, cervical lymph node swelling
2	Upper/lower lip swelling	Intra-oral ulceration and cobblestoning	17	Upper/lower lip swelling, cobblestoning and gingival hyperplasia	Upper/lower lip swelling
3	Right cheek swelling	Upper/lower lip swelling	18	Upper lip swelling and intra-oral ulceration	Lower lip swelling, cobblestoning, cervical lymph node swelling
4	Upper lip swelling	Lower lip swelling, cobblestoning and tags	19	Upper/lower lip swelling and fissuring	Perioral erythema, cobblestoning
5	Upper lip swelling	Intra-oral ulceration and cobblestoning	20	Lower lip swelling + intra-oral ulceration	Gingival hyperplasia
6	Upper lip swelling	None	21	Upper lip swelling and angular cheilitis	Lower lip swelling
7	Lower lip swelling	Intra-oral ulceration	22	Upper/lower lip swelling and fissuring, angular cheilitis, tags and cobblestoning	Gingival hyperplasia, perioral erythema
8	Lower lip swelling	Upper lip swelling, intra-oral ulceration	23	Upper lip swelling and gingival hyperplasia	Cheek swelling
9	Lower lip swelling	Perioral erythema	24	Lower lip swelling + intra-oral ulceration	None
10	Lower lip swelling	Upper lip swelling	25	Lower lip swelling + intra-oral ulceration	None
11	Lower lip swelling	Cervical lymph node swelling	26	Upper/lower lip and cheek swelling	None
12	Lower lip swelling	None			
13	Lower lip swelling	None			
14	Lower lip swelling	None			
15	Lower lip swelling	None			

Table 3.11 (Cont.) Clinical features of the 49 patients with OFG at disease onset and long-term follow-up

Patient	Manifestations at presentation	Subsequent manifestations	Patient	Manifestations at presentation	Subsequent manifestations
	Group 3 *Oral ulceration only (14 Patients)*			***Group 4*** *Other intra-oral manifestations (5 Patients)*	
27	Intra-oral ulceration	Upper/lower lip swelling	41	Tongue swelling	Gingival hyperplasia
28	Intra-oral ulceration	Upper/lower lip and cheek swelling, cobblestoning	42	Gingival hyperplasia	Upper/lower lip swelling and cobblestoning
29	Intra-oral ulceration	Lower lip swelling	43	Gingival hyperplasia	Upper lip swelling, cobblestoning
30	Intra-oral ulceration	Upper/lower lip swelling, angular cheilitis	44	Gingival hyperplasia and cobblestoning	Lower lip swelling
31	Intra-oral ulceration	Lower lip swelling, cobblestoning, tags, cervical lymph node swelling	45	Cervical lymph node swelling + gingival hyperplasia	Intra-oral erythema and mucosal tags
32	Intra-oral ulceration	Cobblestoning		***Group 5*** *Neurological manifestations (4 Patients)*	
33	Intra-oral ulceration	Lower lip and cheek swelling, tags and cobblestoning	46	Facial palsy	Upper lip and cheeks swelling, perioral erythema
34	Intra-oral ulceration	Lower lip swelling, cervical lymph node swelling	47	Facial palsy	Upper/lower lip swelling, cobblestoning
35	Intra-oral ulceration	Upper/lower lip swelling, lip abscess and mucosal tags	48	Chronic paroxysmal haemicrania	Upper/lower lip swelling
36	Intra-oral ulceration	Lower lip swelling, perioral erythema, cobblestoning, tags, cervical lymph node swelling	49	Facial palsy	Lower lip swelling, gingival hyperplasia, cobblestoning and tags
37	Intra-oral ulceration	Upper lip swelling			
38	Intra-oral ulceration	Lower lip swelling			
39	Intra-oral ulceration	Lower lip and cheek swelling, cobblestoning			
40	Intra-oral ulceration	Upper lip and cheek swelling, angular cheilitis, cobblestone-ing, cervical lymph node swelling			

Table 3.12 Abnormal haematological and serological events in relation to type of therapy (topical* or combined$ [systemic** and topical])

Therapy	Elevated events		Reduced events		Total
	Topical	Combined	Topical	Combined	
Haematological and serological assessments					
Red blood cell count	0	10	3	3	16
White Blood Cell	0	5	0	0	5
Absolute lymphocytes	0	0	7	16	23
Haemoglobin					
Female	0	0	2	1	3
Male	0	0	8	3	11
Platelets	0	3	2	0	5
Hepatic biochemistry					
Alanine aminotransferase	1	9	0	1	11
Alkaline phosphatase	2	0	0	0	2
Albumine	1	2	0	0	3
Renal biochemistry					
Sodium	0	0	0	0	0
Potassium	0	0	0	1	1
Urea	5	19	0	0	24

* One or more of the following agents (topical or intralesional corticosteroids, topical tacrolimus or pimecrolimus).
** One or more of the following agents (systemic corticosteroids, azathioprine, dapsone, clofazimine, thalidomide, mycophenolate mofetil, pentoxifylline, systemic tacrolimus).
$ Any combination of * and **.

Table 3.13 Abnormal haematological and serological events per patient in relation to type of therapy (topical* or combined$ [systemic** and topical])

Therapy	Elevated events		Reduced events		Total
	Topical	Combined	Topical	Combined	
Haematological and serological assessments					
Red blood cell count	0	3	1	2	5
White Blood Cell	0	5	0	0	5
Absolute lymphocytes	0	0	4	7	11
Haemoglobin					
Female	0	0	1	1	2
Male	0	0	5	2	7
Platelets	0	2	1	0	3
Hepatic biochemistry					
Alanine aminotransferase	1	3	0	1	5
Alkaline phosphatase	2	0	0	0	2
Albumine	1	2	0	0	3
Renal biochemistry					
Sodium	0	0	0	0	0
Potassium	0	0	0	1	1
Urea	4	4	0	0	8

* One or more of the following agents (topical or intralesional corticosteroids, topical tacrolimus or pimecrolimus).
** One or more of the following agents (systemic corticosteroids, azathioprine, dapsone, clofazimine, thalidomide, mycophenolate mofetil, pentoxifylline, systemic tacrolimus).
$ Any combination of * and **.

Table 3.14 Different topical and systemic agents used to control OFG lesions in the present cohort of patients

Agent	No of patients	%
Topical		
Fluticasone propionate 0.05% cream- Cutivate	23	47
Clobetasol propionate 0.05% cream - Dermovate	7	14.3
Fluticasone propionate,400 mcg in 15 ml water as mouthwash	2	4.1
Fluticasone propionate,50 mcg spray	15	30.6
Fluticasone propionate inhaler -Flixotide	2	4.1
Betamethasone mouthwash	10	20.4
Triamcinolone acetonide -Adcortyl	6	12.2
Hydrocortisone	2	4.1
Intralesional triamcinolone acetonide	6	12.2
Tacrolimus 0.03%	5	10.2
Tacrolimus 0.1%	22	44.9
Pimecrolimus 1%	1	2.0
Systemic		
Prednisolone	13	26.5
Deflazacort	8	16.3
Azathioprine	7	14.3
Mycophenolate Mofetil	2	4.1
Clofazimine	1	2.0
Dapsone	1	2.0
Thalidomide	7	14.3
pentoxifylline	3	6.1
Systemic tacrolimus	1	2.0

Table 3.15 Total number of topical and systemic agents employed in the management of this cohort of patients with OFG

No of agents	Number of patients		
	Topical	Systemic	Total (topical and systemic)
0	5	28	4
1	12	9	8
2	17	8	15
3	5	1	4
4	5	1	6
5	3	1	4
6	2	1	4
7	0	0	1
8	0	0	2
11	0	0	1
Total number of patients	49	49	49

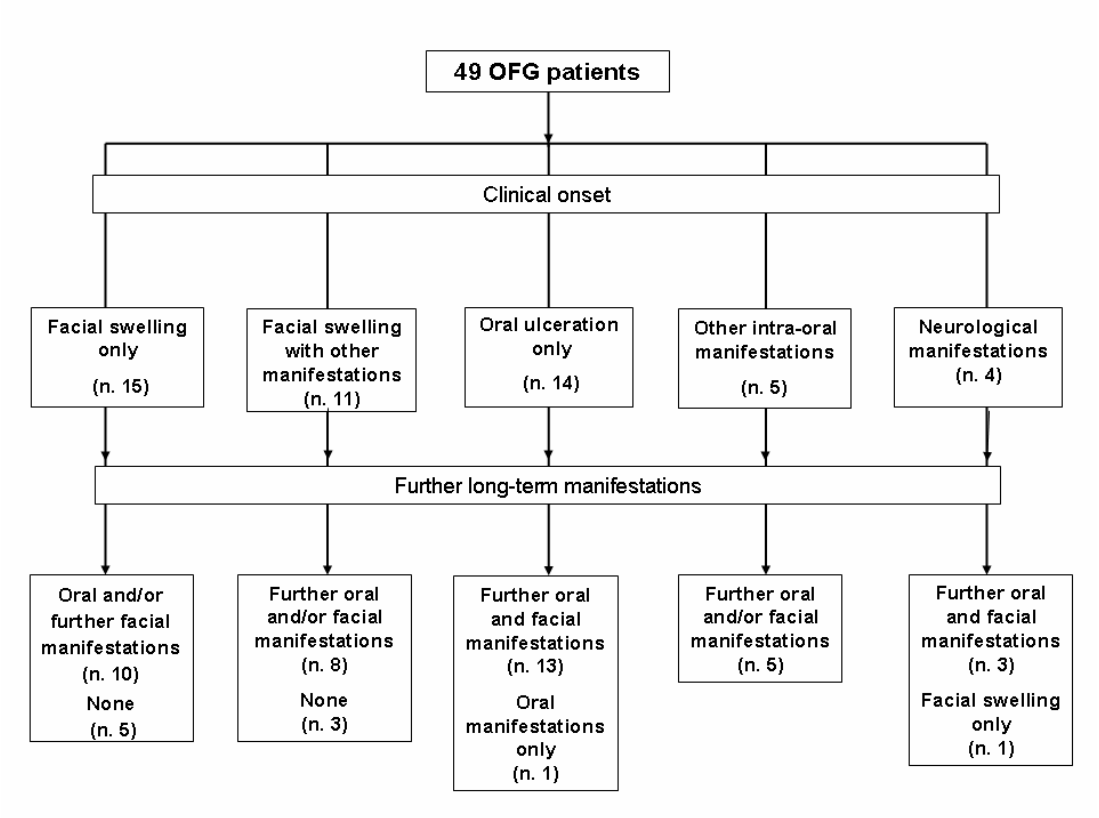

Figure 3.1 Major patterns of disease onset in this cohort of 49 patients

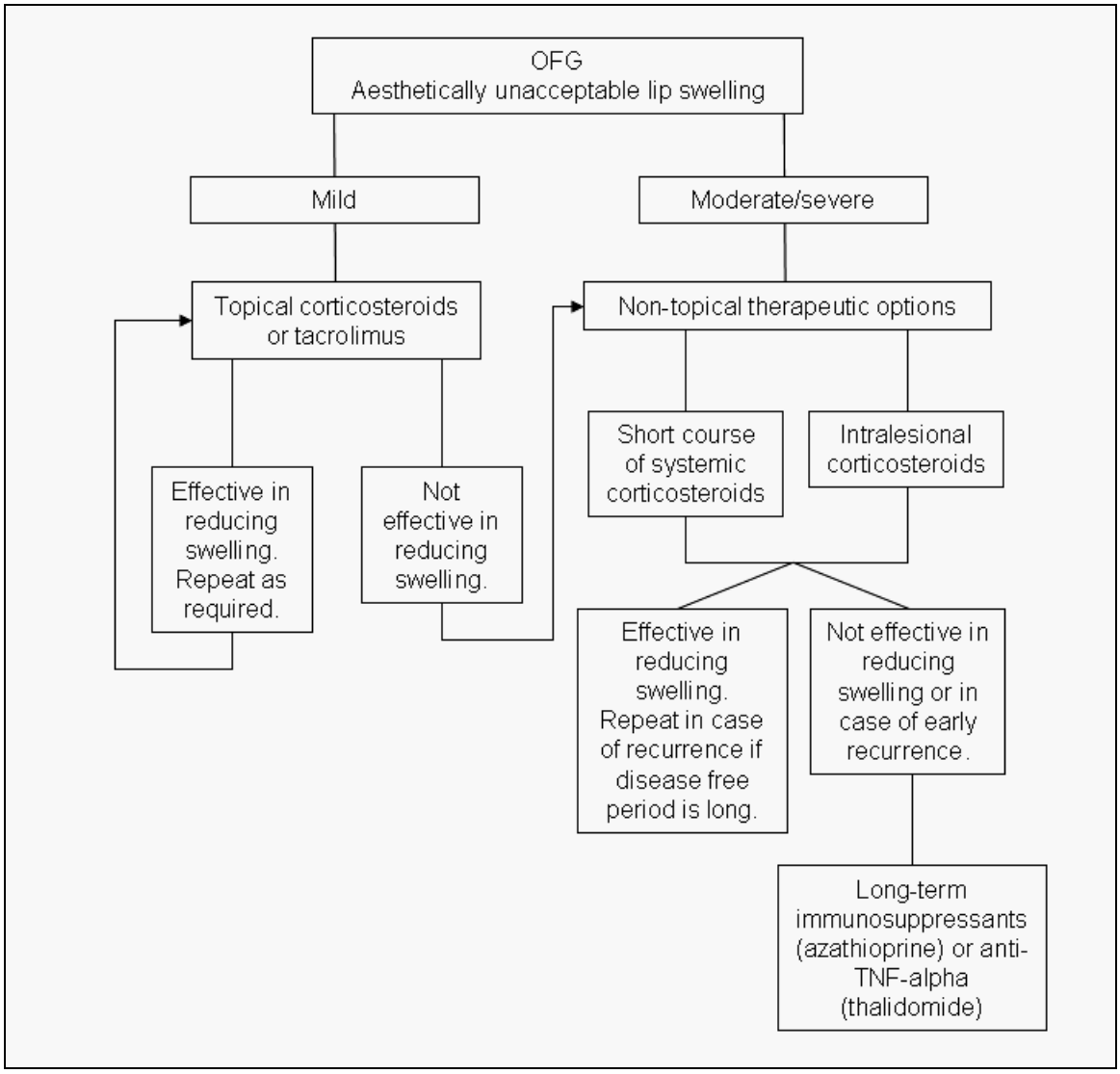

Figure 3.2 Therapeutic ladder of lip swelling of oro-facial granulomatosis

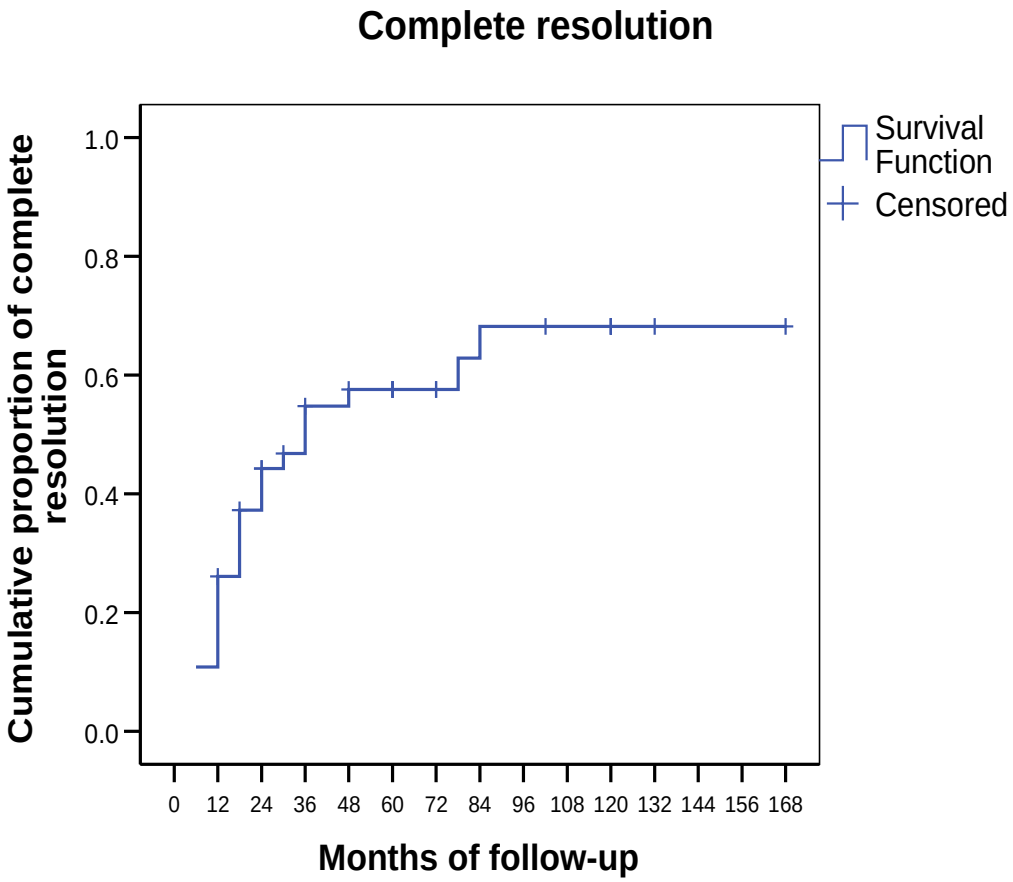

Figure 3.5 Kaplan Meier plot of clinical outcome of soft tissue swelling. The graph shows that 23 (50%) of the patients had complete resolution of the orofacial swelling within 3 years of treatment. Also, about a quarter of patients had complete resolution of swelling within the first year of therapy. However, there were still 6 patients who did not have complete resolution of swelling during the follow-up period.

CHAPTER 4

MUCOUS MEMBRANE PEMPHIGOID

4.1 INTRODUCTION

Mucous membrane pemphigoid (MMP), sometimes termed cicatrical pemphigoid, is a group of uncommon acquired, autoimmune disorders characterised by the generation of autoantibodies directed to the hemidesmosomal protein junction of the epthelial surface, creating a disruption of cell adhesion and tissue integrity. The resultant vesiculoulcerative lesions predominately affect mucous membranes and, to a lesser degree, the skin (Chan et al., 2002).

There is a wide range of other acquired pemphigoid-like immune-mediated sub-epithelial blistering diseases (IMSEDs), including bullous pemphigoid, pemphigoid gestationis, lichen planus pemphigoides, dermatitis herpetiformis, linear IgA disease, anti-p200, anti-p105, and anti-p450 pemphigoid, bullous systemic lupus erythematosus, chronic bullous dermatosis of childhood, and epidermolysis bullosa acquisita, but MMP is the most common of these disorders affecting the oral mucosa (Chan et al., 1993; Verdolini and Cerio, 2003; Darling and Daley, 2005; Eschle-Meniconi et al., 2005).

Although some authors have suggested that MMP could be subdivided into ocular and oral variants (Chan et al., 1993; Mobini et al., 1998; Hoang-Xuan et al., 1999; Dayan et al., 1999), an International Consensus Conference in 1999 concluded that there is only one disorder, which they recommend identifying as mucous membrane pemphigoid, with different clinical presentations (Chan et al., 2002). MMP has been termed cicatrical pemphigoid (Latin word means scar) however, not all patients, indeed very few, experience scar formation. Also some authors have employed the term “benign” MMP as oral lesions are usually self-limiting without major complications, such as scar formation (Dayan et al., 1999), although ocular lesions may lead to blindness. The most recent consensus view has recommended using mucous membrane pemphigoid instead of all other terms (Chan et al., 2002).

4.1.1 Prevalence

MMP usually affects people in their middle to late life (Laskaris et al., 1982; Silverman et al., 1986) and rarely affect young individuals (Cheng et al., 2001; Musa et al., 2002; Lourenco et al., 2006). Desquamative gingivitis may be a common presenting oral sign in young patients (Lourenco et al., 2006).

The mucocutaneous lesions in young patients are more common and the disease may be more severe than in older persons. There is no racial or ethnic predilection, although females are more frequently affected than males (Laskaris et al., 1982; Silverman et al., 1986; Cotell et al., 2000; Rauz et al., 2005) with a ratio of 1.5:1 (Laskaris et al., 1982).

MMP is rare (Gallagher and Shklar, 1987), and little is known about its epidemiology. However, an idea of the prevalence of MMP can be obtained from reviewing other immune mediated subepidermal diseases (IMSEDs) studies. A mean annual incidence of IMSEDs was reported as 10.4 per million people in a French population, with an estimated 590 new cases annually (Bernard et al., 1995). A 2-year retrospective study of 67 IMSED patients in Singapore reported bullous pemphigoid (BP) was the most common disorder (59; 88%), while four (6%) had epidermolysis bullosa acquisita, two (3%) linear IgA disease, and two (3%) bullous systemic lupus erythematosus; there were no MMP cases identified (Wong and Chua, 2002).

The prevalence of MMP in the United Kingdom is unknown. However, a recent population-based study identified 869 people with BP (Langan et al., 2008) indicating an incidence rate of 4.3 per 100,000 individuals and a yearly increase of 17%. The annual incidence of BP in Grampian region of Scotland was estimated to be 14 cases per million per year (Gudi et al., 2005).

4.1.2 Clinical features

MMP can affect any mucosal surface with oral mucosa involved in most instances. Skin lesions can also develop; however, this is less common than in bullous pemphigoid (Yeh et al., 2003). The clinical features of MMP and

their effect on quality of life depend upon the lesion site, the severity, and duration of the disease.

4.1.2.1 Oral involvement

Oral lesions are present in most cases, either alone or in combination with other mucocutaneous surfaces (Table 4.1).

Laskaris and co-workers (1982) reported that all of their 55 MMP patients presented with oral mucosa lesions, but only 3 (5.5%) patients developed skin lesions. In nearly all the patients (96.4%) oral mucosal lesions preceded cutaneous involvement and all patients who presented initially with skin lesions eventually developed oral lesions. The gingivae was the most common intra-oral site involved (35 patients), followed by buccal mucosa (32), palate (14), alveolar ridge (9), tongue (8), and lips (4). About half of this cohort developed extra-oral lesions such as ocular (12 patients), pharyngeal (9), nasal (4), and genital mucosa (3).

In another case series of 23 patients with MMP, 83% presented with oral lesions, 70% had ocular involvement, and 22% had cutaneous lesions (Vincent et al., 1993). Agbo-Godeau and co-workers (2004) reported that 15 of their 17 MMP patients had gingival lesions (in six, this was the only manifestation), other affected sites included skin, ocular, nasal, and/or laryngeal mucosa.

The oral manifestations of MMP typically commence as recurrent tense clear or blood-filled blisters, which generally last longer than those of pemphigus vulgaris. The blisters usually burst, creating areas of pseudomembrane-covered, superficial ulceration, and erosions with irregular margins (Gallagher and Shklar, 1987). These areas of ulceration may coalesce to produce large eroded patches. Oral scarring is rare (Shklar and McCarthy, 1959). Nikolsky's sign may be positive in some patients. The disorder typically affects sites of trauma such as the attached gingivae, and palatal mucosa although lesions are found less commonly on the tongue and labial

and buccal mucosa (Chan et al., 2002). As a consequence of the oral ulceration, patients complain of pain, dysphagia, and/or dysarthria, which may lessen quality of life (Sami et al., 2002a).

Gingivitis is common among MMP patients; this may be a manifestation of disease (desquamative gingivitis) or a consequence of the accumulation of local factors (e.g., plaque) due to the patient's inability to practice effective oral hygiene. The gingivae appear deep red and eroded/ulcerated, and desquamation will usually involve the facial/buccal gingival margin and attached gingivae. Patients may report bleeding gums following tooth cleaning (Silverman et al., 1986; Gallagher and Shklar, 1987).

Patients with active MMP and under therapy have higher plaque indices than those in remission (Tricamo et al., 2006). In addition, Class 1 recession is more common among patients having the disease more than 5 years (Tricamo et al., 2006). The risk of developing lesions in any other mucocutaneous surface in patients presenting initially with oral mucosal lesions has been estimated to be only 0.12 per person-year (Thorne et al., 2004).

4.1.2.2 Ocular involvement

Eye involvement represents one of the serious complications of MMP (Ahmed et al., 2004; Rauz et al., 2005). In a case series of 65 MMP patients, 7 (11%) patients had evidence of symblepharon (Silverman et al., 1986) and it estimated that 40% of patients with oral lesions also developed ocular lesions (Dayan et al., 1999). Thorne et al. (2004) reported that the risk of ocular involvement in MMP patients is 0.05 per person-year.

As with oral involvement, ocular MMP affects older individuals (mean age of 64; range of 20-87) years (Foster, 1986) and more common in women than men, with a ratio of 1.6:1 (Mondino and Brown, 1981).

Initially, patients may complain of dry eyes, irritation, discomfort, and photophobia due to chronic progressive conjunctivitis. Vesicles are rarely observed on the conjunctiva and lesions usually present as conjunctivitis (Cotell et al., 2000). Conjunctival erosions, scarring, symblepharon, ankyloblepharon, entropion, trichiasis, and squamous metaplasia may occur and lead to decreased or complete loss of vision (Cotell et al., 2000). Initially, one eye usually involved, with the inflammatory process involving the other eye within 2 years (Yeh et al., 2003).

There are a number of staging systems for ocular MMP. The Mondino and Brown (1981) method is based on the conjunctival destruction and the presence of symblepharon: (i) chronic conjunctivitis and subepithelial fibrosis, (ii) fornix foreshortening, (iii) any degree of symblepharon, and (iv) ankyloblepharon and a frozen globe (Mondino and Brown, 1981).

Another is based on the percentage of conjunctival shrinkage and inferior fornix depth at 4 stages; (i) $\leq$25% , (ii) 25% to 50%, (iii) 75%, and (iv) end stage with complete obliteration of the conjunctival fornices (Tauber et al., 1992).

Rowsey, et al. (2004) measure the distance between the lower limbus and the posterior edge of the retracted lower eyelid margin in 3 different gaze positions: looking up, looking up to the right, and looking up to the left. Foster and co-workers (1982) used specific clinical signs for staging. This scoring system comprised 4 staging (i) conjunctival inflammation, mucous discharge, small patches of rose bengal-staining conjunctival epithelium, and conjunctival subepithelial fibrosis, (ii) fornix shortening and blunting of the angle of reflection of the conjunctiva from the eyelid and fornix onto the globe, (iii) symblepharon, and (iv) sicca syndrome, keratinization, and ankyloblepharon.

Older patients ($\geq$70 years) have milder ocular disease compared to younger patients, where the disease progresses more rapidly and is less responsive to treatment. However, mucocutaneous lesions are more prevalent in the older patients (Rauz et al., 2005).

Extra-ocular involvement in patients with eye disease is not uncommon. In one cohort of 36 patients with ocular MMP, oral mucosal lesions were found in 55.6% patients, nasopharyngeal in 30.6%, genital in 27.8%, and 22% of this cohort had cutaneous lesions (Rauz et al., 2005).

4.1.2.3 Other mucosal involvement

Although more commonly found in oral and ocular mucosa, MMP also may affect the nasal, pharyngeal, laryngeal, and genital mucosa (Mobini et al., 1998).

MMP patients with nasal involvement may complain of epistaxis or chronic discharge. Ulceration of the septum may lead to scarring and adhesions resulting in nasal airway obstruction (Whiteside et al., 2003).

Dysphonia, dysphagia, and discomfort may develop if oropharyneal or laryngeal mucosa is affected. The laryngeal mucosa can be the only site involved (Fisher et al., 1980), with lesions presenting as erythema, edema, or blisters in the supraglottis area which may rupture leading to ulceration and erosions and subsequent mucosal scarring (Ojha et al., 2007).

Patients with oesophageal lesions may complain of dysphagia and odynophagia due to strictures and web formation. Acid reflux, aspiration, and a chronic cough also may be present (Syn and Ahmed, 2004). In some patients the esophagus may be the only site involved (Sallout et al., 2000).

In a large cohort of 110 MMP patients, nasal mucosa was the most affected upper aeriodigestive mucosa (35 patients), followed by pharynx (19), and larynx (10) (Alexandre et al., 2006).

Involvement of the bronchial tract is uncommon. Muller and Salzer (1988) reported a young patient who developed severe stenosis of the left mainstem bronchus. If the genitalia are involved, painful erosions and ulcers may

present leading to pruritus, discomfort, and/or dysuria (Schoeffler et al., 2004; Alkali et al., 2007).

4.1.2.4 Skin involvement

Although rare, cutaneous lesions have been found on the scalp, neck, or the trunk and resemble those of bullous pemphigoid. There is a wide variation in skin involvement reported in the literature. It ranges between 0-10.6% in reported cohorts of MMP patients with oral lesions primarily (Shklar and McCarthy, 1971; Laskaris et al., 1982; Silverman et al., 1986; Mobini et al., 1998), however, some of these studies excluded patients with skin lesions initially (Silverman et al., 1986; Mobini et al., 1998).

Skin lesions can either be recurrent tense bullae, similar to those seen in bullous pemphigoid, which rupture and heal without significant scarring, or flaccid blisters surrounded by erythema and usually associated with scaring (Brunsting-Perry cicatricial pemphigoid) which is usually restricted to the head and neck area. Blisters generally rupture within 2 days leading to denuded eroded areas covered by fibrin. Healing is often associated with either hyperpigmentation or hypopigmentation areas and sometimes with scar formation (Brunsting and Perry, 1957; Scott and Ahmed, 1998; Miziara et al., 2002; Yu et al., 2007).

4.1.3 Associated disorders

MMP had been reported to be associated with other autoimmune diseases, including systemic lupus erythematosus (Redman and Thorne, 1981) and rheumatoid arthritis (Spigel and Winkelmann, 1978). In one cohort 32% of patients with MMP found to have other autoimmune disorders (Nayar et al., 1991).

Patients with anti-epiligrin MMP have been reported to be at risk of malignancy (Fujimoto et al., 1988; Uchiyama et al., 2000). Sadler et al (2007) summarized all the reported 15 cases of anti-epiligrin MMP who developed malignancy. In a cohort of 35 with anti-epiligrin cicatricial pemphigoid, ten

(29%) patients developed solid tumours. Tumours involved the lung (3 patients), stomach (3), colon (2), or uterus (2) (Egan et al., 2003).

On the other hand, ocular MMP patients with antibodies to human β4 integrin subunit (Letko et al., 2007) and patients with oral MMP with antibodies to α6 (Malik et al., 2007) have been reported to have a reduced relative risk for developing cancer.

4.1.4 Pathogenesis

The aetiopathogenesis of MMP is largely unknown. In immune-mediated subepithelial blistering diseases (IMSEBDs), antigen-provoked-autoantibodies attack different antigens in the hemidesmosomal structure in the basement membrane zone (BMZ) leading to the deposition of immunoglobulins, complement activation, and chemotactic factor production that eventually result in the loss of attachment between dermis and epidermis and subepithelial blister formation. Antibodies targeting different basement membrane components may give rise to clinically indistinguishable disease. IgG autoantibodies, particularly IgG4, are the main antibodies in MMP; however, IgA also has been found in some patients (Eversole, 1994).

The antigenic targets of MMP are highly variable and extend to an epitope level (Hingorani and Lightman, 2006). MMP is associated most frequently with IgG to BP180 (bullous pemphigoid 180 antigen) and less often with antibodies against BP230, laminin 5, laminin 6, uncein, type VII collagen, and integrin subunits β4 or α6 (Chan et al., 2002; Parisi et al., 2003; Yancey, 2005).

In a study of 124 patients designed to identify serum autoantibody profiles characteristics, Oyama and co-workers (2006) found 75% of patients had IgG and/or IgA (51%) antibodies against BP180 or its soluble ectodomains. Other antigens targeted by IgG autoantibodies include BP230 (27%), β4 integrin (21%), and laminin 5 (2%). The presence of both IgG and IgA anti-BP180 were associated with more severe disease process (Oyama et al., 2006).

Oral involvement is usually associated with autoantibodies against α6 integrin (Bhol et al., 2001; Rashid et al., 2006), while ocular involvement is more often associated with autoantibodies against laminin 5 or β4 integrin (Yancey, 2005; Rashid et al., 2006). In the study by Oyama and co-workers (2006), most of the patients (85%) with anti β4 integrin had ocular involvement.

Levels of serum IgG and IgA antibodies may correlate with clinical severity (Setterfield et al., 1999). A direct correlation has been described between levels of antibodies to β4-integrin with both disease activity and response to therapy in patients with MMP attacking multiple mucocutaneous surfaces (Yeh et al., 2004). However this requires specific antigenic targets to be used that are not typically used in the clinical practice.

4.1.5 Aetiology

The precise aetiology of MMP is unknown. A number of factors such as environmental agents and genetic susceptibility have been suggested for the induction of antibodies that ultimately give rise to MMP. Moreover, some drugs can evoke lesions that mimic MMP.

4.1.5.1 Genetics

A statistically significant increase in the frequency of DR4 and DQw3 HLA antigens has observed in a group of MMP patients (Nayar et al., 1991). Human leukocyte antigen DQB1*0301 found to be significantly associated with oral pemphigoid in Caucasian patients from United States (Yunis et al., 1994) and Italy (Carrozzo et al., 2001). However, this was also associated with other subgroups of MMP, such as patients with ocular involvement (Chan et al., 1997; Setterfield et al., 2001).

4.1.5.2 Cellular autoimmunity

T-cell lymphocytes, especially those involved in Th2 immunity may have a role in pemphigoid. The pathogenesis may be mediated by an autoantibody-induced complement and subsequent cytokine and leukocyte recruitment and

adhesion and enzyme release resulting in blister formation (Rico et al., 1999; Verdolini and Cerio, 2003).

Vascular and intercellular cell adhesion molecules (VCAM and ICAM-1) on endothelial cells of dermal vessels and perivascular fibroblasts are higher in lesional biopsies of MMP patients than in BP patients or healthy controls (Giomi et al., 2005). The high levels of endothelial ICAM-1/VCAM and VLA-4 enhance secretion of interleukin (IL-4) by Th2- lymphocytes which could results in fibroblast activation and induces CAM and subsequent chronic cycles of inflammation have been suggested to cause the resulting scar formation (Giomi et al., 2005).

4.1.5.3 Drugs

The drugs likely to induce pemphigoid-like lesions have been reported in a detailed review by Vassileva (1998). These drugs including furosemide (Koch et al., 1996; Lee and Downham, 2006), 5-aminosalicylic acid (Ferris et al., 2005), ampicillin (Hodak et al., 1990), penicillin (Wozniak et al., 2006) and terbinafine (Aksakal et al., 2003).

4.1.6 Diagnosis

Immune-mediated subepithelial blistering diseases cannot be differentiated on clinical grounds alone, as they share the same features. Histopathological studies are often not of value if the epithelial layer lost.. Even when present, the sub-epithelial clefting could be a feature of several different bullous disorders. Direct immunofluorescence (DIF) is commonly used to diagnose this group of disorders, and in differentiating many of these conditions; however conventional DIF cannot distinguish between subsets of MMP (Solomon et al., 2007).

4.1.6.1 Histopathology

Unlike the histopathological features of PV, which is characterized by intraepithelial bulla formation and presence of acantholysis, MMP and other IMSEDs are histologically characterized by a definite cleavage between

dermis and epidermis at the basement membrane level. Acantholysis is not a feature of MMP. The bulla fluid is usually clear with scattered polymorphonuclear leukocytes, lymphocytes, histiocytes, and, rarely, eosinophils (Shklar and McCarthy, 1959; Sciubba, 1996; Casiglia et al., 2001).

4.1.6.2 Immunofluorescence

Direct immunofluorescence (DIF) of MMP perilesional tissue demonstrates a linear tissue-fixed deposition of IgG/IgA and/or C3 at the BMZ (Chan et al., 2002). DIF, most often performed on perilesional skin or mucous membrane tissues, is usually used to confirm the diagnosis of MMP (Chan et al., 2002; Thorne et al., 2004). In a cohort of 33 patients with oral MMP lesions, DIF was positive for IgG (97%), IgA (27%), IgM (12%), and C3 (73%) (Laskaris and Angelopoulos, 1981). IgG was present in 57% of another group of 23 MMP patients, and C3 in 66% (Vincent et al., 1993). DIF results were positive in 60%-80% in a retrospective study of 280 patients with ocular disease (Thorne et al., 2004).

However, other disorders such as bullous pemphigoid and epidermolysis bullosa acquisita, share with MMP the deposition of immunoglobulins at the BMZ but can be differentiated from MMP by clinical features (Chan et al., 2002).

4.1.6.3 Indirect immunofluorescence

Indirect immunofluorescence (IIF) does not usually detect circulating IgG antibodies in the serum of MMP patients with lesions limited to oral mucosa (Gallagher and Shklar, 1987; Mutasim, 1997; Bagan et al., 2005). The titre of circulating antibodies in MMP is most commonly absent or significantly lower than in bullous pemphigoid; this may be due to the low sensitivity of the IIF techniques usually used to detect the circulating antibodies or may be that MMP is a limited process (Laskaris and Angelopoulos, 1981). However, negative IIF results do not exclude MMP (Ahmed et al., 2004).

IIF was positive for IgG in 12 of 33 patients (36%) with oral MMP lesions but negative for IgA, IgM, C3, and/or fibrin (Laskaris and Angelopoulos, 1981). In another study, 24% of subjects had circulating autoantibodies, these being most likely in patients with ocular involvement (30.6%) (Thorne et al., 2004). When highly specific antigens are employed in IIF the titers of detectable antibodies to both α6 and β4 and integrin have been found to correlate with disease activity (Letko et al., 2000; Sami et al., 2002b).

4.1.6.4 Other diagnostic methods

A number of additional tools are available to confirm the diagnosis of MMP, but these have not found their way into routine clinical practice. Immunoperoxidase-based assays have been reported to be more sensitive than immunofluorescence in diagnosing of MMP (Power et al., 1995; Ahmed et al., 2004). However, Thorne and co-workers (2004) found the sensitivity of an immunoperoxidase was similar to that of DIF.

Radioimmunoassay (Ahmed et al., 1989) and immunoblot assay (Bhol et al., 1996) may be sensitive methods to detect circulating antibodies of MMP and are used to define target antigens, but they are not considered to be of practical value in everyday clinical practice. Similarly direct immunoelectron microscopy (Bernard et al., 1990) and computer-aided fluorescence overlay antigen mapping and laser scanning confocal microscopy (Solomon et al., 2007) are research tools rather than clinical technique.

4.1.7 Treatment

The goals for the treatment of MMP are to control new blister formation, accelerate healing of ulcers and erosions, and induce long periods of remission. There are few randomized controlled trials (Lozada-Nur et al., 1994) and only one Cochrane-systematic review (Kirtschig et al., 2003) on the treatment of MMP and most relevant information comes from case series and non-randomized trials, reflecting the rarity of the disease (Table 4.2).

Patients may be divided into high-risk and low-risk. The high-risk group includes patients with ocular, pharyngeal, laryngeal, esophageal, and/or genital lesions in whom systemic agents may be necessary to control their disease. Low-risk patients are considered to be those with oral and with or without cutaneous lesions in whom topical corticosteroids may be sufficient to lessen or control the disease (Vincent et al., 1993; Carrozzo et al., 1997; Chan et al., 2002; Agbo-Godeau et al., 2004).

Therapy has historically included systemic corticosteroids, corticosteroid-sparing immunosuppressive drugs and high potency topical corticosteroids. Treatment of widespread mucosal and cutaneous lesions of MMP necessitates a multidisciplinary management and systemic corticosteroids alone or in combination with other agents are still the first choice to control acute exacerbations (Sacher and Hunzelmann, 2005).

A wide range of agents/regimens have been proposed in the treatment of MMP affecting the oral mucosa. These include:

Topical corticosteroids

Oral lesions of MMP are usually managed by topical corticosteroids (Silverman et al., 1986), however some patients with only oral lesions may necessitate treatment with systemic agents (Megahed et al., 2001; Carrozzo et al., 2008). High potency topical corticosteroids (e.g., clobetasol) subsequent to a course of systemic corticosteroids are suggested to usually control MMP lesions (Carrozzo et al., 1997). Candidosis is the most common complication of potent topical corticosteroids hence some authors recommends the use of antifungal agents with potent topical corticosteroids (Silverman et al., 1986; Gonzalez-Moles et al., 2002). Desquamative gingivitis may respond well to 0.05% clobetasol propionate mixed with 100,000 IU/cc of nystatin in an adhesive paste applied in a tray (Gonzalez-Moles et al., 2002; Gonzalez-Moles et al., 2003).

Systemic corticosteroids

Systemic corticosteroids alone or in combination with adjunct immunosuppressive drugs are considered the mainstay of treatment of severe MMP and have proven effective for many patients (Ciarrocca and Greenberg, 1999; Arash and Shirin, 2008). However, in some patients other therapeutic modalities are needed to control the disease activity and decrease the adverse side effects (ASEs) which can develop with long-term corticosteroid use (Megahed et al., 2001; Carrozzo et al., 2008). Combinations of corticosteroids, dapsone and cyclophosphamide have been reported to give good results (Espana et al., 2005).

Ciclosporin

Ciclosporin has been used to treat a limited number of MMP patients (Azana et al., 1993; Williams et al., 1995; Boedeker et al., 2003). The use of topical cyclosporine with other agents (topical and systemic corticosteroids, systemic azathioprine, and tacrolimus) failed to control the oral erosions of one patient with MMP (Salzano et al., 2006). The disease did, however, respond to mycophenolate mofetil and systemic minocycline.

Tetracycline

Tetracycline may be an effective agent in the management of desquamative gingivitis (Ronbeck et al., 1990). A combination of minocycline and nicotinamide was reported effective in the management of MMP (Poskitt and Wojnarowska, 1995a; Reiche et al., 1998). Improvement in MMP was seen in a patient who received topical corticosteroids, oral nicotinamide, and tetracycline (Mallon and Wojnarowska, 1994).

A patient who had a tracheotomy due to laryngeal MMP had dramatic clinical improvement following a course of tetracycline hydrochloride and niacinamide (Sakamoto et al., 2002). Similarly a patient whose lesions were resistant to topical corticosteroids had rapid improvement after treatment with tetracycline and nicotinamide (Kreyden et al., 2001). Resolution of oral lesions and no relapse were reported in a patient who received a mycophenolate mofetil (up to 2 g per day) and systemic minocycline (up to

200 mg per day), although she did not respond to several earlier treatment modalities, including topical and systemic corticosteroids, topical ciclosporin, and several antibiotics (Salzano et al., 2006).

Tacrolimus

Topical tacrolimus has been used to treat oral (Assmann et al, 2004; Suresh et al., 2006), ocular (Letko et al., 2001; Hall et al., 2003; Michel and Gain, 2006), and genital MMP (Gunther et al., 2004; Lebeau et al., 2004). Its application in genital lesions usually resulted in complete remission within 3 months (Gunther et al, 2004; Lebeau et al., 2004). It was used successfully in oral lesions of a patient with long-term mucocutaneous MMP who was resistant to conventional treatment (Suresh et al., 2006). However, in a cohort study of patients with uncontrolled ocular disease treated with conventional immunosuppressive agents, 67% of patients failed to respond to tacrolimus, while two patients responded just partially. The authors conclude that tacrolimus is unable to induce remission of ocular MMP lesions (Letko et al., 2001).

Except for the transient burning sensation at the application site, which is common with topical application of tacrolimus, it usually well tolerated with no major side effects (Assmann et al, 2004; Gunther et al, 2004).

Dapsone

A combination of dapsone and topical corticosteroids resulted in 75% resolution of oral lesions in a cohort of MMP patients (Ciarrocca and Greenberg, 1999). Dapsone may similarly improve MMP skin lesions (Syn and Ahmed, 2004).

Dapsone however requires close monitoring even when low doses are used. In a recent study of 10 patients, Wertheim et al. (2006) reported that 50% had reticulocytosis including four with clinically significant haemolytic anemia with a raised mean cell volume and a steady fall in haemoglobin from baseline levels.

Methotrexate

Methotrexate has been reported to be effective in the management of MMP (Miserocchi et al., 2002; McCluskey et al., 2004). In a retrospective, interventional case series, it was concluded that low-dose oral methotrexate is highly effective and well tolerated. The authors considered it to be a first-line systemic agent for the management of ocular lesions (McCluskey et al, 2004).

Anti-TNF-α agents

Infliximab resulted in rapid clinical improvement in a patient with multiple mucosal involvements of MMP (Heffernan and Bentley, 2006). The tumour necrosis factor alpha antagonist etanercept has also been reported as an effective agent in the management of MMP (Sacher et al., 2002; Canizares et al., 2006). Twice weekly injection of etanercept (25 mg) resulted in improvement of oral lesions of three patients and in stabilizing the ocular disease of the one patient with MMP (Canizares et al., 2006). In a recent case report, etanercept (50 mg weekly) was used successfully to manage eye lesions in one MMP patient and leading to a decrease in prednisolone therapy (John et al., 2007). Thalidomide was used in a patient with resistant MMP lesions (Duong et al, 2002). However, thalidomide is a difficult drug to use and has the potential for many adverse drug affects such as teratogenicty and neuropathy. One MMP patient developed venous thrombosis following treatment with thalidomide (Howell and Johnson, 2004).

Rituximab

Rituximab (862.5 mg intravenously) induced remission in a patient with multiple mucocutaneous involvement recalcitrant to different immunosuppressant agents including pulsed intravenous methylprednisolone, oral prednisolone, cyclophosphamide and dapsone (Ross et al., 2009).

Mycophenolate mofetil

In a recent case report, mycophenolate mofetil (MMF) resulted in significant improvement in the clinical signs of 2 patients with oral MMP (Carrozzo et al., 2008). Prednisolone had been combined to MMF to accelerate healing and achieve remission (Alkali et al., 2007). Thorne et al. (2005) suggested that MMF may be an effective adjuvant agent to corticosteroids in the management of inflammatory eye conditions including MMP. As noted previously MMF (up to 2 g per day) and systemic minocycline (up to 200 mg per day) were used successfully in the management of a patient with severe oral MMP who had responded only partially to different topical and systemic agents and developed many adverse side effects (Salzano et al., 2006). Three patients responded well to treatment with MMF and prednisolone. The patients had no disease recurrence for 6 to 14 months after treatment was discontinued and none had any adverse side effects (Megahed et al., 2001). Adding MMF (1.5 or 2 g per day) to dapsone, achieved good control of mucosal lesions in 10 of the 14 MMP patients not controlled by dapsone and/or sulfasalazine and allowed a decreasing of dapsone dosage (Ingen-Housz-Oro et al., 2005).

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been reported to be a safe and effective intervention for the management of MMP recalcitrant to conventional immunosuppressive agents (Foster and Ahmed, 1999).

In 20 patients with oral MMP, patients who received IVIg had statistically significant shorter treatment duration, fewer relapses, fewer adverse side effects, and a better quality of life in comparison with patients received systemic prednisone with other immunosuppressive agents (e.g. methotrexate, azathioprine, cyclosporine cyclophosphamide) (Ahmed and Colon, 2001). IVIg was effective for the treatment of one woman with severe widespread laryngeal lesions who had been reluctant to use any other immunosuppressive as she was wishing to become pregnant (Gürcan and Ahmed, 2009). Remission was achieved in all of 10 patients with progressive ocular MMP and whose disease had been recalcitrant to a variety of other

therapies (Foster and Ahmed, 1999). The mean treatment duration was 19.3 months (range 16 to 23 months) and there were no reported ASEs. There have now been several additional studies suggesting that IVIg can lessen disease and recurrence of MMP (Sami et al., 2002a; Sami et al., 2002b; Letko et al., 2004; Sami et al., 2004). IVIg (1 g/kg body weight on 2 consecutive days) given every 4 weeks led to dramatic improvement in the oral and ocular lesions of MMP in a patient who failed to respond to different immunosuppressive therapies (Leverkus et al., 2002). Furthermore, IVIg allowed reduction in systemic corticosteroids and other immunosuppressant agents in 6 patients with severe oral MMP (Mignogna et al., 2008). IVIg was administered without any significant ASEs in a cohort with autoimmune mucoucutaneous blistering diseases, which included 15 MMP patients, who had developed ASEs to conventional immunosuppressive therapy (Daoud and Amin, 2006). However, a retrospective analysis of 19 patients with various autoimmune mucoucutaneous blistering diseases reported that only four (21%) achieved complete remission, five (26%) did not respond at all and 10 (53%) had only a partial response (Segura et al., 2007). Daoud and Amin (2006) has suggested that as IVIg seems to give rise to few ASEs that require physician visits, laboratory studies and/or hospitalization such therapy may be statistically significantly less expensive than the conventional immunosuppressive therapy.

The clinical response to IVIg may become weaker with time, Yu and co-workers reported a patient who had a significant improvement in mucoucutaneous lesions after receiving IVIg (1g/kg), however, the clinical response to subsequent cycles of IVIg lessened (Yu et al., 2007).

Plasmapheresis

Plasmapheresis decreases levels of circulating autoantibodies. Bohn et al. (1999) reported two patients with severe oral MMP, neither of whom responded to corticosteroids and other immunosuppressive agents. Their disease improved with plasmapheresis followed by cyclophosphamide

therapy. Although both patients developed urticaria and mild hypotension during treatment, no active disease was observed or additional treatment required over the next 6 years.

Other treatments

Tracheotomy may be required in patients with laryngeal stenosis. Carbon dioxide laser has been found to be effective in the management of supraglottic scarring. Mitomycin was reported to reduce the severity of stenosis with carbon dioxide laser in the management of supraglottic scarring (Whiteside et al., 2003) and also when used in the surgical treatment of cicatricial shrinkage of conjunctival fornices (Secchi and Tognon, 1996). Repeated dilatation using endoscope may be indicated to manage oesophageal strictures (Whiteside et al., 2003).

4.1.8 Clinical outcome

The long-term outcome of MMP is unknown, as there would seem to be no appropriate studies. Certainly it is evident that the long-term outcome of MMP is highly variable. Some patients have only mild disease limited to oral mucosa that never impacts greatly upon morbidity. However other individuals can have significant morbidity due to conjuctival scarring (which may result in loss of vision) or laryngeal scaring that can compromise the airway (Cotell et al., 2000). The risk of death associated with MMP is unknown, although there may be a risk of early death with BP (Langan, et al., 2008), in one report, 48 per cent of patients died within 2 years of diagnosis of BP (Gudi et al., 2005).

There remain few (if any) recent detailed reports on efficacy and safety of long-term therapy of substantial number of MMP patients. The overall aim of this chapter was to describe the long-term outcomes of therapy in a large cohort of MMP patients attending single clinical centre.

4.2 AIMS

The aims of this chapter were to determine:

1. The clinical characteristics of a substantial cohort of patients with mucous membrane pemphigoid resident in England, UK.
2. The clinical outcomes of long-term therapy of mucous membrane pemphigoid.
3. The frequency and nature of adverse side effects of therapy of mucous membrane pemphigoid.

4.3 PATIENTS AND METHODS

4.2.1 Patients group

The study group comprised 62 patients managed by the Oral Medicine Unit of UCL Eastman Dental Institute and UCLH Eastman Dental Hospital, with the diagnosis of mucous membrane pemphigoid (MMP). The patients had been under the care of the clinicians of the unit between 1981 and 2007.

4.2.2 Methods

The case record of each patient was examined using multiple data extraction forms for details of demographics, past medical history, extra-oral and intra-oral clinical features and clinical progress data. Details of diagnostic and monitoring investigations were also systematically extracted. These included: histopathology, full blood cell count, differential white cell count, hepatic and renal biochemistry and details of the different topical and systemic therapies employed in the management of each patient (Appendices 1-5).

Inclusion criteria

Inclusion criteria: (1) evidence of erosion/blistering/scarring of the oral mucosa with/without extra-oral involvement, (2) histopathological evidence of sub-epithelial blistering, (3) evidence of direct immunofluorescence on mucosal/skin biopsies of linear deposits of any one or combinations of the following in the basement membrane zone (BMZ); IgG, IgA and/or C3, (4) evidence of indirect immunofluorescent of circulating autoantibodies to BMZ (Chan et al., 2002). In all patients at least criterion 1 and either 3 or 4 were present to assign a diagnosis of MMP.

Outcome of therapy

The outcome of therapy was evaluated for symptoms and signs separately. Symptoms evaluation was reported as presence, improved or absence of intra-oral pain/soreness and based on comparison between patients' self-reported pain/soreness status before therapy and at last review in 2007.

The outcome of therapy (clinical signs) was analysed by 2 different methods. The first one according to site of the lesion, either gingival or mucosal, using a 2-point scoring system: (0) absence of mucosal and/or gingival lesions and (1) presence of mucosal or gingival lesions. Also, the treatment outcome was analysed by the comparison between disease status (signs and sites) before therapy and last review in 2007. Evaluation of response to therapy was based on clinicians' judgments during clinical examination and/or upon clinical photographs when present in the clinical notes.

Statistical analysis

The differences between females and males in relation to duration of oral symptoms before attending to Oral Medicine clinics and duration of the treatment were analyzed using Student's t-test. McNemar's test was used to compare symptoms and signs before and after treatment in Oral Medicine Clinics. Descriptive and analytical statistics were undertaken using the SPSS program (SPSS for Windows: (Statistical Package for the Social Sciences) software, version 12.0.

4.4 RESULTS

4.4.1 Patient demographics

Age and gender

The mean age of the patients at the time of diagnosis or referral of MMP to the oral medicine unit was 63.9 years (SD 14.7, median 64.1), this being 70.2 for males (SD 12.4), and 60.6 for females (SD 14.7). There was an age range of 11.3 to 94.1 years. The onset of the clinical features of disease was thus usually in the sixth, seventh or eighth decade of life. There were a higher number of females (41; 66.1 %) than males (21; 33.9%), with a female to male ratio of 2:1 (Figure 4.1).

Ethnic group

The majority of patients were white British (52; 83.9%) (self-reported, according to 2001 UK Census) (Office for National Statistics, 2003). In present cohort there were 6 (9.7%) white other than British, 3 (4.8%) Asian, and 1 (1.6%) mixed-White and Black African.

Marital status

Marital status was stated under four categories; married which included married patients and patients in a civil partnership; single, divorced and widowed patients. 29 (46.8%) were married or living with a partner, 13 (21.0%) were widowed, 8 (12.9%) single, 6 (9.7%) were divorced and the marital status was not reported in the case notes of 6 patients.

Tobacco use and alcohol consumption

Sixteen (25.8%) of the patients were previous tobacco users and 8 (12.9%) were current users of tobacco. The mean number of self- reported cigarettes per day by the present tobacco users was 12.6. Forty two (67.7%) of the group currently drank alcohol. The mean total weekly consumption by the present alcohol users was 10.2 units.

Sources of referral to oral medicine

Fifteen (24.2%) of the patients had been referred to the oral medicine unit by general dental practitioners. 13 (21.0%) were referred by specialists in Oral and Maxillofacial Surgery (OMFS). Twelve (19.4%) patients were referred by a periodontist and the remaining patients were referred by their general medical practitioner, medical or a dental specialist (Table 4.3). The patients had been referred to oral medicine clinics for the diagnosis and/or management of variety of oral lesions such as desquamative gingivitis or mucosal blisters and/or ulcers.

4.4.2 Past medical and drug histories

4.3.2.1 Past medical history

The patients had a history of a wide variety of common medical problems (Table 4.4), the most common of which were: allergies, cardiovascular, respiratory, endocrine and gastrointestinal diseases. A wide variety of allergic diseases were reported by the patients: 7 (11.3%) patients were allergic to penicillin, 2 to aspirin, one to plaster (sticky-plaster, e.g. band-aid) and 13 were allergic to a variety of other allergens. Six (9.7%) patients had a history of asthma. Twenty (32.3%) patients were hypertensive while 4 had diabetes mellitus. 12 (19.4%) patients had thyroid disease.

4.3.2.2 Past drug history

The patients were receiving a wide range of medication at the time of their clinical consultation in the Oral Medicine Unit. Some of these agents were being used to control oral and/or mucocutaneous lesions likely to be due to MMP (Table 4.5). And as expected from the medical history, the most common drugs were anti-hypertensives, anti-asthmatic agents and topical corticosteroids (Table 4.6).

4.4.3 Presenting clinical signs and symptoms and duration of symptoms

4.4.3.1 Duration of oral symptoms at first visit

The duration of oral symptoms before attending the oral medicine clinics varied from 2 months to 15 years, with a mean of 23.6 months (median 12 months). The mean duration of pre-consultation symptoms for males (21.7 months) was broadly similar to that of females (24.6 months) (P= 0.77).

4.4.3.2 Presenting clinical signs and symptoms

Intra-oral

At their clinical consultation in the Oral Medicine Unit, most (46; 74.2%) of the 62 patients had symptomatic oral lesions, although 10 patients were asymptomatic at this time. Data concerning symptoms were not available for 6 patients. A total of 119 lesions in 95 oral mucosal sites were recorded in this cohort of patients, with a mean of 2 oral lesions per patient.

Two patients presented initially with oral mucosal scaring. Desquamative gingivitis was the most common intra-oral sign of MMP and reported in 48 (77.4%). Thirty seven (59.7%) patients present initially with desquamative gingivitis only. Five (8.1%) patients presented with mucosal lesions (ulceration/erosion/blister) only, while 18 (29.0%) patients had both mucosal lesions and desquamative gingivitis at their first clinical consultation in Oral Medicine clinics.

Oral ulceration was the second most common sign after desquamative gingivitis: 22 patients (35.9 %) presented with mucosal ulceration, 10 had ulcers on the alveolar ridge, 7 with buccal ulcerations and 7 on the soft palate. The remaining ulcers were on the hard palate, floor of the mouth or tongue. Fifteen patients presented with mucosal erosions and 13 with mucosal blisters in different oral mucosal sites.

With regards to the site of involvement, gingivae were mostly affected. Gingival erosion/blisters were observed in 55 patients (88.7%) and were the

only affected site in 37 patients (59.7%). The second most commonly affected site was the soft palate (12; 19.4%) followed by the buccal mucosa (11; 17.7%), tongue and hard palate (5; 8.1%) labial mucosa and floor of the mouth (3; 4.8%). Scarring of the oral mucosa was present in two patients. More details about clinical presentation features are presented in table 4.7.

Extra-oral

Twenty patients (32.3%) had a history of likely MMP at extra-oral sites (Table 4.8). Most of these patients (13) had just one extra-oral site involvement, three had 2, two had 3 and one had 4 and another had 5 extra-oral sites involved in the MMP course. The eyes were the most common extra-oral mucosal surface affected in the MMP course. 15 patients had had eye lesions ranging from corneal abrasion to conjunctival scaring and loss of vision. The skin was affected in 6 patients and two patients had cutaneous scalp lesions. The pharynx was affected in 3 patients, larynx in 2; nasal mucosa in 4, and vagina in 1.

4.4.4 Histopathological and immunofluorescence studies

Histopathological examination of peri-lesional tissue was undertaken on 50 (80.6%) of the 62 patients. The histopathological reports of the remaining 12 patients were not present in their clinical notes.

In accordance with the clinical presentation, biopsies had been obtained from the gingivae (24; 48%), buccal mucosa (21; 42%), tongue (1; 2%) hard palate (1; 2%) and pharynx (1; 2%). The sites of 2 biopsies were unknown. 28 mucosal biopsies had a demonstrable split between the dermis and epidermis, although 7 had no epithelium. Inflammatory cells were found in 34 sections and the most common infiltrating cells were lymphocytes (11 specimens), plasma cells (7), eosinophils (4) and neutrophils (3).

Direct immunofluorescence was undertaken on 40 biopsy specimens, of which 36 had linear deposits of IgG (34) C3 (26) although 4 specimens had an absence of such immune deposits. 21 of 47 investigated patients had

circulating antibodies to basement membrane components, usually in the range of 1:10-100.

4.4.5 Therapies provided

A wide variety of different topical and systemic agents had been provided in an attempt to control the clinical signs of MMP in this group of 62 patients. Patients with oral lesions alone were almost always managed initially with topical corticosteroids and/or tacrolimus. However, if the signs failed to reduce and/or the patient had sustained painful symptoms with topical agents alone, and/or there was extra-oral mucoucutaneous involvement, systemic agents were prescribed. In this cohort, 3 patients did not require treatment. 58 patients received topical therapies, while systemic agents had been provided for 33 of the 58 patients (56.9%). The mean total number of agents (topical and systemic) prescribed to the patients was 4.6 (3.2 and 1.5 for topical and systemic agents respectively) (Tables 4.9, 4.10 and 4.11).

4.4.6 Clinical outcome

The mean duration of treatment in this cohort of MMP patients was 4.6 years (median 2.7). Most of patients in this group responded well to treatment.

4.3.6.1 Symptoms

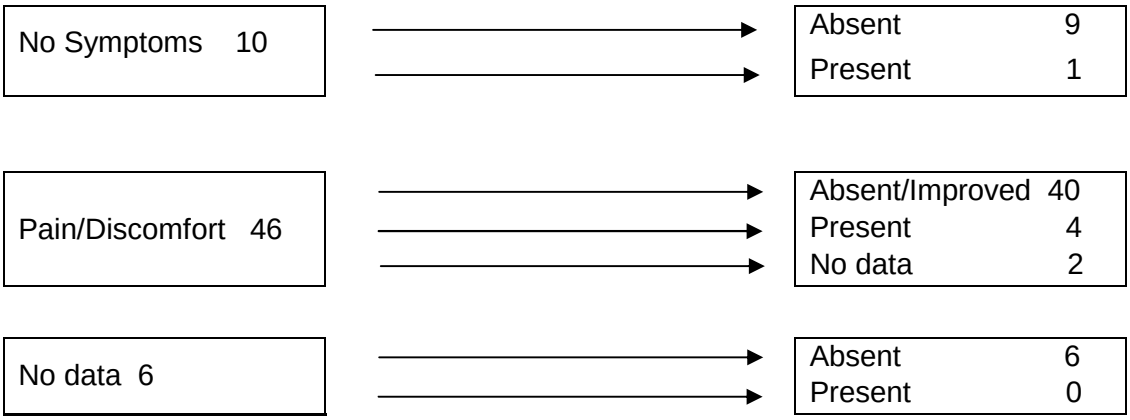

Figure 4.2 Status of patients with regards to intra-oral symptoms at initial visit (left side) and at last visit (right side).

Of the 62 patients, data concerning symptoms (i.e. soreness, pain) were available for 56 patients at initial presentation. Of this group, 10 were asymptomatic at initial presentation to oral medicine clinics and 9 of this group were still pain-free when last examined in oral medicine clinics (median duration of follow up was 3 years), while one patient had a worsening of symptoms at the end of the observation period.

Most of patients (46; 74.2%) had symptoms (pain, discomfort, soreness or burning) at the initial consultation in oral medicine unit and 40 of these had had some self-reported lessening or cessation of these symptoms at the end of the treatment.

4.4.6.2 Clinical signs

i Analysis of clinical outcome according to site

At the end of the observation period (2007), 27 of the 37 (73%) patients with solely gingival involvement at the initial consultation still had gingival lesions (erosion/blisters). The remaining 10 patients (27.0%) had no evident clinical lesions at the gingivae at last review but 1 had developed oral mucosal involvement.

Of the five patients presenting with solely oral mucosal lesions at first visit, 3 (60%) had had a persistence of mucosal ulcerations/erosions or blisters, while 2 (40%) were free of lesions at last review.

Of the 18 patients who presented initially with combined mucosal and gingival involvement, complete absence of clinical lesions was observed in 4 (22.2%) of the end of the observation period. Ten patients (55.6%) showed persistence of gingival lesions but disappearance of mucosal ulceration/blisters. Mucosal lesions were not controlled by therapy in 2 (11.1%) patients who however showed disappearance of gingival erosion/blisters. Gingival and mucosal lesions persisted in 2 other patients (11.1%) at last review. (See Table 4.12).

ii Analysis of clinical outcome according to signs and sites

Desquamative gingivitis:

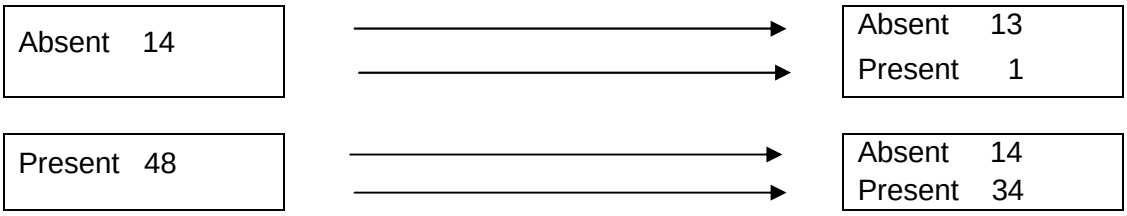

Figure 4.3 Status of patients with regards to desquamative gingivitis at initial visit (left side) and at last visit (right side).

Of the 62 patients, 14 were free of desquamative gingivitis at initial presentation, and 13 of these remained free at the end of the study period.

Most of patients (48; 77.4%) had desquamative gingivitis at the initial consultation in the oral medicine unit and of these 34 still have desquamative gingivitis at the end of the treatment.

The total number of patients with desquamative gingivitis reduced significantly from 48 to 34 (P= 0.001, McNemar's test).

Gingival blisters

53 of the 62 patients were free of gingival blisters at initial presentation. However, 4 developed new blisters at the end of the study.

Nine patients had gingival blisters at the time of their initial consultation in Oral Medicine clinics. All were free of such blistering at the end of the study period.

Buccal mucosal ulceration

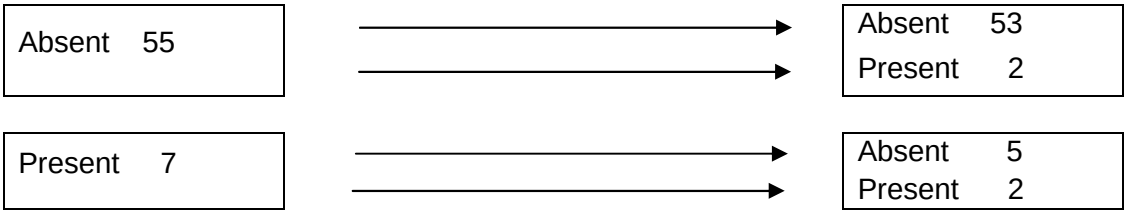

Figure 4.4 Status of patients with regards to buccal mucosa ulceration at initial visit (left side) and at last visit (right side).

Of the 62 patients, 55 were free of buccal mucosa ulceration at their initial presentation to Oral Medicine clinics; however, 2 developed ulcers at the end of the study.

Seven patients had ulceration of the buccal mucosa at their initial presentation to Oral Medicine clinics and of these only 2 still had ulcers of this site at the end of the treatment. This change was not statistically significant (P= 0.453).

Buccal mucosal blisters

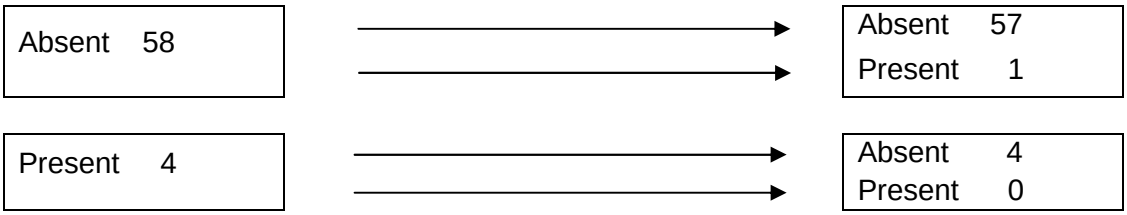

Figure 4.5 Status of patients with regards to buccal mucosa blister at initial visit (left side) and at last visit (right side).

Blisters of the buccal mucosa were observed in 4 patients at their initial consultation in Oral Medicine clinics. All 4 had had resolution of these lesions by the end of the study period. However, one patient who had initially presented without blisters of the buccal mucosa had developed blisters at this site at their last clinical observation.

Hard palate

Two of 61 patients who had not had ulceration of the hard palate at their initial consultation in oral medicine had developed ulceration and 2 had developed blisters at the end of the study period.

All 3 patients who had had ulceration of the hard palate at the time of their initial consultation had had resolution of this at the end of the study period.
One patient with previous erosions at the hard palate had had resolution by the end of the study period.

Floor of the mouth

Three patients had ulceration of floor of the mouth at time of their initial diagnosis. All had resolution of this by the end of the observation period.

4.4.7 Adverse drug reactions

As reported in section 4.4.5, a wide variety of different agents were employed in the management of present cohort of MMP patients.

Thirty one (50%) patients had adverse side effects (ASEs) that included malaise, gastrointestinal upset, nausea, vomiting, diarrhoea, skin rash, oral candidosis, unpleasant taste (dysgusia), and haematological changes lymphopenia and anaemia.

In the majority of instances, patients had only 1 ASEs (20/31; 64.5%). Seven patients had 2 ASEs (7/31; 22.6%), 3 (9.7%) had 3 ASEs and 1 had 4 ASEs. Nineteen (61.3%) and 10 (32.3%) patients had ASEs likely to be due to systemic or topical agents respectively. Two patients (6.5%) developed ASEs due to both topical and systemic therapy.

Most adverse effects in this cohort of MMP patients were associated with azathioprine. Seven of the 15 patients (46.7%) who received this agent developed adverse effects including nausea and vomiting (4 patients), skin

rash (1), sore throat (1), and headache (1). ASEs due to azathioprine were observed in patients with both normal and abnormal levels of TPMT.

Eleven (34.4%) of the 23 patients who received dapsone developed an ADR including malaise (2 patient), photosensitive skin eruption (1), headache (1), and heamatological changes (8).

One patient who was prescribed systemic corticosteroids developed a “moon face” while ten patients on topical corticosteroids had ASEs including candidosis, median rhomboid glossitis and unpleasant taste. Some patients on topical tacrolimus had a burning sensation and/or peppery taste and gastrointestinal upset but these were not related to blood tacrolimus levels. Further details of the adverse drug reactions reported in this cohort of patients are reported in Table 4.13.

4.4.8 Duration of the treatment

In this cohort of MMP patients, treatment duration differed greatly, ranging from a few months to more than 19 years (until data collected). The mean duration of therapy was 4.6 years (SD 4.9, Median 2.7). There was no significant difference between men and women in the duration of management of oral lesions of MMP (mean treatment duration of 3.8 for men and 5.0 for women) (P= 0.352) (Table 4.14).

All but 14 patients remain under the clinical care of the oral medicine unit. Three patients failed to attend their follow up appointments while another four had travelling problems into the clinics or they moved into another city. Three patients were discharged as they were asymptomatic, 4 died and the remainder are still under follow-up.

4.5 DISCUSSION

Although mucous membrane pemphigoid (MMP) has the potential to adversely affect the quality of life of patients, there are few data on the long-term behaviour or effective therapy for the condition. In addition there are no recent reports of the clinical manifestations of a substantial group of patients in the UK.

Results of the study confirmed that MMP is a disease of middle to late age females (mean age of onset, 64 years) (Mobini et al., 1998; Alkan et al., 2003; Chiou et al., 2007). MMP rarely affects children. Of note the present cohort included an 11 years old child. Musa et al. (2002) and Lourenco et al. (2006) published case reports on nine-year old and four-year old children, respectively. Mucocutaneous lesions are more common in younger individuals and the disease may be more severe than in adults (Lourenco et al., 2006).

The mean duration of symptoms before patients attended the oral medicine clinics was 23.6 months, suggesting that mild symptoms, misdiagnosis, or delay in referral occurred in a number of instances. Moreover, as most of this cohort presented initially with only gingival lesions, it could be assumed that some general dental practitioners assume that this clinical presentation represents plaque-related gingivitis and thus explain the delay of referral of some patients.

Oral involvement in MMP is common (Silverman et al., 1986); however, the number of patients in studies from oral medicine clinics is generally lower than those in studies from ophthalmological clinics. This may represent a referral bias, as MMP patients are usually seen by ophthalmologist or dermatologist.

The oral clinical features of MMP resemble those of bullous pemphigoid and other immune-mediated sub-epithelial blistering diseases such as linear IgA disease and epidermolysis bullosa acquisita (Solomon et al., 2007). In the

present study, MMP gave rise to recurrent multiple areas of ulceration with a clear predominance of gingival involvement (as desqumative gingivitis); and thus are in agreement with the results of other reports (Mobini et al., 1998; Chiou et al., 2007).

Of note, however, scarring of the oral mucosa was rarely observed. In the present group, only two had such a feature. It is interesting to note that while scaring is often cited in textbooks as being a feature of MMP, it has actually been rarely documented in previous studies (Shklar and McCarthy, 1959; Chiou et al., 2007). However the previous studies did not provide long-term data of patients, hence it is possible that with time some of the patients would have developed this feature. However as the present study included observation over many years the low frequency of oral mucosal scarring of MMP does seem to be real.

Approximately one-third of the patients had a history or clinical and histopathological evidence of MMP at extra-oral sites, the conjunctivae being the most commonly affected extra-oral site. This is in agreement with previous study by Higgins and co-workers that reported ocular lesions occurring in about 37% of patients with oral MMP (Higgins et al., 2006). However, this is greater than that reported by Chiou et al (2007) who observed two of 29 patients having extra-oral involvement. Although not detailed in the present study, it was the authors' view the severity of oral disease did not correlate with the likelihood of patient having extra-oral manifestations. It would thus seem possible that there are actually subgroups of MMP each with particular anatomical targets.

Thus, the clinical picture of MMP in this cohort of patients who present to an Oral Medicine unit in the UK was dominated by oral ulceration, desquamative gingivitis and less frequently by associated ocular involvement. However, this observation should be interpreted with caution as it might represent a referral bias as the patients oral disease were much more likely to be referred to Oral

Medicine. However, data of patients from ophthalmological units show that oral lesions are common in the MMP patients (Elder et al., 1996).

More than half of the available biopsies (28/50; 56%) in the present cohort showed the characteristic sub-epithelial cleft of MMP. Epithelium has been lost in many specimens possibly during the biopsy surgery or at tissue preparation.

The precise aetiology of MMP is largely unknown but it is characterized by antibody attack of the hemidesmosomal junction of epithelial surfaces, creating a disruption of cell adhesion and tissue integrity (Scully and Lo Muzio, 2008). Direct immunofluorescence demonstrating a linear tissue-fixed deposition of IgG/IgA and/or C3 at the basement membrane zone was evident in about 90% of the tested specimens, which is in agreement with previous results of the oral mucosa (Laskaris and Angelopoulos, 1981) and conjunctivae (Thorne et al., 2004) studies.

Twenty-one of the 47 patients tested for indirect immunofluorescence had demonstrable circulating antibodies to basement membrane components, usually in the range of 1:10 to 1:100. No clear correlation between auto-antibody titre and the extent of clinical features was observed (data not shown). The sera of the present patients were assessed using monkey oesophagus and hence the low frequency of titre of detectable circulating antibodies is perhaps unexpected. As detailed in the introduction to this chapter it is possible that the use of more complex diagnostic tools may allow more frequent detection of circulating antibodies and thus provide more effective methods of diagnosing and monitoring MMP (Ahmed et al., 1989; Bhol et al., 1996; Bernard et al., 1990; Solomon et al., 2007).

Regarding therapy, there are few randomized controlled trials (Foster 1986a; Foster 1986b) and only one systematic review (Kirtschig et al., 2003) on the treatment of MMP. Most information concerning the treatment of MMP has arisen from case series and non-randomized clinical trials (Kirtschig et al.,

2003), perhaps reflecting the rarity of this disease when compared to other oral mucosal (e.g. oral lichen planus) and dermatological (e.g. psoriasis) disorders.

A wide variety of topical and systemic agents were used in an attempt to control the oral MMP of the present group of patients. Patients with oral lesions alone were almost always initially managed with topical corticosteroids. If the signs did not abate or the patient experienced painful symptoms, and/or there was extra-oral mucocutaneous involvement, systemic agents tended to be prescribed. This approach is in accordance with the recommendations by the First International Consensus of Mucous Membrane Pemphigoid (Chan et al., 2002) which divided patients into low and high- risk groups based on the sites involved. In a recent paper, Saw and co-workers (2008) suggested a stepladder immunosuppression approach for treatment of severe MMP disease, starting with cyclophosphamide and a short course of oral corticosteroids followed by drugs with fewer adverse side effects (such as azathioprine or mycophenolate) after the disease was under control. For milder symptoms, they recommended commencing with dapsone or sulfapyridine, stepping up to azathioprine or mycophenolate, and progressing to cyclophosphamide if the disease persists. This regimen resulted in partial or complete controlling of inflammation in 95% of their patients. This recommended regimen was not applied in the present group of patients.

It is suggested that MMP is a chronic disorder with an unpredictable course with periods of remission and relapse (Bruch-Gerharz et al., 2007). Certainly specialist personally indicate that patients may have a waxing and waning of disease for extended periods, even during therapy, but there are no definitive long-term studies assessing the behaviour of this disease. In the present cohort, complete resolution of oral mucosal lesions was evident in just one-third of patients. This may attributed to the high number of patients presenting with desquamative gingivitis, which is known to respond usually partially to topical corticosteroid (Rogers et al., 1982).

The majority of patients with gingival involvement at the initial consultation still had clinical lesions at the last examination. However, persistence of these lesions does not necessarily correlate with symptoms. Accordingly, more than 90% of patients reported absence of significant intra-oral pain at their last review appointment.

Of the five patients presenting with solely oral mucosal lesions at first visit, sixty per cent showed persistence of mucosal ulcerations/erosions or blisters. In the eight patients who presented initially with combined mucosal and gingival involvement, complete absence of clinical lesions was observed in around 20%. Although most patients in this group who still had lesions at last examination also had gingival lesions.

The clinical outcome of the present study does not reflect data from other studies showing effectiveness of topical corticosteroids (Lozada and Silverman, 1980; Lozada-Nur et al., 1994; Gonzalez-Moles et al., 2003). This difference can be explained by the fact that the outcome measure used in the present study did not recorded partial improvement but only presence vs absence of gingival lesions. As a consequence patients with partial clinical improvement of gingival MMP were not identified in our analysis.

It is thus evident that despite therapy MMP of the oral mucosa and gingivae rarely resolves, hence any therapy being provided must at least reduce painful symptoms and be free of adverse side effects.

In the current cohort, three patients did not require treatment. Fifty-eight patients received topical therapies, while systemic agents were prescribed for 33 (56.9%) of them when the initial treatment failed to alleviate their condition. Thirty-one (50%) patients had adverse side effects (ASEs), such as malaise, gastrointestinal upset, nausea, vomiting, diarrhoea, skin rash, candidosis, unpleasant taste, and haematological changes, including lymphopenia and anaemia. The ASEs occurred with both topical and systemic agents, although unsurprisingly the haematological abnormalities

arose in patients who had been receiving azathioprine. It is important to note that the International Consensus of mucous membrane pemphigoid (Chan et al., 2002) seems to strongly advocate the use of systemic immunosuppressives for the treatment of severe MMP. Suggested initial therapy with cyclophosphamide is likely to give rise to haematological and other significant adverse effects, yet in the present group azathioprine (a second line therapy suggested by the consensus) caused notable adverse effects. It would seem important that if a patient with MMP receives agents such as azathioprine there is good communication between the oral medicine specialist and the general medical practitioner to ensure that there is regular and effective haematological monitoring to ensure that any adverse effects are detected at the earliest opportunity. This high proportion of patients who experienced ASE may be attributed to the wide variety of topical and/or systemic agents received. It could also be due to the chronicity of the disease, which necessitates long periods of treatment that may increase the risk of some ASEs, such as osteoporosis and diabetes for patients receiving systemic corticosteroids.

4.6 CONCLUSION

The results of this study indicate that MMP affecting the oral tissue typically manifests as recurrent oral mucosal ulceration and/or desquamative gingivitis. The disease is chronic with symptoms and clinical signs waxing and waning hence necessitating various treatment strategies and long-term follow up to prevent complications.

The main limitation of the present study is its retrospective design and associated methodological inadequacies, including differences in reporting clinical features and outcomes, lack of a control group, and variations in diagnostic and monitoring procedures. The establishment of a national register for these rare disorders would help researchers and practitioners to better understand the clinical symptoms and aetiopathology of these diseases, resulting in earlier diagnoses and initiation of appropriate treatment.

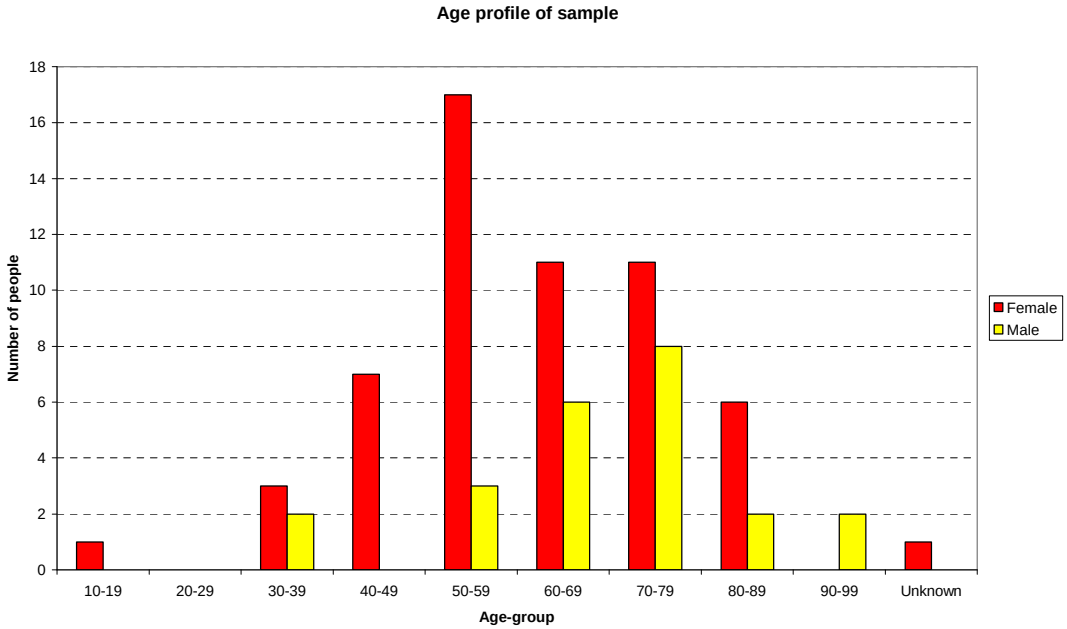

Figure 4.1 Age of mucous membrane pemphigoid patients

Table 4.1 Some of the larger studies in the literature that reported patients with oral MMP

Authors (year)	Patients No.	Age (range)	Gender			Mouth	Gingivae	Eye	Skin	DIF*	IIF**
			Female	Male	F:M ratio						
Lever (1953)	30	60 (30-84)	19	11	1.7:1	27	-	24	-	-	-
McCarthy and Shklar (1958)	15	? (23-75)	9	6	1.5:1	15	-	-	-	-	20% of patients
Shklar and McCarthy (1971)	85	? (23-75)	73	12	6:1	85	-	52	9	-	-
Laskaris and Angelopoulos (1981)	33	? (43-83)	18	15	1.2:1	33	-	10	1	IgG (97%) IgA (27%) IgM (12%), C3 (73%), fibrin (39%)	36% of patients
Laskaris et al (1982)	55	66 (43-80)	33	22	1.5:1	55	35 (63%)	12 (21.8%)	3	-	-
Silverman (1986)	65	59 (19-82)	47	18	2.6:1	65	94%	7 (11%)	0	Positive in 81%	-
Gallagher and Shklar (1987)	120	? (20-90)	105	15	7:1	100%	100 %	95.3 %	10	-	-
Mobini et al (1998)	29	55 (35-76)	24	5	4.8:1	29	27	0	0	Positive in 100%	0
Chiou et al (2007)	29	NR	20	9	2.2:1	93	26	?	?	>70%	?

*DIF direct immunofluorescence, **IIF indirect immunofluorescence. NR: Not reported.

Table 4.2 Studies reported the effectiveness of different therapeutic agents in the management of mucous membrane pemphigoid

Agent*	Study	Site**	Dosage	No of Pt's	Efficacy/Adverse side effects/ Comments
Triamcinolone in orabase	Arash and Shirin., 2008	Oral	3 times/day for 2-4 weeks	5	Effective No adverse side effects (ASEs)
Clobetasol propionate	Carrozzo et al., 1997	Oral	Clobetasol (2-3 times/day)	8	Effective Oral candidosis
	Gonzalez-Moles et al., 2002	Oral	Mouthwash with 10 cc of the solution containing 0.05% clobetasol propionate and 100 000 IU/cc nystatin 3 times/day	3/30	Effective Hirsutism?
Clobetasol with systemic prednisone	Carrozzo et al., 1997	Oral	Clobetasol (2-3 times/ day) prednisone (25 to 100 mg/day)	3	Effective Insomnia, fluid retention, gastralgia and oral candidosis
Topical/systemic corticosteroids, dapsone, cyclophosphamide plasmapheresis	Espana et al., 2005	Multiple mucosal surfaces including oral mucosa	-	5	Effective
Prednisone	Miserocchi et al., 2002	Mainly ocular	1 mg/kg body weight/day	17/61	Effective Leukopenia, gastritis, hypertension, myocardial infarction, transient ischemic attack, thrombosis, bleeding, ecchymosis, osteoporosis, bone fractures, myalgia, myopathy, psychosis, diabetes mellitus, Cushing face, weight change, hyper-triglyceridemia and urinary tract infection.

* Patients may be on other agents, but we report the main one which the authors suggested to be the most effective.
** The site is mainly which reported here however, other site may be involved but to a lesser extend.

Table 4.2 (Cont.) Studies reported the effectiveness of different therapeutic agents in the management of mucous membrane pemphigoid

Agent	Study	Site	Dosage	No of Pt's	Efficacy/Adverse side effects/ Comments
Topical tacrolimus	Assmann et al, 2004	Oral	0.1% ointment twice/day	2	Effective Transient burning sensation
	Hall et al., 2003	Ocular	0.03% tacrolimus	1	Effective No ASEs
	Michel and Gain, 2006	Ocular/ scalp	0.03%, 0.1% ointment 1-2 times/day	1	Effective
	Gunther et al., 2004	Genital	0.1% ointment	1	Effective No ASEs
	Lebeau et al., 2004	Genital	0.1% ointment twice/day	1	Effective No ASEs
Tetracycline and nicotinamide	Poskitt and Wojnarowska, 1995a	Multiple mucosal surfaces including oral mucosa	Oxytetracycline hydro-chloride 500 mg twice/day Nicotinamide (initial dose 500 mg/day)	1	Effective
	Kreyden et al., 2001	Mucocu-taneous	-	1	Effective
Tetracycline/ nicotinamide and topical corticosteroids	Mallon and Wojnarowska, 1994	Mainly skin	-	1	Effective
Tetracycline and niacinamide	Sakamoto et al., 2002	Larynx	Tetracycline (1500 mg/day) Niacinamide (1500 mg/day)	1	Effective

Table 4.2 (Cont.) Studies reported the effectiveness of different therapeutic agents in the management of mucous membrane pemphigoid

Agent	Study	Site	Dosage	No of Pt's	Efficacy/Adverse side effects/ Comments
Minocycline	Poskitt and Wojnarowska, 1995b	-	-	7	Effective Hyperpigmentation, gastrointestinal discomfort
Minocycline and nicotinamide	Reiche et al., 1998	NR	Minocycline (100 mg/day) Nicotinamide (initial dose 500 mg/day)	8	Effective Headache and nausea (nicotinamide), hyperpigmentation (minocycline)
Systemic tacrolimus	Letko et al., 2001	Ocular	(8 mg/day)	6	Not effective. Elevated BUN (Blood Urea Nitrogen), worsening of diabetes mellitus, anaemia, tremor thrombocytopenia and nausea
Dapsone	Miserocchi et al., 2002	Mainly ocular	50-150 mg/day	51/61	Haemolytic anaemia, leucopoenia, fatigue, malaise, fever, myalgia, myopathy, dizziness, tinnitus, skin rash, GI, respiratory and urinary ASEs
Dapsone and fluocinonide (0.05%)	Ciarrocca and Greenberg, 1999	Mainly oral	125-150 mg/day (initial dose: 25 mg/day)	11/20	Fatigue and shortness of breath in association with haemolytic anaemia & methemoglobinemia
Dapsone and triamcinolone in orabase	Arash and Shirin., 2008	Mainly oral	25-100 mg/day	17	Reduced haemoglobin
Dapsone and topical corticosteroids	Wertheim et al., 2006	Ocular	50 mg twice/day	12	Reticulocytosis, clinically significant haemolytic anaemia

Table 4.2 (Cont.) Studies reported the effectiveness of different therapeutic agents in the management of mucous membrane Pemphigoid

Agent	Study	Site	Dosage	No of Pt's	Efficacy/Adverse side effects/ Comments
Methotrexate	Miserocchi et al., 2002	Mainly ocular	0.2 mg/kg body weight/week	24/61	Effective Leucopoenia, gastrointestinal, pulmonary and neurological ASEs.
	McCluskey et al., 2004	Ocular	5 to 25 mg/week	17	Effective Fatigue, lethargy, mouth ulceration, nausea, gingivitis, abdominal pain, derangement of liver function test, cough, alopecia, infection, and hot flushes.
Azathioprine	Miserocchi et al., 2002	Mainly ocular	2–3 mg/kg body weight/day	23/61	Effective Leucopoenia, thrombocytopenia, fatigue, malaise, fever, myalgia, myopathy, skin rash and shingle, GI, pulmonary, urinary, cardiovascular, and neurological ASEs
Cyclophosphamide	Miserocchi et al., 2002	Mainly ocular	2 mg/kg body weight/day	15/61	Effective Leucopoenia, thrombocytopenia, meningitis, hemorrhagic cystitis gastrointestinal and other urinary ASEs
Etanercept	Sacher et al., 2002		Subcutaneous etanercept (25 mg twice/week) with prednisone (initially 60 mg/day)	1	Effective No ASEs
	Canizares et al., 2006	Oral/ ocular	subcutaneous injections of 25 mg/ week	3	Effective No ASEs
	John et al., 2007	Eye	Etanercept 50 mg/week subcutaneously Prednisolone tapered by 1 mg/month	1	No ASEs

Table 4.2 (Cont.) Studies reported the effectiveness of different therapeutic agents in the management of mucous membrane pemphigoid

Agent	Study	Site	Dosage	No of Pt's	Efficacy/Adverse side effects/ Comments
Infliximab	Heffernan and Bentley, 2006	Multiple mucosal surfaces	600 mg with additional infusions at weeks 2 and 6 and then every 8 weeks	1	Effective No ASEs
Rituximab	Ross et al., 2009	Multiple muco-cutanous	862.5 mg intravenously in 2 doses	1	Effective
Thalidomide and topical corticosteroids	Duong et al, 2002	Nose/ Oropharynx/ larynx & skin	100 mg/day	1	Effective
Mycophenolate mofetil and prednisolone	Alkali et al., 2007	Oral	2 g/day	1	Effective
	Megahed et al., 2001	Oral/ genitalia/ skin	MMF (2 g/day) and prednisolone (0.5-1 mg/kg day)	3	Effective No ASEs
Mycophenolate mofetil and systemic minocycline	Salzano et al., 2006	Oral	MMF (up to 2 g/day) and minocycline (up to 200 mg/day)		Effective
	Carrozzo et al., 2008	Oral	MMF (2 g/day) and systemic minocycline (200 mg/day)	2	Effective No ASEs
Mycophenolate mofetil and dapsone	Ingen-Housz-Oro et al., 2005	-	MMF (1.5-2 g/day)	14	Effective

Table 4.2 (Cont.) Studies reported the effectiveness of different therapeutic agents in the management of mucous membrane Pemphigoid

Agent*	Study	Site**	Dosage	No of Pt's	Efficacy/Adverse side effects/ Comments
Intravenous immunoglobulin	Foster and Ahmed, 1999	Mainly eyes	2-3 g/kg body weight/ cycle, divided over 3 days repeated every 2-6 weeks	10	Effective No ASEs
	Leverkus et al., 2002	Oral and ocular	(1 g/kg body weight on 2 consecutive days) every 4 weeks	1	Effective Transient arthralgia and nausea
	Sami et al. 2002a		1-2 g/kg/cycle	15	Effective Headache, palpitation, nausea and vomiting
	Yu et al., 2007	Oral/eye and skin	1g/kg daily for 2 consecutive days	1	Effective but clinical response become weaker with time
	Gürcan and Ahmed., 2009	Oral/ laryngeal	1-2 g/kg per cycle (a cycle consists of the total dose divided into 3 equal doses, each given on 3 consecutive days)	1	Effective No ASEs
	Galdos et al., 2008	Eyes	A total dose of 3 g/kg of body weight per cycle, infused over 3 days on divided doses, repeated every 2-10 weeks up to cycle 13	1	Effective No ASEs
	Mignogna et al., 2008	Oral/eyes	A total dose of 3 g/kg of body weight per cycle, infused over 3 days on divided doses, repeated every 2-10 weeks up to cycle 13	6	Effective Headaches, nausea, chills, flushing, myalgia, and fever.
Plasmapheresis/ cyclophosphamide/ prednisone	Bohn et al., 1999	Mainly oral	Cyclophosphamide 150 mg/day Prednisone 50 mg/day	2	Effective Urticaria and mild hypotension

Table 4.3 Referral pattern of 62 patients with mucous membrane pemphigoid

Source of referral	Frequency	%
General dental practitioners	15	24.2
Periodontist	12	19.4
Oral maxillofacial/oral surgeons	13	21.0
General medical practitioners	4	6.5
Ear, Nose and Throat Specialist	4	6.5
Ophthalmologist	4	6.5
Restorative dentist	2	3.2
Hospital	1	1.6
Dermatologist	1	1.6
Orthodontist	1	1.6
School of hygiene	1	1.6
Self referral	1	1.6
Unknown	3	4.8
Total	60	100

Table 4.4 Past medical history of 62 patients with mucous membrane pemphigoid

Disorder		No.	%
Allergy	Penicillin allergy	7	11.3
	Plaster (band-aid) allergy	1	1.6
	Aspirin allergy	2	3.2
	Other Allergies	13	21.0
Cardiovascular	Heart murmur	1	1.6
	Hypertension	20	32.3
	Angina	4	6.5
	Rheumatic fever	1	1.6
	Palpitation	1	1.6
Respiratory	Asthma	6	9.7
	Allergic rhinitis	1	2.5
	Sinusitis	1	1.3
	Tuberculosis	2	3.2
Haematological	Anaemia	1	1.6
	Perncious anaemia	1	1.6
Endocrine	Diabetes mellitus	4	6.5
	Thyroid abnormalities	12	19.4
Gastrointestinal tract	Peptic ulcer	1	1.6
	Duodenal ulcer	1	1.6
	Gastroesophageal reflux disease	3	4.8
	Hiatus hernia	4	6.5
	Inguinal hernias	1	1.6
	Gastric sarcoidosis	1	1.6
	Irritable bowel syndrome	2	3.2
	Pancreatitis	1	1.6
	Bowel obstruction	1	1.6
	Indigestion	1	1.6
Visual		8	12.9
Central nervous system	Learning disability	1	1.6
	Cerebral vascular accident (CVA)	3	4.8
	Meningioma	1	1.6
	Recurrent headache	2	3.2
Others	Eczema	2	3.2
	Arthralgia	1	1.6
	Arthritis	3	4.8
	Osteoarthritis	1	1.6
	Rheumatoid arthritis	2	3.2
	Raynaud's phenomenon	1	1.6
	Urinary and renal problems	4	6.5
	Back pain	2	3.2
	Carpal tunnel syndrome	2	3.2
	Sjogren's syndrome	1	1.6
	Pre-cancerous lesions of cervix	1	1.6
	Contact dermatitis	1	1.6
	Gout	1	1.6
	Hyperlipidemia	1	1.6
	Laryngeal stenosis	1	1.6
	Lichen Sclerosus et atrophicus	3	4.8
	Ovarian cancer	1	1.6
	Tinnitus	1	1.6
	Vaginal soreness	1	1.6
	Genital lichen planus	1	1.6
	Xerosis (Dry skin)	2	3.2
	Malignancy	3	4.8
	Osteomyelitis	1	1.6
	Lupus erythematosus	1	1.6

Table 4.5 Different therapeutic agents prescribed to patients to manage MMP lesions before attending the Oral Medicine clinics

Drug group	Drug name	No of patients
Corticosteroids	Topical	
	Triamcinolone acetonide in 0.1% carmellose paste (Adcortyl in Orabas)	11
	Hydrocortisone sodium succinate (Corlan pellets)	8
	Betamethasone sodium phosphate (Betnesol)	9
	Betamethasone esters (Betnovate)	1
	Beclomethasone (Bectoid)	5
	Fluticasone propionate (Flixonase spray)	1
	Tri-adcortyl (Triamcinolone, nystatin, neomycin, gramicidin)	1
	Prednisol mouthwash	1
	Other topical corticosteroids	1
	Systemic	
	Prednisolone	8
Anti-infective agents	Anti-viral	
	Aciclovir	
	Antibiotics	
	Metronidazole	7
	Penicillin	1
	Tetracycline	1
	Doxycycline	1
	Others (not specified)	2
	Anti-fungal	
	Nystatin	2
	Others (not specified)	1
Calcinurin inhibitors	Ciclosporin (mouthwash)	1
	Topical tacrolimus (protopic)	1
Others	Azathioprine	4
	Cyclophosphamide	1
	Chlorhexidine gluconate	8
	Benzydamine hydrochloride (Difflam)	9
	Dapsone	5
	Co-codamol Analgesics	1
	Xylocaine	1
	Aloclair	1
	Eludril®	2
	Gengigel (Hyaluronan)	2
	Sulphapyridine	2
	Sulphamethoxypyridazine	2
	Multivitamins	1

Table 4.6 Past drug history of 62 patients with mucous membrane pemphigoid

Drug group	Drug name
Cardiovascular	**Calcium-channel blockers**
	Amlodipine
	Nifedipine
	Beta-adrenoceptor blocking drugs
	Atenolol
	Timpotol maleate
	Sotalol hydrochloride
	Propranolol
	Diuretics
	Bendroflumethiazide
	Frusmaide
	Angiotensin-converting enzyme inhibitors
	Enalapril
	Ramipril
	Perindopril tert-butylamine
	Nitrates
	Glyceryl trinitrate
	Isosorbide mononitrate
	Potassium-channel activators
	Nicorandil
	Others
	Atorvastatin (lipid-regulating drugs). Aspirin, Dipyridamole (antiplatelet) Amiodarone (antiarrhythmic). Amiloride (potassium-sparing diuretic) Digoxin. Doxadura (alpha-blocker). Warfarin sodium (anticoagulants)
Respiratory	Albutamol (salbutamol + etofylline)
	Beclometasone dipropionate (corticosteroids)
	Beclomethasone dipropionate (corticosteroids)
	Salbutamol (selective beta 2 agonists)
	Salmeterol (Serevent) (beta 2 agonists)
Endocrine	Calcichew, Calceos chewable (Vitamin D)
	Hormone replacement therapy
	Insulin (antidiabetic)
	Repaglinide (antidiabetic)
	Thyroxin (thyroid hormones)
	Carbimazole (anti-thyroid drugs)
Anti-infective agents	Doxycycline (antibacterial drugs)
	Mupirocin (antibacterial drugs)
	Acyclovir (antiviral drugs)
Topical corticosteroids	Betamethasone
	Betamethasone esters (Betnovate)
	Hydrocortisone sodium succinate (Corlan)
	Clobetasol propionate cream
	Fluticasone propionate
	Triamcinolone acetonide
Urinary	Detrusitol (urinary incontinence)
	Tolterodine tartrate (urinary incontinence)
	Tamsulosin MR (urinary retention)
Proton pump inhibitors	Omeprazole, Lansoprazole
Others	Acetaminophen/paracetamol (non-steroidal anti-inflammatory drug) Azathioprine (immunosuppressant). Balmosa cream. Benzodiazepine. Cetirizine hydrochloride (antihistamines). Chlorhexidine (gluconate mouthwashes). Contraceptive pills Coproxamol (dextropropoxythene and paracetamol). Dapsone. Fenasteride (Anti-androgens). Hypromellose (tear replacement and eye lubricants). Imipramine hydrochloride (tricyclic anti-depressants) Iron. Ioratadine. Multivitamins. Naproxen (non-steroidal anti-inflammatory drug). Rantidine (H2-receptor antagonists). Sulfinpyrazone (anti-gout). Truspot eye drops. Tamoxifen (breast cancer). 2-Amino-2-deoxyglucose (Glucosamine) antiarthritis

Table 4.7 Presenting clinical signs of oral mucous membrane pemphigoid in 62 patients at initial and final clinical appointment

Signs	First visit	Last visit
Buccal mucosa		
ulceration	7	4
erosion	2	1
bullae	4	1
Lip		
ulceration	0	0
erosion	0	0
bullae	0	0
Labial mucosa		
ulceration	1	0
erosion	0	0
blister	2	0
Lingual		
ulceration	1	3
erosion	4	0
bullae	1	0
Desquamative gingivitis	48	35
Alveolar ridge/ gingival		
ulceration	10	5
erosion	5	1
blister	9	4
Soft palate		
ulceration	7	0
erosion	4	1
bullae	0	0
Hard palate		
ulceration	3	2
erosion	1	0
bullae	0	2
Floor of mouth		
ulceration	3	0
erosion	0	0
bullae	0	0

Table 4.8 Extra-oral involvement in this cohort of 62 patients with oral mucous membrane pemphigoid

Site	Frequency	%
Skin	6	9.7
Eye	15	24.2
Pharynx	3	4.8
Larynx	2	3.2
Nasal mucosa	4	6.5
Genitalea	1	1.6

Table 4.9 Topical agents employed to limit the signs of mucous membrane pemphigoid of the mouth

Topical agent	No of patients	%
Fluticasone propionate 0.05% cream- Cutivate	29	46.8
Clobetasol propionate 0.05% cream - Dermovate	18	29.0
Fluticasone propionate,400 mcg in 15 ml water as mouthwash	16	25.8
Fluticasone propionate,50 mcg spray	25	40.3
Fluticasone propionate inhaler	13	21.0
Betamethasone mouthwash	40	64.5
Beclomethasone dipropionate inhaler	3	4.8
Triamcinolone acetonide in Orabase	16	25.8
Hydrocortisone pellets	2	3.2
Prednisol mouthwash	7	11.3
Fluocinolone acetonide 0.025% cream	1	1.6
Tacrolimus 0.1% ointment	17	27.4
Tacrolimus 0.03% ointment	1	1.6
Pimecrolimus 1% ointment	1	1.6
Doxycycline mouthwash	4	6.5
Ciclosporin mouthwash	3	4.8

Table 4.10 Different systemic agents employed to limit the signs of mucous membrane pemphigoid of the mouth

Systemic agent	No of patients	%
Prednisolone	11	17.7
Deflazacort	9	14.5
Azathioprine	15	24.2
Mycophenolate mofetil	11	17.7
Dapsone	23	37.1
Tacrolimus	1	1.6
Sulfamethoxypyridazine	6	9.7
Cyclophosphamide	1	1.6
Methotrexate	2	3.2
Thalidomide	1	1.6
Doxycycline	2	3.2
Nicotinamide	1	1.6
Ciclosporin	1	1.6
Minocycline	4	6.5
Intravenous immunoglobulin (IVIG)	1	1.6

Table 4.11 Total number of topical and systemic agents employed in the management of this cohort of 62 patients with MMP of the mouth

No of agents	Topical	Systemic	Total number of agents (topical & systemic)
0	3	28	3
1	9	10	6
2	12	10	6
3	15	6	13
4	9	5	10
5	6	1	6
6	2	1	6
7	1	0	2
8	2	1	2
9	2	0	2
10	0	0	0
11	1	0	2
12	0	0	2
13	0	0	0
14	0	0	1
15	0	0	1
Total number of patients	62	62	62

Table 4.12 Status of gingival and mucosal surfaces before and after therapy

Before therapy	After therapy
37 patients had gingival lesions only	27 patients (73%): persistence of lesions 9 patients (24.3%): no lesions 1 patient (2.7%): No gingival lesions but developed mucosal involvement
5 patients had mucosal lesions only	3 patients (60%): persistence of lesions 2 patients (40%): no lesions
18 patients had combined lesions (mucosal and gingivae)	10 patients (55.6%): gingival lesions only 4 patients (22.2%): no lesions 2 patients (11.1%): mucosal lesions only 2 patients (11.1%): combined lesions (mucosal and gingivae)

Table 4.13 Clinically apparent and patient-reported drugs reactions

Drugs involved	Adverse Drug Reaction	No
Systemic agents		
Prednisolone	Moon face	1
Mycophenolate mofetil	Vomiting	1
	Diarrhoea	1
	Abdominal discomfort	1
Azathioprine	Nausea	4
	Vomiting	1
	Rash	1
	Patient feel unwell	1
	Fever	1
	Sore throat	1
	Headache	1
	Paraesthesia	1
Dapsone	Stomach cramp	1
	Headache	1
	Rash	1
	Paraesthesia	1
	Fatigue	1
	General malaise	1
	Chest infection	1
	Exfoliative cheilitis	1
	Photosensitive skin eruption	1
Sulfamethoxypyridazine	Headache	1
	Skin rash	1
Systemic tacrolimus and/ or deflazacort	Mild indigestion	1
Thalidomide	Paraesthesia	1
Minocycline	Arthralgia	1
Topical agents		
Betamethasone (Betnesol)	Median rhomboid glossitis	1
	Pseudomembranous candidosis	2
Fluticasone propionate,50 mcg-(Flixonase)	Pseudomembranous candidosis	1
Clobetasol propionate (Dermovat)	Unpleasant taste	1
	Oral thrush	2
Fluticasone propionate (Cutivate)	Mouth soreness	1
Fluticasone propionate (Flixonase nasules)	Pseudomembranous candidosis	1
Topical tacrolimus	Burning sensation	1
	GI upset	1

Table 4.14 Duration of treatment of MMP patients

Duration (Years)	Number of patients		
	Female	Male	Total
< 3	19	16	35
3- < 6	8	2	10
6- < 9	5	0	5
≥ 9	9	3	12

CHAPTER 5

PEMPHIGUS VULGARIS

5.1 INTRODUCTION

Pemphigus is a group of rare, chronic, intra-epithelial, immunologically-mediated disorders characterized by humoral immune attack of epithelial cell-adhesion and that manifests clinically as vesiculobullous disease of the skin and/or mucous membranes. There are many types of pemphigus; the two most frequently observed are deep pemphigus vulgaris (variant, vegitans) and superficial pemphigus foliaceous (variant, erythematosus). Other less common forms include IgA pemphigus, drug-induced pemphigus, pemphigus herpetiformis, and paraneoplastic pemphigus (Robinson et al., 1999; Yeh et al., 2005).

5.1.1 Disease forms

5.1.1.1 Pemphigus vulgaris

Pemphigus vulgaris (PV), the most common and severe form, was considered a fatal condition before the availability of immunosuppressive therapy. This disorder affects both genders and can arise at any age, but is most commonly observed in middle aged and elderly individuals. In a recent population-based retrospective study in the UK, the median age at presentation was 71 (range: 21 to 102) years (Langan et al., 2008). Although rare in children, it has been observed in individuals as young as 3 years (Robinson et al., 1997). As a consequence of transplacental transfer of IgG class antibodies pemphigus vulgaris can transiently occur in neonates of affected mothers (Shieh et al., 2004; Fenniche et al., 2006). PV affects all ethnic groups; however it frequently affects Ashkenazi Jewish. It has been estimated that PV is found four to 10 times more frequently among the Ashkenazi Jewish population than other Caucasian groups (Pisanti et al., 1974; Gazit and Loewenthal, 2005; Mimouni et al., 2008).

Pemphigus vulgaris does not typically have a familial pattern of involvement, although there have been case reports on a familial tendency (Starzycki et al., 1998; Gokdemir et al., 2006). In a large cohort of pemphigus patients from Iran

(Chams-Davatchi et al., 2005), 1.5% of patients had a familial pattern. PV is strongly associated with HLA haplotypes DRB1*0402 and DQB1*0503 (Mobini et al., 1997; Carcassi et al., 1996; Gonzalez-Escribano et al., 1998; Lombardi et al., 1999), thus suggesting an immunogenitic basis of the disease.

Clinical features

PV may predominantly affects the skin with minimal mucosal lesions or affect mainly mucous membranes with little dermal involvement or it may affect both simultaneously (Chams-Davatchi et al., 2005). Imunologically, the mucocutaneous variant with wide spread skin involvement presents with both anti-desmoglein 3 and anti-desmoglein 1 autoantibodies while patients with mainly mucous membrane involvement usually have only circulating anti-desmoglein 3 antibodies (Yeh et al., 2005).

The majority of PV patients present initially with oral involvement (Uzun et al., 2006; Benchikhi et al., 2008). In a large cohort of 1209 patients, 62% presented with initial lesions of the mouth, and ultimately the oral mucosa was involved in 81.5% of affected patients (Chams-Davatchi et al., 2005).

In another study 82.1% of 123 patients with PV had oral lesions before skin involvement (Uzun et al., 2006). This increased with time to affect 116 (94.3%) patients. Both skin and oral mucosa involvement were reported at same time by three (2.4%) patients. Nine patients had lesions limited to the mouth (Uzun et al., 2006).

The mean time lag between oral mucosa involvement and skin has been reported as six months (Uzun et al., 2006). In another study, the time lag was reported as 7.6 and 8.8 months in female and male patients, respectively (Sirois et al., 2000).

Oral lesions in pemphigus are characterized by flaccid blisters that rapidly rupture in response to mechanical trauma, resulting in painful, wide areas of erosions or irregular ulcers. The blisters usually affect the soft and hard palate, buccal mucosa, gingivae, and lips. However in general any surface in the oral mucosa (or gingivae) can be involved and blisters and ulcers can commence in one area and spread to others. Because of the continuous mechanical trauma to oral mucosa, there is often a separation between epithelium and underlining connective tissue (positive Nikolsky sign). With therapy the oral lesions heal slowly, usually without scarring (Yeh et al., 2003).

Gingival involvement is common in PV. In one series of pemphigus patients the gingivae were the most commonly affected site (Iamaroon et al., 2006). Gingival involvement leads to desquamative gingivitis characterized by diffuse erythema, a glazed appearance, and areas of atrophy or erosions which usually resulting in pain or discomfort. However, it should be noted that desquamative gingivitis can be a manifestation of other disorders.

Extra-oral mucosal surfaces such as the conjunctiva, pharynx, larynx, esophagus, rectum, and genitourinary mucosa can also be affected. In a cohort of 148 patients from Turkey, nasal mucosa involvement was reported in 4.0% of patients, larynx in 3.2%, esophagus in 0.8%, and conjunctiva in 1.6% (Uzun et al., 2006).

Histopathological and immunological features of PV

In PV, autoantibodies of the IgG class attack desmosomes which leads to acantholysis- loss of cohesion between keratinocytes in the stratum spinosum. Characteristic Tzanck cells may be observed in the developing blisters while the basal cell layer remains attached to the basement membrane. In pemphigus foliaceus (PF), the autoantibodies attack keratinocytes in more superficial layers, resulting in subcorneal separation with acantholysis.

Immunopathologically, PV is characterized by the presence of cell-attached and circulating IgG autoantibodies against extracellular components of desmosomal desmoglein. There may also be a deposition of C3 (Yeh et al., 2003).

Tissue bound antibodies can be observed by direct immunofluorescence studies of peri-lesional tissue, demonstrating that the effect of the antibodies is not severe enough to disrupt the cell-cell attachment and produce clinical blisters. Applied pressure can enhance the development of blisters in Nikolsky's sign (Hameed and Khan, 1999), although this is not always unique to pemphigus.

5.1.1.2 Pemphigus vegetans

Pemphigus vegetans is a rarely diagnosed subset of pemphigus vulgaris. It gives rise to ulceration and erosion that mimic vulgaris; however, in the healing process hypertrophic, hyperpigmented vegetative plaques develop particularly in the groin, axillae, neck, scalp, and mouth. The tendency for bulla formation (e.g., of the skin) is less than that of pemphigus vulgaris. Oral involvement is common in pemphigus vegetans (Ahmed and Blose, 1984; Markopoulos et al., 2006; Cozzani et al., 2007). Pemphigus vegetans has two forms: Hallopeau, characterized by pustular formation and a benign course with spontanous remission , and the more common and aggressive Neumann form, where the oral lesions mimic those of pemphigus vulgaris and heal with hypertrophic, vegetating plaques (Ahmed and Blose, 1984; Downie et al., 1998; Cozzani et al., 2007). Among 1,209 patients with pemphigus, pemphigus vegetans was observed in 33 patients, 30 of who had the Neumann type and 3 the Hallopeau type (Chams-Davatchi et al., 2005).

Histopathological examination of lesions of pemphigus vegetans reveals papillomatous, proliferating, suprabasal acantholytic lesions in the epidermis, an eosinophilic infiltrate in the dermis together with intra-epidermal microabscesses formation. Direct immunofluorescence reveals intercellular IgG and C3 deposits usually found in the lower layers of the epidermis while IgG class autoantibodies

can be present in the serum (Markopoulos et al., 2006; Danopoulou et al., 2006; Cozzani et al., 2007).

5.1.1.3 Pemphigus foliaceous

Pemphigus foliaceous (PF) is primarily a cutaneous disorder that rarely affects the mucous membranes. Autoantibodies targeting desmoglein 1 cause acantholysis in the subcorneal layer of epithielium, and the erosions are usually more superficial, less severe, and less painful than that of pemphigus vulgaris. Foliaceous and its variants may have a better prognosis than PV (Warren et al., 2000; Uzun et al., 2006; Ishii et al., 2008a).

PF is more likely found in certain developing countries and arises at an earlier age than pemphigus vulgaris (Bastuji-Garin et al., 1996). It is strongly associated with DRB1*0102, 0404, 1402 or 1406 (Petzl-Erler and Santamaria, 1989; Moraes et al., 1991; Moraes et al., 1997). Histopathological features of PF are indistinguishable from those of PV; however, the autoantibodies attack keratinocytes in more superficial layers than in PV, resulting in subcorneal separation with acantholysis.

There are two forms of PF: a non-endemic-pemphigus erythematosus (Senear-Usher syndrome) and an endemic form, known as fogo selvagem. Both conditions share the same clinical, histopathological, and immunopathological features. Clinically, patients have facial erythematous, scaly, crusted lesions. Other areas such as the scalp, back, and chest may be involved.

Fogo selvagem appears more prevalent in some countries (Tunisia and Peru) (Bastuji-Garin et al., 1996; Loayza et al., 2006) perhaps reflecting an autoimmune response to local environmental factors (Aoki et al., 2004) however unlike other types of pemphigus this disease is characterized by a familial tendency.

Additionally fogo selvagem can affect patients at a younger age than those with non-endemic pemphigus foliaceous (Chiossi and Roselino, 2001). In Tunisia fogo selvagem characteristically affects young women without a familial pattern and presents as the herpetiform variant (Morini et al., 1993).

Immunopathologically, PF is characterized by the presence of cell-attached and circulating IgG autoantibodies against desmosomal desmoglein. In variant, fogo selvagem, the antibodies are mainly of the IgG4 class. Moreover, anti-desmoglein 1 antibodies were found to be high among resident in areas of endemic fogo selvagem (Warren et al., 2000).

5.1.1.4 Paraneoplastic pemphigus

Paraneoplastic pemphigus (paraneoplastic autoimmune multiorgan syndrome (Nguyen et al., 2001) is an autoimmune disorder associated with an underlying neoplasm that primarily affects elderly persons and may be more common in females. Paraneoplastic pemphigus (PNP) is typically associated with malignant process, more commonly, non-solid haematological proliferative process (e.g. non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, Castleman's disease, Waldenstrom's macroglobulinemia, Hodgkin’s lymphoma, and monoclonal gammopathy). However 16% of reported patients have had PNP associated with non-haematological malignancies (e.g., carcinoma, sarcoma, and malignant melanoma) (Kaplan et al., 2004). In PNP there are autoantibodies targeting desmoplakin I, desmoplakin II, bullous pemphigoid antigen, periplakin and envoplakin (Horn and Anhalt, 1992; Kaplan et al., 2004).

Although perhaps the least common, PNP is the most serious form of pemphigus. It presents clinically as do other types of pemphigus. Painful oral mucosal erosions and ulcerations are found in almost all affected individuals and can be the initial clinical manifestation. Erosions also may affect the lips, esophagus, larynx, conjunctivae, and genitalia (Kimyai-Asadi and Jih, 2001; Nguyen et al., 2001). Histopathologically, PNP gives rise to epidermal

acantholysis, suprabasal cleft formation, dyskeratotic keratinocytes, and epidermal exocytosis (Horn and Anhalt, 1992). Perivascular infiltration mainly with lymphocytes is common, but without vasculitis (Zhu and Zhang, 2007).

Patients with cutaneous lesions present clinically with blisters/erosions on the upper trunk, head, neck, and proximal extremities. The lesions mimic other types of pemphigus, lichen planus, graft-versus-host disease, erythema multiforme, and Stevens–Johnson syndrome. PNP may also present as lichenoid eruptions, keratotic lesions on the palms and soles, psoriasiform, and vegetative or pustular lesions (Zhu and Zhang, 2007).

The aetiopathogenesis of PNP is largely unknown; however, several mechanisms have been postulated. The tumour cells are thought to initiate the development of anti-epithelial humoral response that lead to the production of autoantibodies to desmosomal and hemidesmosomal antigens (Billet et al., 2006; Zhu and Zhang, 2007).

5.1.1.5 IgA pemphigus

IgA pemphigus is a rare subset of pemphigus mediated by IgA (as opposed to IgG) class antibodies. Although more likely to occur in middle to late life, children can be affected. There are two forms of IgA pemphigus, subcorneal pustular dermatosis (SPD; also known as IgA pemphigus foliaceus) and less commonly intra-epidermal neutrophilic IgA dermatosis (IEN; also known as IgA pemphigus vulgaris) (Robinson et al., 1999; Heng et al., 2006). Patients usually present with cutaneous pruritus, superficial pustules, erythema, and crusts (Hashimoto et al., 2002).

Histopathologically, SPD gives rise to subcorneal pustules mimicking pemphigus foliaceus with neutrophilic infiltration, while IEN shows pustular formation in deeper layers (as with pemphigus vulgaris) and the presence of a

neutrophilic infiltration. Acantholysis is usually present in both variants (Hashimoto et al., 2002).

Direct immunofluorescence of SPD lesions usually demonstrates IgA bound to superficial layers of epidermis, while IEN lesions are characterized by IgA bound to keratinocytes throughout the epidermis (Hashimoto et al., 2002). The antigenic target of SPD type is desmocollin 1, whereas in IEN the targets are desmogleins 1 and 3 or desmocollin 1 (Hashimoto et al., 2002; Heng et al., 2006), hence underlying the different clinical presentation of the 2 disorders.

5.1.1.6 Drug-induced pemphigus

A number of drugs can give rise to pemphigus-like diseases including (i) sulfhydryl radical containing agents (e.g., penicillamine and captopril), (ii) masked thiols that contain S molecule and can be converted to a thiol (e.g., penicillin), and (iii) non-thiol or other drugs (e.g., cephalosporins) (Heymann et al., 2007).

The clinical features of drug-induced pemphigus usually mimic pemphigus foliaceus. Eliminating the causative agent usually results in complete healing of the lesions. However, identifying the precise causative drug can be difficult (and hence delayed) if patients are receiving multiple drugs (Cotell et al., 2000).

5.1.2 Diagnosis

There are a number of disorders that can give rise to oral mucosal and gingival features similar to those of PV (e.g. mucous membrane pemphigoid, erythema multiforme) and therefore, diagnosis should be based on correlation of clinical, histopathological, and immunofluorescence studies. Definitive diagnosis of PV can be delayed when disease affects younger people or is restricted to oral mucosa (Ariyawardana et al., 2005).

Disease that solely affects the oral mucosa seems to be particularly delayed in diagnosis, and the number of clinical consultations can be higher for oral as opposed to cutaneous disease (4.3 versus 2.1 clinicians respectively) (Sirois et al., 2000), possibly reflecting the clinical interests of the attending clinicians. The delay in diagnosis can also reflecting the type of pemphigus, in a cohort of 148 patients, the mean time between disease onset and diagnosis of PV was 20 months, 27 months for PF, 10 months for PE, and much longer for PNP (3 years) (Uzun et al., 2006).

5.1.3 Treatment

Pemphigus has the potential to be life threatening if not treated, and occasionally patients still die as a consequence of adverse drug reactions rather than the disease itself (Mignogna et al., 2000). A wide range of agents have been used to control pemphigus, these being assessed in placebo-controlled trials (Werth et al., 2008), randomized controlled trials (Ioannides et al., 2000; Fernandes and Perez, 2001; Rose et al., 2005; Mentink et al., 2006; Beissert et al., 2006; Chams-Davatchi et al., 2007), case series and case reports (Enk and Knop, 1999; Mignogna et al., 2000; Sirois et al., 2000; Williams et al., 2000 ; Ljubojevic et al., 2002; Mimouni et al., 2003a; Sheehan and Lesher, 2004; Kawashita et al., 2005; Salmanpour et al., 2006). Treatment is directed towards decreasing the number of circulating antibodies to achieve disease remission and healing of lesions.

In the past, systemic corticosteroids were often the only effective agents but there is now a substantial literature on the role of other agents including pilocarpine gel (Iraji and Yoosefi, 2006), azathioprine (Chams-Davatchi et al., 2007), dapsone (Heaphy et al., 2005), mycophenolate mofetil (Chams-Davatchi et al., 2002), ciclosporin (Gergely et al., 2003), cyclophosphamide (Bhat et al., 2005), intravenous immunoglobulins (IVIG) (Engineer et al., 2000), chlorambucil (Shah et al., 2000) and rituximab (Cecchi and Gasperini, 2005). Some agents, such as high doses of corticosteroids, plasmapheresis, and IVIG can induce

clinical response rapidly, while more slowly acting agents include azathioprine, methotrexate, and mycophenolate mofetil (Bystryn, 2002). Although there are many therapies available, few have been assessed in well-designed randomized clinical trials. To date no single agent or protocol is widely accepted in the management of PV.

Researchers dealing with the treatment of pemphigus face many challenges. Rarity of the disease and resulting limited number of patients is a major factor in development of high quality controlled studies; a multicentre approach may be the solution for this problem. An additional complication is the lack of widely accepted measurements for clinical outcomes and definitions used in the treatment of pemphigus such as remission, active disease, and relapse. A recent consensus statement from the International Pemphigus Committee (Murrell et al., 2008) addressed most of these issues, aiming to develop uniform outcome measures and to initiate more multicentre controlled trials to define effective therapies for pemphigus.

This section reviews the different treatment modalities available to treat different types of pemphigus including PV. Generally, there have been equivocal results of the efficacy of different agents, apart from systemic corticosteroids.

Treatment could be divided into control, consolidation, and maintenance stages, based upon the activity of the disease (Bystryn, 2002). In the control stage, high dose and sometimes multiple agents are used to suppress new lesion development and induce healing. In the majority of instances, if appropriate drugs and dosage are employed, PV usually responds rapidly to therapy. In the second stage, the patient should continue the effective agents and dose until most lesions have healed. In the maintenance stage, the therapeutic agents are gradually tapered to the minimum dose effective in preventing the development of new lesions. In all three stages, the longer the stage and/or continued

disease activity may be an indication of either misdiagnosis or inadequate treatment (Bystryn, 2002).

Topical corticosteroids

Topical corticosteroids are usually prescribed in addition to systemic agents to manage and accelerate healing of persistent oral mucosal ulceration (Ben Lagha et al., 2005; Camacho-Alonso et al., 2005). In one cohort, most of pemphigus patients were treated with topical corticosteroid and other topical creams (Ljubojevic et al., 2002). All patients responded favourably with resolution of oral lesions in another cohort of 14 patient who received triamcinolone acetonide (0.5% suspension preparations, 3 times/day) and systemic prednisone (60 mg/day for 4 weeks). One patient necessitates the addition of intralesional parametasone (Once every 2 weeks for 6 weeks) (Camacho-Alonso et al., 2005).

Complete resolution of oral lesions within 2 weeks was reported in an infant after treatment with topical application of triamcinolone in an orabase gel (Shieh et al., 2004). Occlusive therapies with triamcinolone acetonide (Endo et al., 2005) and dexamethasone (Robinson et al., 2004) were reported as effective methods in managing oral lesions, especially desquamative gingivitis. However, topical therapy is generally inadequate and systemic corticosteroids with or without immunosuppressants is required to decrease the circulating antibodies and control the immunological process (Mignogna et al., 2000). Candidosis is the most common complication of long-term use of topical corticosteroids (Thongprasom and Dhanuthai, 2008) especially with the more potent agents.

Systemic corticosteroids

Systemic corticosteroids are currently the mainstay of initial treatment of PV. Moreover, adding an adjuvant agent significantly reduces the mortality rate compared to corticosteroids alone (Carson et al., 1996).

There is however no consensus on the appropriate initial corticosteroids dosage. An initial dose of 1 to 1.5 mg/day is often suggested to be required to produce beneficial effects and control lesions (Mimouni et al., 2003b). However, higher doses may be needed to obtain remission and rapid healing of lesions. Due to the chronic recurrent course of PV and the adverse effects of corticosteroids, or if there is a poor initial clinical response, corticosteroids have been used in combination with other immunomedulatory or immunosuppressant agents (Mignogna et al., 2000; Bystryn, 2002), such as azathioprine (Robinson et al., 1997), cyclophosphamide (Cummins et al., 2003), dapsone (Benchikhi et al., 2008) or gold (Lange et al., 2006).

In a survey of 24 pemphigus experts, half of them prescribed 1mg/kg/day of prednisone as an initial dose, while 31% and 19% prescribe 1 to 1.5 and 1.5 to 3 mg/kg/day, respectively (Mimouni et al., 2003b). In a cohort of 221 patients, 151 (68.4%) received a combination of prednisolone and azathioprine; 45 (20.3%) were prescribed prednisolone alone; and dapsone was added to prednisolone and azathioprine for 25 (11.3%) patients (Salmanpour et al., 2006).

In another cohort of 262 patients (mean follow-up 24.8 months), all patients received systemic corticosteroids: 212 (80.9%) received 1 mg/kg/day and 34 (12.9%) received 1.5 mg/kg daily (Benchikhi et al., 2008). A bolus of methylprednisolone (1 g/day for 3 days) followed by oral corticosteroids, was given to 37 patients (14.1%). Adjuvant agents were used in 48 (18.5%) patients. The most common was azathioprine which was prescribed to 33 patients. Cyclophosphamide or dapsone was each taken by 15 patients. Topical corticosteroids were prescribed to 89 patients while all patients were instructed to use topical antiseptics. Fifty-seven (21.7%) patients were lost to follow-up. 133 patients (50.7%) had complete remission, 49 (18.7%) had partial remission, and 23 (8.7%) had a flare-up of their disease. Seventeen (6.4%) patients died with the most common cause of death was septicemia (Benchikhi et al., 2008).

Fernandes and Perez, (2001) used two regimens in the treatment of 71 patients: high (>120 mg/day) and low (<100 mg/day) doses of prednisone. There was no significant difference between the 2 dosages in initial control of lesions. Response to treatment was reported in 24 and 27 patients who received the low and high prednisone doses respectively. The authors concluded that an initial dose of 1 to 2 mg/kg/day with maximum of 120 mg/day of systemic corticosteroids was adequate to control pemphigus lesions without increasing mortality or morbidity.

Systemic prednisone remains the first-line treatment in the management of pregnant women with pemphigus (Lehman et al., 2008). Prednisone may reduce the risk of passive transmission of the autoantibodies to the fetus and as a result minimizing the risk of neonatal PV.

A high initial dose of deflazacort (120 mg) was used in the management of 14 patients with PV (Mignogna et al., 2000). Eight patients had complete healing within 2 to 4 weeks. The other 6 had partial or no response; however, when these patients received azathioprine in addition to deflazacort all went into remission within 2 to 4 weeks. In comparison with prednisone, deflazacort has a lesser adverse effect on bone metabolism (Mignogna et al., 2000), however 10 of the 14 patients treated with deflazacort had adverse side effects such as insomnia, mood alterations, acute psychosis, hyperglycemia, cataract, or cushingoid (Mignogna et al., 2000).

In a randomized trial involving 33 patients, the addition of ciclosporin (5 mg/kg) to oral methylprednisolone (prednisone equivalent, 1 mg/kg) offered no advantage over treatment with methylprednisolone alone using different outcome measures such as time for healing of majority of lesions, flare up on tapering, percentage of patients in complete or partial remissions, and total dose of systemic corticosteroids required to control disease activity (Ioannides et al., 2000).

A combination of dexamethasone-cyclophosphamide pulse therapy has been reported to be effective for PV. This regimen resulted in long-term remission and accelerated lesions healing in addition to a shorter hospital stay (Kanwar et al., 2002; Mahajan et al., 2005). In a multicentre randomized trial, the combination of dexamethasone and cyclophosphamide appeared to be well tolerated and was associated with fewer recurrences than a methylprednisolone and azathioprine regimen (Rose et al., 2005).

However, in a randomized controlled trial with 20 patients, there was no significant difference between patients who did or did not receive oral dexamethasone pulse therapy (300 mg pulses/3 days/month) in addition to prednisolone (80 mg/d) and azathioprine (3 mg/kg/day). The authors concluded that the oral dexamethasone pulse therapy is not beneficial when used in addition to systemic corticosteroids and azathioprine (Mentink et al., 2006).

In a study of 30 PV patients, pulse therapy (140 mg of dexamethasone dissolved in 200 mL of 5% dextrose with 500 mg of cyclophosphamide) resulted in asymptomatic ventricular arrhythmias in two patients and sinus bradycardia in 10 patients (Jain et al., 2005).

Clinical improvement was reported within a week in patients with severe oropharyngeal pemphigus using pulse therapy with intravenous methylprednisolone (30 mg/kg body weight to a maximum of 1 g for 3 to 5 days) (Mignogna et al., 2002). It has been suggested that the effect of methylprednisolone is due to both the up-regulated synthesis and post-translational modification of the keratinocyte adhesion molecules (Nguyen et al., 2004).

The use of different therapeutic agents in the treatment of PV has the potential for adverse side effects (ASEs) particularly with systemic corticosteroids. In one case series with 159 patients, 37 (23%) patients developed hyperglycemia, skin

infections reported in 26 (16%), arterial hypertension in 23 (14%), cardiorespiratory diseases in 22 (14%) and sepsis in nine (6%) patients (Ljubojevic et al., 2002).

Corticosteroids adjuvant agents

Because of the known ASEs of long-term systemic corticosteroid use, an adjuvant non-corticosteroid immunosuppressive regime is often provided to allow a lowering of corticosteroid dose (Ljubojevic et al., 2002).

However there are many problems with the use of adjuvant agents in particular there is no definitive agent or dosage that seems to be of particular benefit. Additionally all of the suggested immunosuppressants have the potential to give rise to adverse side effects, some of which can be life-threatening. Furthermore, there are no guidelines regarding how long the adjuvant agents should be used when managing most immune-mediated disorders including PV. In the previously cited survey, about half of physicians maintain corticosteroids adjuvant agents for 6 to 12 months, 36% prescribed them for 1 to 2 years and the rest for an indefinite period (Mimouni et al., 2003b).

Azathioprine

Among one group of specialists, azathioprine was the most commonly used corticosteroid-sparing agent followed by mycophenolate mofetil, cyclophosphamide, and ciclosporine (Mimouni et al., 2003b). Azathioprine is an inhibitor of purine metabolism and hence may lessen the proliferation of lymphocytes.

In a recent randomized controlled trial with 120 patients comparing four different treatment regimens (prednisolone alone, or with either azathioprine, mycophenolate mofetil, or intravenous cyclophosphamide pulse therapy), systemic corticosteroid efficacy was improved with the adding of the adjuvant

agents, azathioprine being the most effective agent in reducing the dose of corticosteroids (Chams-Davatchi et al., 2007).

However, in a multicentre, randomized, non-blinded study, both azathioprine and mycophenolate mofetil were reported to have the same efficacy and safety as adjuvant agents to oral methylprednisolone (Beissert et al., 2006).

Azathioprine should be prescribed with caution in view of the risk of bone marrow suppression, hepatotoxicity as well as risk of malignancies. It is however suggested that azathioprine can be provided to pregnant women or those planning to be pregnant as corticosteroid-sparing agent (Lehman et al., 2008).

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid which selectively inhibits proliferation of both T and B lymphocytes (Allison and Eugui, 2000) resulting in suppression of both cell-mediated and humoral immunity. MMF is a relatively recently introduced immunosuppressive agent and hence its exact benefit in the management of pemphigus is perhaps is not as evident as agents such as azathioprine.

In a case series of 12 relapsed pemphigus patients, MMF was prescribed as an alternative to azathioprine as an adjuvant to systemic corticosteroids. Adding MMF (2 g/day) to prednisolone (2 mg/kg/day) resulted in lessening the disease of 11 patients. The remaining patient did not respond (Enk and Knop, 1999). There have since been a number of reports suggesting the efficacy of MMF as an effective adjuvant agent in patients with recalcitrant PV (Chams-Davatchi et al., 2002) without (in general) major adverse drug reactions (Kawashita et al., 2005; Sarma and Ghosh, 2007). In a case series of 31 patients with PV, MMF was effective in lessening the clinical lesions of 67.7% patients. However, it was less effective in the management of patients with severe wide-spread disease

than those with limited disease (Esmaili et al., 2008). In another cohort of 42 patients treated with MMF and prednisone (median time 22 months), 27 patients had complete healing of lesions while 5 had partial remission and 10 did not respond. The median time to achieve complete remission was 9 months (range, 1-13 months). Eight patients had gastrointestinal ASEs, one musculoskeletal and another had neutropenia. Two patients discontinued MMF, one because of reversible neutropenia and the other due to nausea (Mimouni et al., 2003a). Powell and co-workers (2003) used slightly high doses of MMF (2.5 g/day; range from 750 mg to 3.5 g/day as appose to the typical dose of 2-3 g/day) to control refractory pemphigus in 17 patients who also had systemic disorders such as diabetes and ischemic heart disease. MMF had a beneficial effect for 12 of the 17 and permitted the reduction of systemic corticosteroids dose without disease flare-up.

MMF has also been reported to be found effective for some, but not all, patients with paraneoplastic pemphigus (Sirois et al., 2000; Williams et al., 2000; Sheehan and Lesher, 2004).

The evidence that MMF is safe and effective means of managing PV is thus rather mixed, and based upon small number of patients. Like azathioprine MMF has the potential to give rise to adverse systemic effects and long-term use may increase the risk of malignancy. This agent is more expensive than azathioprine and required similar long-term haematological and chemical/ biochemical monitoring.

Dapsone

By virtue of its immunosuppressive action the anti-leprotic dapsone has been employed in the treatment of PV. Dapsone has been reported to be beneficial when combined with oral or intramuscular corticosteroids (Mahajan et al., 2005) or cyclophosphamide (Tirado-Sanchez and Leon-Dorantes, 2006) in the management of PV.

In a retrospective evaluation, eight of nine PV patients had their disease controlled with dapsone as an adjuvant agent allowing patients to taper corticosteroid therapy without worsening of the disease (Heaphy et al., 2005).
In a detailed literature review of 792 patients, after excluding systemic corticosteroids, dapsone considered as a first-line oral therapeutic agent in the management of PV (Yeh et al., 2005). In a recent randomized, double-blind, placebo-controlled trial using dapsone in the maintenance phase of treatment of pemphigus patients in whom corticosteroids tapering was unsuccessful, 73% of the patients receiving dapsone were able to reduce their prednisone dosage to ≤ 7.5 mg/day while only 30 % of those receiving placebo were able to do so (Werth et al., 2008).

There are no detailed reports of the precise benefits of dapsone therapy upon PV limited to the oral tissue. Additionally dapsone can give rise to adverse effects including “dapsone syndrome” following initiation of therapy and haemolytic anaemia. As with aforementioned immunosuppressive agents careful long-term clinical and haematological monitoring is warranted for all patients receiving this agent.

Ciclosporin
Ciclosporin is a calcineurin inhibitor that ultimately inhibits T cell proliferation (Beauchesne et al., 2007). There is some evidence that ciclosporin may be an effective agent for the treatment of some, but not, all patients with PV.

A patient with B cell lymphoma who developed paraneoplastic pemphigus partially responded to corticosteroids, cyclophosphamide, plasmapheresis, and IVIG, was successfully treated using ciclosporin A (7 mg/kg) and all mucocutaneous lesions healed within 6 weeks (Gergely et al., 2003).

Lieb et al. (2006) reported on a patient with PV nail lesions who did not respond completely to cyclophosphamide (150 mg/day), gold (intramuscular

100 mg/week), and methylprednisolone (1 g/day for 5 days) and who developed hemorrhagic cystitis secondary to the use of cyclophosphamide, responded well to ciclosporin 50 mg twice daily and gold (intramuscular 50 mg twice weekly) after the flare up was controlled by methotrexate (25 mg/week).

Ciclosporin (2.5 mg/kg daily) achieved rapid resolution of PV oral ulceration in an HIV-positive patient and circulating IgG antibodies disappeared. A later flare up of the disease was controlled within 9 days of ciclosporin as a monotherapy (Hodgson et al., 2003). However, ciclosporin was stopped after 6 weeks in an HIV patient with oral PV after he exhibited fatigue, headache, and gastrointestinal upset and was diagnosed with acute renal toxicity due to ciclosporin interaction with hyperactive antiretrovirus therapy (HAART). Interestingly, oral lesions completely healed (Mignogna et al., 2005).

A meta-analysis concluded there is a risk in treating patients with autoimmune disorders with ciclosporin and recommended strict monitoring of renal function (creatinine) and ciclosporin levels during therapy for these patients and for those receiving ciclosporin for more than a year (Vercauteren et al., 1998).

Topical ciclosporin (100 mg in 5 mL suspension 2-3 times/ day) has been reported to maintain remission of oral lesions of PV (Gooptu and Stoughton, 1998; Hodgson et al., 2003).

In a case report of a woman with mucocutaneous lesions whose painful oral ulcerations did not responded to a wide verity of topical and systemic agents such as prednisolone, azathioprine, methotrexate, dapsone, chloroquine, cyclophosphamide, intramuscular sodium aurothionate and potent topical corticosteroids agents (or she stopped using some of the agents due to ASEs) responded well to topical ciclosporin (Gooptu and Stoughton, 1998).

Cyclophosphamide

Cyclophosphamide is an alkylating agent that may be useful as an immunosuppressant in severe immunologically-mediated disease. Cyclophosphamide has been suggested as effective and safe in combination with prednisolone (Bhat et al., 2005) and dexamethasone (Sehgal et al., 2005). Pulse therapy with 100 mg dexamethasone in 5% glucose daily for 3 consecutive days in addition to cyclophosphamide (500 mg on first day followed by 50 mg/day) achieved complete remission of pemphigus lesions (Sehgal et al., 2005).

In an open-label clinical trial, 26 pemphigus patients who partially responded to corticosteroids received intravenous cyclophosphamide (15 mg/kg/month) in addition to prednisolone (1 mg/kg/day). All patients had a significant improvement in their signs and symptoms. Cutaneous healing preceded that of mucosa by a mean time of 1.5 months. The most common adverse drug reaction was weight gain due to the corticosteroids (Bhat et al., 2005).

Due to the adverse side effects associated with cyclophosphamide and methylprednisolone, some authors reserved their use to resistant patients not responding to high doses of systemic corticosteroids (Mignogna et al., 2000).

In a randomized clinical trial with 22 patients, a dexamethasone-cyclophosphamide regimen was found better tolerated and had more remission periods than methylprednisolone-azathioprine therapy (Rose et al., 2005). Within 2 years after treatment initiation, three of the 11 patients who received dexamethasone-cyclophosphamide treatment had a complete remission while 2 had partial remission. Three patients treated by methylprednisolone-azathioprine combination had complete remission while 6 had partial remission. However, there were more relapses in methylprednisolone-azathioprine group than in dexamethasone-cyclophosphamide group (Rose et al., 2005). Ablative intravenous cyclophosphamide (50 mg/kg per day for 4 days) without stem cell

rescue was shown to be relatively safe in treating a patient with oral and skin PV that had been recalcitrant to other agents (Hayag et al., 2000).

Similar to other immunosuppressants cyclophosphamide therapy warrants close clinical and haematological monitoring, probably in view of the risk of bone marrow suppression and haemorrhagic cystitis (Mukhtar and Woodhouse, 2010).

Other therapeutic regimes

Chlorambucil

Chlorambucil is an alkylating agent that been used to treat patients with chronic lymphocytic leukemia. It also has been employed in the treatment of some immune-mediated disorders such as nephrotic syndrome and bullous pemphigoid (Milligan and Hutchinson, 1991; Chave et al., 2004; Hodson et al., 2008). There is a very limited report on chlorambucil efficacy in the management of PV. A retrospective study reported that 6 of 9 patients prescribed chlorambucil had a lessening of their mucocutaneous disease (Shah et al., 2000). However, the patients also received concurrent prednisone and thus the clinical effect may have reflected the corticosteroids. Three of the 9 patients developed haematological abnormalities including pancytopenia, lymphopenia, and thrombocytopenia (Shah et al., 2000).

Intravenous immunoglobulin

The efficacy of intravenous immunoglobulin (IVIG) in the management of PV was reviewed by Engineer et al., (2000) who reported that it is safe and effective in the treating recalcitrant PV, but, long-term outcome data are not available yet. Guidelines have been suggested for the use of IVIG in the treatment of pemphigus (Akerman et al., 2005).

At least 3 cycles of IVIG with a minimum dose of 2 g/kg is reported to induce clinical remission of PV recalcitrant to other regimens (Engineer et al., 2000);

however, clinical improvement may not arise until the sixth cycle (Baum et al., 2006). Complete remission may be as high as 50% (Baum et al., 2006).

Intravenous immunoglobulin therapy is expensive and should only be provided by appropriate specialists. There is little place for such therapy for disease limited to the oral mucosa and there seems to be no studies of the benefit of IVIG upon such clinical presentations.

Rituximab

Rituximab is a monoclonal antibody that binds to CD20- positive cells (pre-B and mature B lymphocytes) resulting in their lysis. It does not affect the CD20-negative plasma cells that may produce autoantibodies PV (Belgi et al. 2006; Niedermeier et al., 2006) hence clinical benefit may be delayed.

A recent review indicates that rituximab may be of application for the treatment of PV (El Tal et al., 2006). Most of the reported patients (88%) had resolution of disease following rituximab therapy, although one patient died as a consequence of opportunistic infection (El Tal et al., 2006). All 11 patients of another study (Ahmed et al., 2006) responded well to rituximab between the third and sixth infusion. Nine (82%) of the patients had rapid healing and a remission period of 22 to 37 months. The other two patients (18%) had recurrence 6 months after the tenth infusion of rituximab. Both had complete remission after receiving additional rituximab infusions alone (once a week for 3 consecutive weeks); however, one had another flare-up and received another rituximab infusion (once a week for 3 consecutive weeks) which resulted in complete remission (Ahmed et al., 2006).

Rituximab therapy is expensive and requires carful clinical monitoring in view of the risk of adverse side effects (e.g. systemic infection, infusion reactions). There are few reports of rituximab therapy for PV limited to the oral tissue (Arin et al., 2005; Niedermeier et al., 2006).

Plasmapheresis

Plasmapheresis has been suggested to be a means of providing rapid control of severe PV in patients who have not had clinical benefit to conventional treatment with systemic corticosteroids and other agents. Long-term remission may be occasionally achieved (Ljubojevic et al., 2002). There are however only small number of reports of the efficacy of plasmapheresis in the management of PV and no studies of the benefit of this treatment modality for disease limited to the oral tissue.

Others

The treatment of PNP clearly requires identification and management of causative malignancy. However there may be a need for concomitant corticosteroids/immunosuppressant therapy of the accompanying PNP (Menenakos et al., 2007).

In conclusion, there is some evidence of the role of all aforementioned therapeutic agents however, well designed randomized controlled studies with good number of patients is needed to support the use of each agent in the treatment of mucocutaneous pemphigus vulgaris lesions.

5.1.4 Outcome of pemphigus

Despite significant advances in therapy, particularly the range of potentially effective immunosuppressants, the long-term behaviour of PV is unclear as long-term data are often lacking. Recent studies suggesting that just over half of all patients have complete remission, with the remainder having variable recurrence of disease (Benchikhi et al., 2008). Mortality due to disease, or associated therapy or unknown causes may range from 1.5 to 8.3 (Uzun et al., 2006; Chams-Davatchi et al., 2005; Michailidou et al., 2007).

5.2 AIMS

The aims of this chapter were to determine:

1. The clinical characteristics of a substantial cohort of patients with pemphigus vulgaris resident in England, UK.
2. The clinical outcomes of long-term therapy of pemphigus vulgaris.
3. The frequency and nature of adverse side effects of therapy of pemphigus vulgaris.

5.3 PATIENTS AND METHODS

5.3.1 Patients group

The study group consisted of 40 patients referred to the Oral Medicine Unit of UCL Eastman Dental Institute and UCLH Eastman Dental Hospital between 1975 and 2007, with clinical and usually histopathological features consistent with the diagnosis of pemphigus vulgaris (PV).

5.3.2 Methods

The case record of each patient was examined using multiple data extraction forms for details of demographics, past medical history, extra-oral and intra-oral clinical features and clinical progress data. Details of diagnostic and monitoring investigations were also systematically extracted. These included: histopathology, full blood cell count, differential white cell count, hepatic and renal biochemistry. Details of the different topical and systemic therapies employed in the management of each patient were also recorded (Appendices 1-5).

Inclusion criteria

(1) evidence of erosion/ulceration/blistering of the oral mucosa with/without extra-oral involvement, (2) histopathological evidence of intra-epithelial cleavage and acantholysis, (3) evidence of direct immunofluorescence on mucosal/skin biopsies of intercellular tissue-fixed antibodies (4) evidence of indirect immunofluorescent of circulating autoantibodies to desmosomes.

In all patients at least criterion 1 and either 3 or 4 were present to assign a diagnosis of PV.

Outcome of therapy

The outcome of therapy was evaluated for symptoms and signs separately. Symptoms evaluation was reported as improved, presence or absence of intra-oral pain/soreness and based on comparison between patients' self-reported pain/soreness status before therapy and at last review in 2007.

The outcome of therapy (clinical signs) was analysed on the basis of the comparison between disease status before therapy and last review in 2007 utilising 2 different methods. (i) The first one according to site of the lesion, either gingival or mucosal, using a 2-point scoring system: (0) absence of mucosal and/or gingival lesions and (1) presence of mucosal or gingival lesions. (ii) The second method was a comparison between disease status (signs in different anatomical sites) before therapy and at last review.

Evaluation of response to therapy was based on clinicians' judgments during clinical examination and/or upon clinical photographs when present in the clinical notes.

Statistical analysis

The differences between females and males in relation to duration of oral symptoms before attending to Oral Medicine Clinics and duration of the treatment were analyzed using Student's t-test. McNemar's test was used to compare symptoms and signs before and after treatment in Oral Medicine Clinics. Descriptive and analytical statistics were undertaken using the SPSS program (SPSS for Windows: (Statistical Package for the Social Sciences) software, version 12.0.

5.4 RESULTS

5.4.1 Patient demographics

Age and gender

The mean age of the patients at the time of diagnosis was 51.1 years (SD 16.4); 46.3 for males (SD 12.5) and 53.5 for females (SD 17.8). The age range was 18.8 to 95.8 years. The onset of the clinical features of disease was usually in the fifth and sixth decade of life. There were more females (27; 67.5 %) than males (13; 32.5%) (Figure 5.1).

Ethnic Background

The majority of patients were white British (14; 35%) (self-reported, according to 2001 UK Census) (Office for National Statistics, 2003). The second most common ethnic group was Indian (11; 27.5%) (Table 5.3).

Tobacco use and alcohol consumption

Three (7.5%) patients were previous tobacco users and 3 were current users with a mean number of self-reported cigarettes per day of 6.4. Twenty one (52.5%) patient currently drank alcohol with a mean total weekly consumption of 3.2 units.

Sources of Referral to Oral Medicine Unit

Eleven (27.5%) of the patients had been referred to the oral medicine unit by general dental practitioners; 11 by a specialist in the Oral and Maxillofacial Surgery and the remainder by their general medical practitioner or a medical or dental specialist (Table 5.4). The patients had been referred to oral medicine clinics for the diagnosis and/or management of variety of oral lesions such as desquamative gingivitis or mucosal blisters and/or ulcers.

5.4.2 Past medical and drug histories

5.4.2.1 Past medical history

The patients had a history of a variety of common medical problems (Table 5.5), the most common of which were allergic, cardiovascular, respiratory, endocrine, and gastrointestinal disorders.

Five (12.5%) patients had diabetes mellitus and 4 (10%) had a history of hypertension; 2 (5%) patients had a history of asthma and two (5%) patients had thyroid disease. Among the gastrointestinal conditions reported were gastroesophageal reflux disease 2 (5%) and abdominal hernia (3; 7.5%) while others had a variety of signs and symptoms. Additional medical history details are provided in Table 5.5.

5.4.2.2 Drug history

The patients were receiving a wide range of medications at the time of their clinical consultation. As expected from past medical history reviewed above, the most common drugs were anti-hypertensives, and anti-asthmatic agents. A wide range of topical and/or systemic agents had been prescribed to present cohort of patients to control their oral and/or mucocutaneous lesions likely due to PV and. (Tables 5.6 and 5.7).

Triamcinolone acetonide (Adcortyl in Orabase) was prescribed to 7 (17.5%) patients; betamethasone sodium phosphate and hydrocortisone sodium succinate were prescribed to 6 and 5 patients, respectively. Patients also were prescribed other preparations of topical corticosteroids, antimicrobial and/or analgesic agents. Systemic corticosteroids (prednisolone) prescribed to 17 patients by different medical and dental specialist before attending Oral Medicine clinics. Additional details on different agents used to control the patients' disease before attending Oral Medicine clinics are summarised in Table 5.7.

5.4.3 Presenting clinical signs and symptoms and duration of oral symptoms

5.4.3.1 Duration of oral symptoms at first visit

The duration of oral symptoms before attending the oral medicine clinics varied from 1 month to 26 years, with a mean of 30.9 months. Males had a shorter duration of pre-consultation symptoms (23.1 months) compared to females (34.2 months), however, this was not statistically significant (P= 0.595).

5.3.3.2 Presenting clinical signs and symptoms

Intra-oral

At their clinical consultation at the oral medicine unit, most patients (38; 95%) had symptomatic oral lesions, although 1 patient was asymptomatic at this time and another had pain related to TMJ. A total of 151 lesions were recorded in present cohort of patients, with a mean of 3.8 oral signs. Oral ulceration was the most common sign: buccal ulcerations (21 patients), gingivae (18), tongue (15), soft palate (12), floor of the mouth (6), hard palate (5), and labial mucosa (5) (Table 5.8).

Extra-oral

Eighteen (45%) patients had a history of PV at extra-oral sites. Most of these patients (15) had just one extra-oral site involvement, two had 2, and one had 3 extra-oral sites involved in the PV course. Skin was the most common extra-oral site affected (17) followed by eyes (2), genitals (2), and nasal mucosa (1).

5.4.4 Diagnostic clinical investigations

5.4.4.1 Histopathological features

Histopathological examination of peri-lesional tissue was undertaken on 26 (65%) of the 40 patients. The histopathological reports of the remaining 14 patients were not present in their clinical notes as they had been diagnosed by other medical specialists and referred for the treatment of oral lesions.

In accordance with the clinical presentation, biopsies tended to be taken from the buccal mucosa (12). Although specimens were also obtained from tongue (3), labial mucosa (2), lip (1), gingivae (1), hard palate (1), soft palate (1) and unknown site (5). Inflammatory cells were found in 22 sections. In 24 (92%) of patients who had histopathological report, histopathological examination confirmed or was suggestive of PV diagnosis. Intraepidermal cleavage and acontholysis (Tzanck cells) found in most (22/26) of the tested lesional specimens.

5.4.4.2 Immunofluorescence features

Direct immunofluorescence was undertaken on 17 biopsy specimens, of which intercellular deposits of IgG found in (16) and C3 in (9) although one specimen had an absence of such immune deposits. Thirty four of the 36 patients tested for indirect immunofluorescence had circulating antibodies to intercellular components of monkey/human epithelium substrate with a very wide range of titres (1:10 to 1:5120).

5.4.5 Therapy

A number of different topical and systemic agents had been prescribed to control the clinical signs of PV. Initial treatment consisted of prednisolone and topical corticosteroids. Patients who required long-term therapy also received adjunctive agents such as azathioprine, dapsone or methotrexate. Topical agents included different preparations of fluticasone propionate, clobetasol

propionate, and betamethasone and other topical agents (Table 5.9). Due to the long periods of using potent topical corticosteroids, some patients receive multiple courses antifungal agent, either to treat or prevent candidosis.

Thirty nine patients (97.5%) received topical therapies and 37 (92.5%) systemic agents. The mean number of topical agents prescribed was 2.9, while the mean number of systemic agents was 3.3 (5.8 and 5.9). Initial systemic therapy usually consisted of a moderate dose of prednisolone (60 mg/day; range 20-80 mg/day) with/without adjunctive agent such as azathioprine (1-3 mg/kg per day). Additional details about systemic therapies and number of agents in Tables 5.10 and 5.11.

5.4.6 Outcomes of therapy

The mean duration of treatment in this cohort of PV patients was of 4.8 years (median 3.5 years). Most of patients responded well to treatment.

5.4.6.1 Symptoms

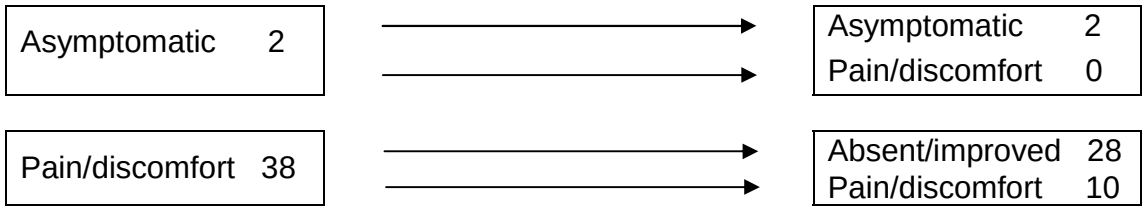

Figure 5.2 Patients' symptoms at initial visit (left side) and at last visit (right side).

Of this group of PV patients, 2 were asymptomatic at initial presentation and remain pain-free when last examined in oral medicine (median duration of follow up was 3.5 years).

Most patients (38; 95%) had symptoms (pain, discomfort, soreness or burning) at initial consultation and 28 of this group (73.7%) had self-reported lessening or cessation of the symptoms at the end of the treatment.

5.4.6.2 Clinical signs

i Analysis of clinical outcome according to site

Of the 19 patients who had solely oral mucosal lesions without gingival involvement at the initial consultation, ten (52.6%) patients had complete healing of oral ulcerations at the last review. Six (31.6%) patients showed persistence of mucosal ulcerations/erosions or blisters while two patients developed combined mucosal and gingival lesions and another developed gingival lesions alone.

Of the 15 patients who presented initially with combined mucosal and gingival lesions, complete absence of clinical lesions was observed in seven (46.7%) patients. Combined gingival and mucosal lesions persisted in five patients (33.3%), while 3 patients present at last review with just oral mucosal lesions.

Of the three patients presenting with solely gingival lesions at their first oral medicine consultation, two showed healing of gingival lesions but one developed mucosal ulceration. The third patient also developed mucosal with the gingival lesions. There were no apparent lesions in three patients who attend for consultation at oral medicine clinics. In general, half (21/40; 52.5%) of patients had complete absence of clinical lesions at last review (Table 5.12).

ii Analysis of clinical outcome according to signs and sites

Desquamative gingivitis:

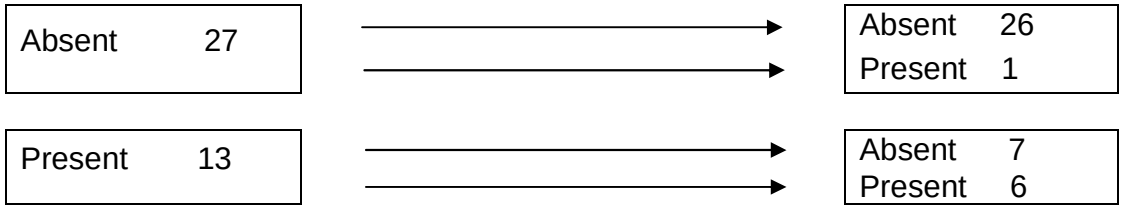

Figure 5.3 Status of patients with regards to desquamative gingivitis at initial visit (left side) and at last visit (right side).

Twenty-seven patients (67.5%) were free of desquamative gingivitis at initial presentation and only one had developed gingival features of pemphigus by the end of the study period.

The number of patients with desquamative gingivitis fell from 13 to 7 within the observation period, but this was not statistically significant (P= 0.07).

Buccal mucosa ulceration

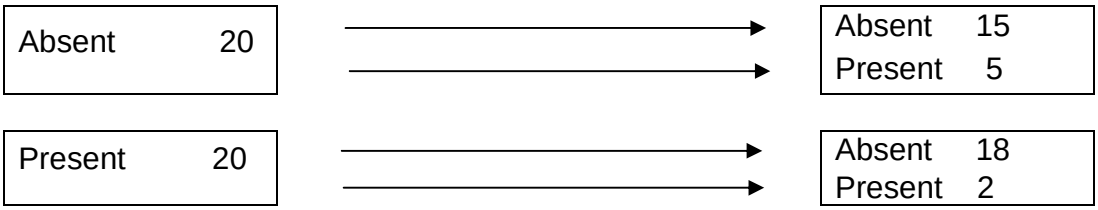

Figure 5.4 Status of patients with regards to buccal mucosa ulceration at initial visit (left side) and at last visit (right side).

Twenty patients were free of buccal mucosa ulceration at their initial presentation; however, 5 of them developed ulcers at this site by the end of the study.

Twenty patients had buccal mucosa ulceration at their initial presentation but only 2 still had ulcers at this site at the end of the treatment. This change was statistically significant (P= 0.01).

Buccal mucosal erosions

Erosions in buccal mucosa were observed in 6 patients at their initial consultation, which resolved in 4 of them by the end of the study period. None of the 34 patients who presented initially without erosions developed any lesions at the buccal mucosa.

Soft palate

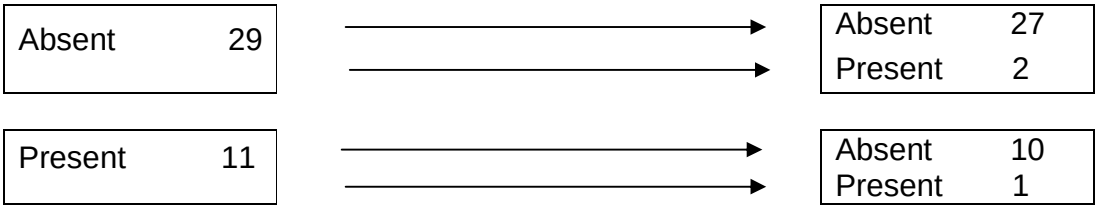

Figure 5.5 Status of patients with regards to soft palate ulcerations at initial visit (left side) and at last visit (right side).

Most patients (29) were free of soft palate ulceration at their initial presentation; however, 2 developed ulcers at the end of the study.

Eleven (27.5%) patients had ulceration of the soft palate at their initial clinical presentation but only 1 still had ulcers of this site at the end of the observation period. This change was statistically significant (P= 0.039).

Seven patients with previous erosions at the soft palate had had resolution by the end of the study period which one patient who had no erosions had developed lesions at soft palate at the end of the observation period.

Hard palate

One of the 5 patients who had ulceration of the hard palate at their initial consultation still had ulceration at the end of observation period while two patients with previous erosions at the hard palate had resolution of disease at this site.

Floor of the mouth

Six patients had ulceration of the floor of the mouth at their initial presentation to oral medicine and all were free of ulcers at this site at the end of treatment. Only one patient who was free of floor of the mouth ulceration developed ulcers at this site by the end of the study. Also, another patient developed new erosions at floor of the mouth at the end of the study while, 4 patients had their erosions resolved at the end of the study.

5.4.7 Adverse drug reactions

The mean number of agents prescribed to patients was 6.1 (2.9, 3.3 were the mean numbers of topical and systemic agents respectively). Thirty nine (97.5%) patients received topical agents and 37 (92.5%) received systemic agents. 20 patients had adverse side effects (ASEs) such as malaise, gastrointestinal upset, nausea, vomiting, diarrhoea, cushingoid appearance, skin rash, candidosis and unpleasant taste, and haematological changes such as lymphopenia and haemolysis.

Eight patients had one ASE, 9 had two, 2 had three and 1 had 4 ASEs. 19 of the 37 patients on systemic agents developed 29 ASEs events; while 7 of the 39 patients who received topical agents developed 7 ASEs events.

Most adverse effects in this cohort of PV patients were associated with azathioprine. It was prescribed to 24 patients; adverse effects developed in 9 of these patients including nausea (4 patients) and vomiting (2), diarrhoea (1), skin rash (1) , headache (1) lymphopenia (2) and abnormalities in liver enzymes (1).

Prednisolone was prescribed to 28 patients; adverse effects developed in 7 patients including dyspepsia (1), osteoporosis (1), hypothalamic-pituitary-adrenal (HPA) axis suppression (1), diabetes (2), cataract (1), moon face and cushingoid appearance (3). Deflazacort was prescribed to 18 patients; adverse affects developed in 3 patients including, irritability and morning waking, diabetes, and osteoporosis.

Five patients on topical corticosteroids had ASEs including candidosis, and blurred vision. Some patients on topical tacrolimus had burning sensation or peppery taste. More details about adverse drug reactions in table 5.13.

5.4.8 Duration of treatment

In this cohort of PV patients, treatment duration differed greatly, ranging from a few months to more than 25 years (until data collected). The mean length of therapy was of 4.8 years (SD 5.2). Men had a longer treatment duration (mean, 5.9 years) than women (mean, 4.3 years), however, this was not significant (P= 0.374) (Table 5.14).

Thirty patients remain under the care of the oral medicine unit. Three have been discharged as they were asymptomatic, while three referred to other units for follow-up. One patient failed to attend and the other (3 patients) died. The cause of death of these 3 patients is unknown but unlikely to reflect PV or its treatment.

5.5 DISCUSSION

Although pemphigus vulgaris (PV) has the potential to adversely affect the patient's quality of life (Paradisi et al., 2009), there are few data on the long-term behaviour or effective therapy for this condition.

Pemphigus vulgaris is a rare disease that gives rise to oral and other mucocutaneous blistering and ulceration (Murrell et al., 2008). Oral involvement gives rise to recurrent, sometimes extensive ulceration and pain, which can result in dysphagia, dysarthria and poor dietary intake, all of which can adversely affect quality of life. In the present study PV was typically diagnosed in middle to late life (mean age of onset, 51.1 years) and predominantly affected females, a finding reported by others (Robinson et al., 1997; Ljubojevic et al., 2002; Chams-Davatchi et al., 2005; Iamaroon et al., 2006; Shamim et al., 2008). The female-to-male ratio (2.1:1) was higher than that reported in some studies (Ljubojevic et al., 2002; Chams-Davatchi et al., 2005; Kavusi et al., 2008), but in agreement with other reports (Tallab et al., 2001; Sirois et al., 2000; Iamaroon et al., 2006). PV rarely affects children (Laskaris and Stoufi 1990; Robinson et al. 1997; Harangi et al., 2001; Chams-Davatchi et al. 2005a) and there was only one teenage patient (18 years of age) in the present cohort.

In the present cohort, White-British and Asian-Indian were the most common ethnic backgrounds (35% and 27.5%, respectively), the remaining 37.5% represented by other ethnic groups. This distribution reflects that of general London population in 2001 census (Office for National Statistics, 2003) and does not indicate any ethnically-oriented predisposition. PV had been reported in patients from many parts of the world such as US (Woldegiorgis and Swerlick, 2001), Brazil (Chiossi and Roselino, 2001), UK (Langan et al., 2008), Greece (Michailidou et al., 2007), Morocco (Benchikhi et al., 2008), Israel (Mimouni et al., 2008), Saudi Arabia (Tallab et al., 2001), Iran (Salmanpour et al., 2006), India (Kumar, 2008), and Japan (Ishii et al., 2008a) and other countries (Alsaleh et al., 1999; Goon and Tan, 2001; Iamaroon et al., 2006; Budimir et al., 2008);

however, a predominance of Ashkenazi Jewish patients has been suggested in some studies (Pisanti et al., 1974; Gazit and Loewenthal 2005).

The mean duration of symptoms before patients attended the oral medicine clinics was 30.9 months, suggesting that mild symptoms, misdiagnosis, oral lesions treated by other medical specialists (e.g., dermatologists), or delay in referral, are likely to have occurred in a significant number of patients. This delay in diagnosis of PV and other vesiculobullaous disorders is not uncommon (Uzun et al., 2006; Ariyawardana et al., 2005) as mouth ulcers are common and may be diagnosed as one of the more common oral diseases, such as recurrent aphthous stomatitis (Daneshpazhooh et al., 2009) or oral lichen planus. Although males had a shorter duration of pre-consultation symptoms (23.1 months) compared to females (34.2 months), this was not statistically significant and probably not of clinical relevance.

The clinical features of PV often resemble those of mucous membrane pemphigoid and other vesiculobullaous disorders. In the present study, PV gave rise to recurrent bout of ulcers that typically affected multiple oral mucosal sites. In the majority of patients, the disease was characterised by mild onset and lesions were usually localized. The buccal mucosa and gingivae were the most affected intraoral sites, as previously reported (Robinson et al., 1997; Shamim et al., 2008; Iamaroon et al., 2006). Desquamative gingivitis was observed in 13 patients. This condition may also present in other immunological-mediated disorders, commonly mucous membrane pemphigoid and lichen planus (Leao et al., 2008), which may lead to delay in an accurate diagnosis.

Approximately half of the patients in present cohort had a history of clinical and histopathological evidence of PV at extra-oral sites, with the skin being the most common. Oral lesions usually preceded other mucocutaneous lesions and were the sole manifestation in most cases. However, this observation should be interpreted with caution, as there may be a referral bias since as this was study

carried in an oral medicine unit. However, other studies support the observation that oral disease may be the first and/or only manifestation of PV (Robinson et al., 1997; Shamim et al., 2006).

The diagnosis of PV should base on clinical, histopathological, and immunological results. Most of the available biopsies (22/26; 84.6%) of the present cohort showed the characteristic supra-basal intraepithelial cleft of PV. Direct immunofluorescence revealed intercellular deposits of IgG and C3 throughout the epidermis in approximately 94% of the tested specimens, which is in agreement with previous studies (Sano et al., 2008). Thirty-four of the 36 patients who underwent indirect immunofluorescence examination had circulating antibodies to intercellular components of monkey/human epithelium substrate with titre ranging from 1:10 to 1:5120. Although the levels of circulation anti-epithelial antibodies have been reported to be associated with the patient's clinical condition in one study (Sams and Jordon, 1971), other reports have not found this correlation (Judd and Lever, 1979; Judd and Mescon, 1979) or has observed that this association was inconsistent throughout the course of PV (Acosta et al., 1985). In the present cohort, the titre of circulating antibodies tended to decrease in response to treatment and sometimes reflected the clinical course of the disease.

There are few randomised controlled trials (RCTs) (Mentink et al., 2006; Ratnam et al., 1990; Rose et al., 2005; Tabrizi et al., 2007; Werth et al., 2008) and only one systematic review (Martin et al., 2009) of the treatment of pemphigus. Most information concerning the efficacy of therapies has come from case series and non-randomized trials. A recent Cochrane review (Martin et al., 2009) identified 11 RCTs for the treatment of pemphigus. However, the authors concluded that there is insufficient evidence to provide clear guidelines for the treatment of this disorder.

An initial dosage of systemic corticosteroids of 60 to 80 mg/day (typically of prednisone) is often recommended (Robinson et al., 1997). Most recommendations for the treatment of PV have been based on cohort studies and attending clinician experience (Harman et al., 2003). The daily dose being gradually reduced or increased by increments of 10 to 20 mg daily until optimum dose is established. However as noted above there is evidence-based protocol for the treatment of PV.

The cutaneous blisters, erosions, and ulcers can be portal of entry for infection and ultimately septicemia which can result in death. It is thus essential to initiate therapy in the early stages of the disease to induce remission and to reduce the dosage of corticosteroids as quickly as possible to avoid associated adverse side effects (Bystryn, 2002). A wide range of corticosteroids-sparing immunosuppressant agents are available to control PV, but most of them have not been evaluated by well-designed RCTs (Bystryn, 2002).

In the present study, a variety of topical and systemic medications were used to control the oral lesions. Patients usually received an initial dose of prednisolone (20 to 80 mg) or deflazacort (18 to 42 mg) with or without azathioprine (25 to 50 mg three times daily) the corticosteroids being maintained at the initial dose for 2 to 3 weeks, to suppress new ulcer formation and induce lesion healing. Prednisolone (or deflazacort) was usually prescribed as a single dose taken in the early morning to minimise adverse side effects (ASEs). The treatment usually continued until most lesions had healed and symptoms resolved. Some authors (Lever and Schaumburg-Lever, 1984) have recommended higher doses of prednisolone than those used in the present group of patients while others (Chams-Davatchi and Daneshpazhooh, 2005) used moderate to high doses (1-2 mg/kg). In a randomised trial, there were no long-term significant differences between high- (120 mg/day) and low-dose (60 mg/day) prednisolone regarding frequency of flare ups or complications (Ratnam et al., 1990). In the present cohort, as with other patients receiving systemic corticosteroids, administration

of systemic prednisolone was usually gradually reduced to the minimum effective dose, concomitant with the use of topical agents. In severe cases which necessitated long periods of systemic corticosteroid therapy, an adjunctive agent such as azathioprine (25-50 mg 3 times/day) was usually prescribed when prednisolone therapy was initiated, since these agents generally require several weeks to become effective (Bystryn, 2002). Also other adjunctive agents such as dapsone or methotrexate were used in present cohort. Nearly all the patients received topical agents, commonly topical corticosteroids, including high potency agents such as clobetasol propionate, to accelerate oral mucosal healing.

Some patients may be prescribed a gastric mucosal protectant (e.g. proton pump inhibitors) to help avoid gastric ulcers aiming to decrease the potential gastrointestinal adverse side effects of corticosteroids. Other patients undergoing long-term systemic corticosteroid treatment may be, referred for bone scans and, based on the results, may receive vitamin D supplements to decrease adverse effects, such as osteoporosis. Some of the present group of patients received antifungal therapy to treat candidal infections which developed as an ASE of the topical corticosteroids. All patients were monitored for weight and blood pressure.

The clinical outcome of treated PV patients that of the mouth is not well documented this may be as a result of lacking a widely, reproducible and objective outcome measuring system for recording oral mucosal diseases.

In the present cohort, complete resolution of oral mucosal lesions was evident in about half of the patients, and there was a trend of decreased severity in those patients who did not response completely to therapy (Data not shown).

About half of the 19 patients with only oral mucosal lesions and no gingival involvement at the initial consultation had complete healing at the last examination. Six patients showed persistent mucosal ulcerations/erosions or blisters, while two patients developed combined mucosal and gingival lesions and another developed gingival lesions alone.

Of the 15 patients who presented initially with combined mucosal and gingival lesions, complete resolution of the clinical lesions was observed in seven (46.7%); gingival and mucosal lesions persisted in five patients (33.3%); and three presented with just oral mucosal lesions at the last examination.

Two of the three patients presenting with solely gingival lesions at their first visit showed healing of gingival lesions, but one developed mucosal ulceration. The third patient developed mucosal lesions.

The high number of patients who did not have complete remission may reflect the study being at oral medicine unite, a specialised (tertiary) care centre and it may be that patients with probably severe disease are referred to this unit as evident by the majority of patients being referred by specialists.

In the current cohort, 39 patients received topical therapies, while systemic agents were prescribed for 37 patients. Twenty patients reported ADRs, including malaise, gastrointestinal upset, nausea, vomiting, diarrhoea, cushioned appearance, skin rash, candidosis and unpleasant taste sensation, and haematological changes such as lymphopenia and haemolysis. This high proportion may be attributed to the wide variety of topical and/or systemic agents they received. It could also be due to the chronic nature of these diseases, which necessitates long periods of treatment that may increase the risk of some ADRs, particularly osteoporosis and diabetes in patients receiving systemic corticosteroids. In present study, morbidity and mortality in pemphigus vulgaris patients was higher than MMP (Chapter 4).

5.6 CONCLUSION

The present data confirm previous studies that PV is a chronic disease most frequently occurs in women and affected patients usually in their middle decades of life. Most of the patients present initially with oral mucosal lesions where general dental practitioner may have a role in early diagnosis. Therapy is complex although adverse side effects are more likely with azathioprine. The main limitation of the present study is its retrospective design and associated methodological inadequacies, including differences in reporting clinical features and outcomes, lack of a control group, and variations in diagnostic and monitoring procedures. The establishment of a national register for these rare conditions would help researchers and practitioners better understand the clinical symptoms and aetiopathology of these diseases, resulting in earlier diagnosis and initiation of appropriate treatment.

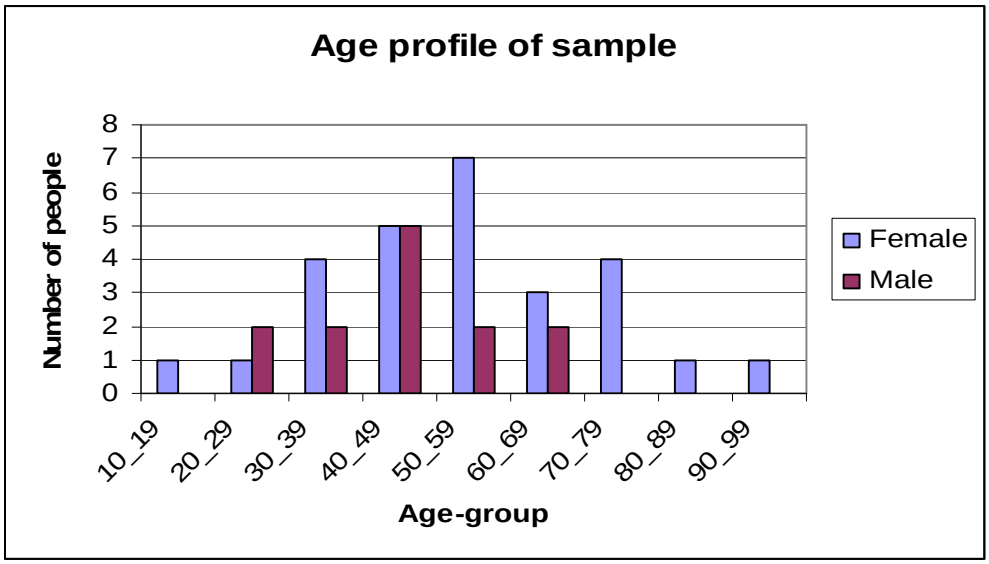

Figure 5.1 Age of this cohort of pemphigus vulgaris patients

Table 5.1 Some of the larger studies in the literature that reported patients with oral pemphigus

First author/Year	Country	No of Pts	Female	Male	F:M ratio	Age (range)	Prevalence	Incidence	Oral mucosal involvement		Mortality rate
									Initial	Total	
Kumar/2008	India	13	9	4	2.3	? (25-82)	-	4.4 per million	-	-	-
Budimir/2008	Croatia	15	10	5	2:1	? (20-95)	-	-	40%	87%	-
Ishii/2008a	Japan	55	37	18	2.1	55.3 (15-83)	-	5 new cases/year	21	28	-
Benchikhi/2008	Morocco	262	171	91	1.9	47 (18–90)	-	-	69/111 (62%)	-	6.4%
Mimouni/2008	Israel	155	?	?	1.5:1	-	-	-	88	-	-
Michailidou/ 2007	Greece	129	88	41	2.25:1	? (30-83)	-	0.8 per 100,000	99.3%	-	2.3
Heymann/2007	Iseael	363	192	171	1.1:1	49.8 (?)	-	5.3 per 100,000	-	-	-
Iamaroon/2006	Thailand	18	12	6	2:1	37.7 (18-55)	-	-	100%	-	-
Salmanpour/ 2006	Iran	221	126	95	1.33:1	38 (12-93)	-	0.67 per 100,000	59.3%	-	-
Chams-Davatchi/2005	Iran	1209	717	492	1.5	42 (4-82)	-	110	750 (62%)	978	6.2%
Mahajan/2005	India	54	29	25	1.16:1	?(10-95)	-	-	6.81%	63.6%	0
Uzun/2006	Turkey	148	85	63	1.3	43 (11–85)	1.46 per 100,000	0.24 per 100,000	104	116	4.8
Ljubojevic/ 2002	Croatia	203	126	77	1.6:1	53 (19-89)	-	-	31%	-	-

Table 5.2 Different pemphigus types in some published studies and the results of immunofluorescent studies

First author/Year	Total No of pt	No of patients with								DIF	IIF
		PV	PF	P veg.	P ery.	PNP	Drug-induced	P herp.	PIgA		
Budimir/2008	15	15	0	0	0	0	0	0	0	-	-
Kumar/2008	13	10	2	0	1	0	0	0	0	8	-
Ishii/2008a/b	55	28	15	2	3	4	0	3	0	55	51 (93%)
Benchikhi/2008	262	111	15	20	116	0	0	0	0	-	-
Mimouni/2008	155	145	9	0	0	1	0	0	0	-	-
Michailidou/2007	129	129	0	0	0	0	0	0	0	-	-
Salmanpour/2006	221	194	20	7	0	0	0	0	0	-	-
Chams-Davatchi/2005	1209	1111	89	33	0	0	2	0	4	93%	78%
Mahajan/2005	54	44	8	1	1	0	0	0	0	-	-
Uzun/2006	148	123	13	1	6	1	0	0	0	-	-
Ljubojevic/2002	203	154	30	5	13	0	0	0	1	89%	77%

PV= pemphigus vulgaris, PF= pemphigus foliaceous, P veg.= pemphigus vegetans, P ery.= pemphigus erythmatosus; P herp.=pemphigus herpetiformis, PNP= paraneoplastic pemphigus, P IgA= IgA pemphigus

Table 5.3 Ethnicity of pemphigus vulgaris patients

Ethnic group	Frequency	%
White British	14	35
Asian-Indian	11	27.5
Other White	7	17.5
Asian-Pakistani	1	2.5
Asian-other Asian	1	2.5
Chinese	1	2.5
Black-Caribbean	1	2.5
Black-African	1	2.5
Other ethnic group	3	7.5
Total	40	100

Table 5.4 Referral pattern of pemphigus vulgaris patients

Source of referral	No.	%
General dental practitioners	11	27.5
Oral maxillofacial/oral surgeons	11	27.5
General medical practitioners	5	12.5
Dermatologist	6	15.0
Hospital	1	2.5
Periodontist	1	2.5
Ear, Nose and Throat specialist	2	5.0
Missing data	3	7.5
Total	40	100

Table 5.5 Past medical history of patients with pemphigus vulgaris

Disorder		No.	%
Allergic	Penicillin allergy	4	10.0
	Other allergies	4	10.0
Cardiovascular	Hypertension	4	10.0
	Ischemic heart disease	1	2.5
	Cardiac arrhythmia	1	2.5
Respiratory	Asthma	2	5.0
	Hay fever	1	2.5
	Recurrent pneumonia	1	2.5
Haematological	Sickle cell disease	1	2.5
Endocrine	Diabetes mellitus	5	12.5
	Thyroid disorders	2	5.0
Gastrointestinal	Gastroesophageal reflux disease	2	5.0
	Hernia	3	7.5
	Crohn's disease	1	2.5
	Irritable bowel syndrome	2	5.0
	Constipation	3	7.5
	Gastritis	1	2.5
	Diverticulitis	2	5.0
	Jaundice (transient)	1	2.5
Visual		6	15.0
Hearing		1	2.5
Central nervous system	Epilepsy	1	2.5
	Viral meningitis	1	2.5
	Psychiatric illness	2	5.0
Others	Migratory arthralgia	1	2.5
	Arthritis	1	2.5
	Osteoarthritis	4	10.0
	Psoriatic arthritis	1	2.5
	Rheumatoid arthritis	1	2.5
	Raynaud's disease	1	2.5
	Osteoporosis	1	2.5
	Ill-defined dermatitis	1	2.5
	Finger dislocation	1	2.5
	Vertigo	1	2.5
	Malaria as child	1	2.5
	Ill-defined back pain	1	2.5
	Ankylosing Spondylitis	1	2.5
	Cutaneous lichen planus	1	2.5
	Human Immunodeficiency Virus Infection	1	2.5

Table 5.6 Past drug history of patients with pemphigus vulgaris

Drug group	Drug name	No of patients
Cardiovascular	Calcium-channel blockers	
	Amlodipine	1
	Nifedipine	1
	Beta-adrenoceptor blocking drugs	
	Bisoprolol Fumarate	1
	Co-tenidone	1
	Timolol Maleate	1
	Diuretics	
	Bendroflumethiazide	1
	Frusmide	1
	Angiotensin-converting enzyme inhibitors	
	Losartan potassium	1
	Ramipril	1
	Perindoprid	1
	Others	
	Doxazosin (alpha-adrenoceptor blocking)	1
	Warfarin sodium (anticoagulants)	1
	Digoxin (cardiac glycosides)	1
Respiratory	Beclomethasone dipropionate (corticosteroids)	1
	Salbutamol (selective beta 2 agonists)	2
Endocrine	Thyroid hormones	
	Thyroxin	1
	Antidiabetic	
	Insulin	1
	Metformin	1
	Tolbutamid	1
	Vitamin D	
	Calceos chewable	1
	Adcal-D3	1
	Calcichew	4
	Others	
	Contraceptive pills	1
Gastrointestinal	Rantidine (H2-receptor antagonists)	2
	Sulfasalazine (aminosalicylates)	1
	Lansoprazole (proton pump inhibitors)	1
	Omeprazole (proton pump inhibitors)	2
Antibacterial	Amoxicillin	1
	Clarithromycin	1
corticosteroids	Topical	
	Betamethasone	5
	Clobetasol propionate	1
	Fluticansone propionate (flixonase spray)	2
	Rimexolone eye drops	1
	Systemic	
	Prednisolone	17

Table 5.6 (Cont.) Past drug history of patients with pemphigus vulgaris

Drug group	Drug name	No of patients
Immunosuppressants and immunomodulator agents	Mycophenolate mofetil (antiproliferative)	5
	Azathioprine (antiproliferative)	4
	Mrthotrexate (antimetabolites)	3
	Topical tacrolimus (calcineurin inhibitors)	2
	Sirolimus	2
	Ciclosporin (calcineurin inhibitors)	1
Nutrition and blood	Vitamin B-12	2
	Folic Acid	2
	Cyanocobalamin	1
	Ferrous Sulphate	1
	Hydroxocobalamin	1
	Potassium chloride	1
	Iron supplements	1
Agents used for the treatment of glaucoma	Timoptol maleate (beta-blockers)	1
	Travatan (prostaglandin analogues)	1
Bone metabolism	Alendronic acid	4
	Risedronate sodium	1
Others	Acetaminophen (paracetamol)	2
	Chlorhexidine gluconate mouthwashe	2
	Metoclopramide hydrochloride (drugs used in nausea and vertigo)	1

Table 5.7 Different agents prescribed to patients to control their PV lesions before attending oral medicine clinics

Drug group	Drug name	No of patients
Corticosteroids	Topical	
	Triamcinolone acetonide (Adcortyl in Orabas	7
	Beclomethasone (Bectoid)	1
	Betamethasone sodium phosphate (Betnesol)	6
	Budesonide	1
	Clobetasol propionate (Dermovate)	1
	Fluticasone propionate (Flixonase spray)	2
	Hydrocortisone sodium succinate (Corlan pellets)	5
	Other topical corticosteroids	3
	Systemic and intravenous	
	Prednisolone	17
	Intravenous corticosteroids	1
	Anti-viral	
Anti-infective agents	Aciclovir	1
	Antibiotics	
	Amoxicillin	1
	Co-amoxiclave	1
	Doxycycline	1
	Flucloxacillin	1
	Metronidazole	3
	Tetracycline	1
	Others (not specified)	7
	Anti-fungal	
	Miconazole	2
	Nystatin	4
	Others (not specified)	1
Calcinurin inhibitors	Ciclosporin (mouthwash)	2
	Ciclosporin (systemic)	1
	Topical tacrolimus (protopic)	1
Others	Azathioprine	4
	Methotrexate	4
	Mycophenolate mofetil	4
	Dapsone	2
	Thalidomide	1
	Sirolimus	1
	Intravenous immunoglobulin	1
	Gold	1
	Aspirin	1
	Bonjela®	1
	Carbenoxolone	1
	Chlorhexidine gluconate	4
	Benzydamine hydrochloride (Difflam)	4

Table 5.8 Clinical signs of patients with oral pemphigus vulgaris at initial and final clinical appointment

Signs	First visit	Last visit
Buccal mucosa		
ulceration	20	7
erosion	6	2
bullae	3	0
Lip		
ulceration	4	1
erosion	2	0
bullae	0	0
Labial mucosa		
ulceration	5	2
erosion	3	1
blister	1	0
Lingual		
ulceration	15	9
erosion	8	2
bullae	0	0
Desquamative gingivitis	13	7
Alveolar ridge/ gingival		
ulceration	5	1
erosion	1	1
blister	0	0
Soft palate		
ulceration	11	3
erosion	7	1
bullae	2	1
Hard palate		
ulceration	5	1
erosion	2	0
bullae	1	0
Floor of mouth		
ulceration	6	1
erosion	4	1
bullae	0	0

Table 5.9 Topical agents employed to limit the signs of pemphigus vulgaris of the mouth

Topical agent	No	%
Betamethasone mouthwash	30	75.0
Fluticasone propionate,50 mcg spray	18	45.0
Fluticasone propionate,400 mcg in 15 ml water as mouthwash	15	37.5
Triamcinolone acetonide in Orabase	10	25.0
Fluticasone propionate 0.05% cream- Cutivate	9	22.5
Clobetasol propionate 0.05% cream - Dermovate	8	20.0
Fluticasone propionate inhaler	8	20.0
Prednisol mouthwash	4	10.0
Beclomethasone dipropionate inhaler	1	2.5
Hydrocortisone pellets	1	2.5
Fluocinolone acetonide 0.025% cream	2	5.0
Tacrolimus 0.1% ointment	7	17.5
Tetracycline mouthwash	1	2.5

Table 5.10 Different systemic agents employed in the management of 40 patients with pemphigus vulgaris

Systemic agent	No	%
Prednisolone	28	70.0
Deflazacort	18	45.0
Intravenous methylprednisolone	4	10.0
Azathioprine	24	60.0
Mycophenolate mofetil	18	45.0
Dapsone	5	12.5
Tacrolimus	3	7.5
Sulfamethoxypyridazine	1	2.5
Cyclophosphamide	4	10.0
Methotrexate	4	10.0
Thalidomide	1	2.5
Intravenous immunoglobulin (IVIG)	5	12.5
Colchicine	2	5.0
Ciclosporin	3	7.5
Sirolimus	3	7.5
Rutiximab	2	5.0
Infliximab	1	2.5

Table 5.11 Total number of topical and systemic agents employed in the management of 40 patients with pemphigus vulgaris

No of agents	Topical	Systemic	Total
0	1	3	0
1	11	4	2
2	8	11	4
3	8	6	4
4	6	7	3
5	3	3	9
6	1	2	3
7	0	3	3
8	1	0	4
9	0	0	3
10	1	1	1
11	0	0	0
12	0	0	1
13	0	0	0
14	0	0	1
15	0	0	1
16	0	0	1
Total number of patients	40	40	40

Table 5.12 Status of gingival and mucosal surfaces before and after therapy

Before therapy	After therapy
19 patients had mucosal lesions only	6 patients (31.6%): persistence of lesions 10 patients (52.6%): no lesions 1 patient (5.2%): no mucosal lesions but developed gingival lesions 2 patients (10.5%)had combined lesions (mucosal and gingivae)
15 patients had combined lesions (mucosal and gingivae)	3 patients (20.0%): buccal mucosa lesions only 7 patients (46.7%): no lesions 5 patients (33.3%): combined lesions (mucosal and gingivae)
3 patients had gingival lesions only	1 patient (33.3%): patient had combined lesions (mucosal and gingivae) 1 patient (33.3%): no lesions 1 patient (33.3%): no gingival lesions but developed mucosal involvement
3 patients did not have any lesions	3 patients did not have any lesions

Table 5.13 Clinically detected and patient-reported drugs reactions

Drugs involved	Adverse Drug Reaction	No of Pts
Systemic agents		
Prednisolone	Dyspepsia	1
	Osteoporosis	1
	Adrenal suppression	1
	Diabetes	2
	Cushingoid appearance	3
	Cataract	1
Deflazacort	Irritability and morning waking	1
	Diabetes	1
	Osteoporosis	1
Mycophenolate mofetil	Nausea	1
	Diarrhoea	1
	Abdominal discomfort	2
	Skin rash	1
Azathioprine	Nausea	4
	Vomiting	2
	Diarrhoea	1
	Headache	1
	Rash	1
Dapsone	Lethargy/unwell	1
Sulfamethoxypyridadin	Skin rash	1
Methotrexate	Nausea	1
Rituximab	Sever malaise and fatigue	1
Ciclosporin	Gingival hyperplasia	1
Topical agents		
Topical corticosteroids	Candidal infection	5
	Blurred vision	1
Topical tacrolimus	Burning sensation	1
	Peppery taste	1

Table 5.14 Duration of treatment of pemphigus patients

Duration (Years)	Number of patients
< 3	19
3 - < 6	10
6 - < 9	5
> 9	6
Total	40

CHAPTER 6
GENERAL DISCUSSION

General discussion

Painful oral mucosal disease can adversely affect the ability to speak, eat and swallow, and ultimately can lessen quality of life (Hegarty et al., 2002; Rozycki et al., 2002). Additionally disorders that also affect the profile of the lips or face (e.g. orofacial granulomatosis) have the potential to cause patient embarrassment and upset, particularly if they arise in children or young adults. In the last two decades there have been significant advances in relation to oral medicine. The clinical skills of specialists in oral medicine have potentially widened as a consequence of the introduction of medical training (at least in the UK), the establishment of international societies (e.g. the European Association for Oral Medicine), and workshops (e.g. the World Workshop in Oral Medicine), the establishment of new specialised journals (e.g. Oral Disease and Oral Oncology) and the availability of therapies may collectively have enhanced the ability to improve the patients care. Against this background there remain few detailed studies of the effectiveness and safety of contemporary oral medicine practice for the management of common oral mucosal disorders or at least disorders that are commonly seen in oral medicine clinics in the developed world.

The present series of studies has sought to retrospectively determine if the clinical care of large groups of patients with well defined oral mucosal diseases is effective and safe. The study included groups of patients with oral lichen planus, mucous membrane pemphigoid, pemphigus vulgaris and orofacial granulomatosis as these are amongst the major immunologically-mediated disorders that affect the mouth. Potentially malignant and malignant diseases were not included as their management (generally) does not involve solely non-surgical therapies and indeed certainly with respect to epithelial dysplasia there is a paucity of data on the most effective means of managing these disorders (Lodi and Porter, 2008).

Immune-mediated disorders (IMDs) are usually characterized by persistent or recurrent oral mucosal ulceration/erosions. Oral lesions may precede, follow or occur simultaneously with other mucocutaneous involvement. In most of the disorders discussed in the present study, patients had oral mucosal involvement before other mucocutaneous sites; however, this may represent referral bias as patients with other mucocutaneous involvement were most probably referred to other specialist units such as dermatology, ophthalmology or gynaecology.

In addition to oral mucosal lesions, many IMDs can give rise to lesions of other areas such as the conjunctival and genital mucosa and skin. A careful examination of the patient's medical history with specific questioning about potential affected sites is important, as many patients may have undiagnosed involvement in other sites. Many studies reporting on dental and oral cohorts do not include proper extra-oral examination and this means they are most likely underreported (Bidarra et al., 2008). In the present cohort, many patients referred by oral medicine specialists to other medical specialists were found eventually to have extra-oral involvement suggesting that reports in the oral/dental literature may underreport non-oral involvement of IMDs.

Prevalence

The prevalence of IMDs that affect the oral mucosa is largely unknown. However the true prevalence has been suggested to be higher than that suggested previously in published papers as some patients may be asymptomatic (e.g. reticular oral lichen planus). There are few well structured published papers detailing the prevalence of these disorders, however (as noted above) they may be complicated by the referral bias as they are conducted on selected groups of patients. There is little population-based research to determine the true prevalence of these disorders, and usually there are methodological problems to such studies. At present it would seem that orofacial granulomatosis (OFG), mucous membrane pemphigoid and pemphigus vulgaris are not as common as oral lichen planus or recurrent

aphthous stomatitis, but it is evident that specialists in oral medicine are treating more patients with these diseases (e.g. OFG). This may reflect a true increase in the prevalence of these disorders, an increasing recognition of them by primary care provider or a reflection of improved referral systems between different specialised units. The establishment of a national and international register for these rare disorders would help researchers and practitioners to better understand the clinical features and prevalence of these diseases, resulting in earlier diagnoses and initiation of appropriate treatment (although there are some in some countries (e.g. Italian Group for Epidemiologic Research in Dermatology)).

The present study explored aspects of the clinical presentation and behaviour of 4 disorders:

Oral lichen planus (OLP)

Lichen planus is the most common mucocutaneous disorder that can affect the oral mucosa and OLP is one of the most common chronic immunologically-mediated oral mucosal diseases (Mignogna et al., 2005). It represents one of the most challenging disorders that oral medicine physicians have to manage on a regular basis (Mignogna et al., 1998; Mignogna et al., 2005; Gonzalez-Moles et al., 2003). The results of the present study indicate that symptomatic OLP remains difficult to manage. Tacrolimus is not superior to topical corticosteroids, and malignant transformation is rare with topical corticosteroids and/or tacrolimus.

Orofacial granulomatosis (OFG)

The present study has confirmed that onset of OFG is characterised by facial swelling in only half of the patients whilst in the other half early disease gives rise to intra-oral or neurological manifestations only. Mucosal cobblestoning, gingival enlargement and other intra-oral mucosal changes are more common than oral ulceration. The long-term behaviour of OFG is characterised by

development of further clinical manifestations with most patients developing orofacial swelling and/or intra-oral ulceration. The response of OFG to therapy is typically remitting but some improvement of tissue swelling and oral ulceration can be achieved in most of patients. Complete remission of facial swelling is possible in about half of patients within 36 months of therapy but may be achieved quicker when intra-lesional corticosteroids are used. Intra-oral ulceration is usually less responsive. Significant adverse side effects are rarely observed and spontaneous remission may occur in only a few patients.

Mucous membrane pemphigoid (MMP)

The results of this study indicate that MMP affecting the oral tissues typically manifests as recurrent oral mucosal ulceration and/or desquamative gingivitis. The disease is chronic with symptoms and clinical signs waxing and waning hence necessitating various different treatment strategies and long-term follow up to prevent complications.

Pemphigus vulgaris (PV)

The present data confirm previous studies that PV is a chronic disease of middle age most frequently affecting women. Most of the patients present initially with oral mucosal lesions. Management is challenging and necessitates topical and systemic therapy which may be associated with adverse side effects.

It is evident that treatment of such disease is likely to be long-term and does not lead to complete resolution of any of the investigated disorders. Additionally while major adverse side effects are not common, probably as a consequence of the predominant use of topical corticosteroids, such effects are possible with systemic agents, notably azathioprine. The need for such long-term therapy together with the requirement to change therapies frequently suggest that there needs to be a drive to develop more effective therapies and/or adopt new generation agents such as the anti-TNF-α agents or other newly recombinant

biologically-active agents for the potential treatment of IMDs that affect the oral mucosa. However although there have been small numbers of reports of the use of such agents for the treatment of such disease (Hegarty et al., 2003; Cardoso et al., 2006; Heffernan and Bentley, 2006) there remain no published well-designed RCTs for such clinical application. In addition the new biologically active agents are costly, necessitate detailed clinical monitoring and carry a risk of significant adverse side effects (e.g. risk of reactivation of tuberculosis with anti-TNF-α agents). Another potential therapeutic avenue would be to develop systems that permit delivery of conventional (e.g. corticosteroids) or new (anti-TNF-α) agents to the site of immunological attack (perhaps particularly for oral lichen planus and orofacial granulomatosis).

At present there are no studies that definitively demonstrate that adhesive agents such as carmellose (Orabase®) truly improve the clinical effectiveness of any corticosteroids used for oral mucosal disease. In the light of the advances in biomaterials and nanoparticles it would be hoped that formulations be developed that permit controlled release of immunologically active agents at the site of oral mucosal disease.

Most of the studies on therapeutic agents used to manage IMDs of the oral mucosa have comprised small patient groups; as a result, the management of such diseases is largely based on clinical experience not controlled research. There is a need for more detailed, well-designed studies to provide high quality evidence on the efficacy of different treatment plans and different therapeutic agents. One problem with implementing such research is the limited number of patients that attend individual clinical units, as well as the high cost of developing appropriate protocols and trial designs. Nevertheless well-planned multicentre randomised, double-masked, placebo-controlled clinical trials are now warranted to evaluate the effect of different agents and therapeutic protocols used in the management of different IMDs of the oral mucosa.

The extent of the oral mucosal ulceration/erosions (measured in mm) and pain levels have been the main outcome measures in most published papers (Nolan et al., 2009; Mousavi et al., 2009). Measuring disease activity and response to treatment is one of the most challenging issues in patient management. However, there is no widely used reproducible and objective scoring system for recording symptoms or signs of oral mucosal diseases (Piboonniyom et al., 2005) which can assist practitioners in determining effective patient management. The importance of developing a reliable scoring measure for clinical trials of oral mucosal disorders was highlighted in a Cochrane review (Chan et al., 2000).

It is not difficult to assess the outcome of recurrent aphthous stomatitis in terms of duration of ulcers, length of interval between episodes and ulcer size. However, it is more difficult to determine the outcome and estimate the response to therapy of PV, MMP, OLP and OFG since, as noted above; there are no widely accepted reliable outcome measures that can capture the changes in clinical features. There have been some efforts to design tools to overcome this obstacle. Some of these were clinician-centred (Thongprasom et al., 1992; Piboonniyom et al., 2005) others were patient-centred (Slade and Spencer, 1994; McGrath and Bedi, 2001) and some combined both approaches (Escudier et al. 2007). However, those scoring systems are used mainly in prospective studies, not in routine patient examinations as clinicians may find it difficult and time consuming. Hence, there is a need to develop simple and reliable scoring measure that can be employed in daily clinical practice to record signs and symptoms of different oral mucosal diseases.

There is an urgent need to establish the effects of oral mucosal diseases upon the quality of life (QoL) of affected individuals. A number of tools such as the oral health impact profile (OHIP) (Slade and Spencer, 1994) and the oral health related quality of life (OHQoL-UK) (McGrath and Bedi, 2001) are available. However these QoL measures have been used mainly in clinical trials and it will

take considerable time before they are implemented as part of routine patient management. A simple scoring system, such as well-known visual analogue scale (VAS), is a valuable aid to assessing pain if it is recorded at every clinical examination but it does not provide an indication of how much the patient oral and systemic health is being affected by the oral disease.

The development and implementation of a universally accepted, simple, objective, reproducible and reliable scoring system that incorporates aspects of quality of life is essential to enable clinicians and researchers to compare the results of different studies, assess the efficacy of different therapeutic agents, and measure disease activity. In addition this may help to establish guidelines for follow-up intervals.

Patient education is crucial in the management of IMDs of the oral mucosa as most of the relevant disorders are chronic, requiring long periods of treatment and follow-up. Sources include the attending clinician, support groups, internet sites and brochures. Detailed information on clinical presentation, diagnosis, treatment options and prognosis should be provided as well as information on the presumed increased risk of cancer either from the disease (e.g. OLP) or treatment (e.g. topical tacrolimus and immunosuppressants) and more general advice on tobacco smoking cessation, alcohol consumption, maintaining a healthy diet, and regular review by a general dental practitioner. The chronic nature of IMDs that entitles long-term treatment with a number of different topical and systemic agents should be emphasized, including the potential adverse side effects. For example, patients on long-term systemic corticosteroids should be informed of the small risk of adrenal cortex hypofunction and the importance of informing always their physicians and dentists about their medication.

Limitations of the present study

The main limitation of the present study is its retrospective design and the associated methodological inadequacies. Hence, the results must be interpreted with caution. Although retrospective studies are less expensive and time consuming than prospective studies and can cover extended periods and often used to report rare diseases they might be limited by bias, lack of agreement on exclusion and inclusion criteria, incomplete data, differences in reporting clinical features and outcomes, variations in diagnostic and monitoring procedures and definition of some terms (e.g. remission, flare up and therapeutic response).

One of the problems in conducting the present study was the diagnostic criteria. A definitive diagnosis is important in determining patient eligibility for enrolment in a specific study. However, definitive diagnosis can be difficult for patients as they may present with some, but not all, of the defined criteria. For example, some authors (Williams et al., 1991) considered oral Crohn's disease, as a component of OFG while others do not (Gibson, 2000; Sanderson et al., 2005).

Missing data are one of the main limitations with reported trials including the present study. Important information such as treatment dosage, social and/or drug histories and adverse side effects were not found in all the examined patients' notes in the present study. This may be due to recall bias or incomplete record keeping by the attending clinical team.

A standardized method of reporting signs and symptoms during routine clinical reviews is important to obtain maximum benefit of a patient's observations, as these are a useful source of information when evaluating long-term outcomes and the efficacy of different therapies. Clinicians should include clear and complete information on dosage, form and preparation, and duration of the therapeutic agents provided at every treatment stage in each patient chart. Patient records should also contain all clinical, histopathological, serological, and haematological test results. A clear clinical charting of the mucosal lesions

utilizing one of the available previously published, even invalidated systems, should be included. The present study demonstrates the need to establish a simple, widely accepted standardized scoring system to record the oral lesions of IMDs which will improve patient's evaluation and to determine the efficacy of the therapy.

As with other aspects of patient management, there are no guidelines on which diagnostic test or how regular the monitoring investigation should be undertaken and these decisions are currently made by the attending clinician. In addition, laboratory test results, as evident in the present study, vary considerably in terms of the range of normal values and how they are reported. This is not unexpected, as these tests are administered over long periods of time and may be processed by different laboratories. This situation makes it difficult to compare and interpret data, even within the same patient cohort. It is possible that all test results could be recorded using computer software which could automatically be updated as new data is directly uploaded to the patient's electronic record and presented as an updated graphic.

Homogeneity of reported data is important for analyses of information from different studies. Various methods of reporting signs and symptoms and different follow-up intervals make it difficult to compare studies, even those describing the same disease or therapeutic agents. As noted above, there is a need to uniformly define terms such as relapse, flare-up, disease extent, disease activity and resolution and therapeutic response. Recently a consensus on pemphigus terminology has been published (Murrell et al., 2008) which could perhaps be generalized and used in other similar disorders.

Conclusions

There are many challenges in the management of IMDs of the oral mucosa. Most of these disorders affect patients in middle to late life and may be complicated by existence of other diseases which may increase the burden of overall disease, influence quality of life and increase the risk of drug interactions. However therapeutic outcomes have improved over the past few decades due to pharmaceutical advances expanding the armamentarium available to clinicians. Nonetheless, as this thesis illustrates, there are still several areas of controversy regarding the diagnosis and management of IMDs. The results of this present study indicate that the treatment of IMDs of the oral mucosa is challenging to patients and their attendant clinicians. While many patients do experience an improvement in their disease status, many do not. The impact of their oral disease upon their quality of life and activities of their daily living are not known. There is thus much to be done to improve the management of immunologically-mediated oral mucosal diseases.

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Orofacial granulomatosis

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Mucous membrane pemphigoid

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Appendices

APPENDIX 1

Demographic/general data

UCL Eastman Dental Institute
Oral Medicine

Outcomes of therapy of immunologically-mediated diseases of the oral mucosa study

Contact No.
D.O.B
Gender: Male Female
Post Code:

Marital Status:
Single Married
Divorce Widow/Widower
Unknown

Occupation:

Ethnicity (2001 Census Class):

……

Chief Complaint

Date of first episode

……

Pt. referred from:
GDP GP
OMF Dermatologist
Other (specify):

Referral date:

Cause of referral:

Diagnosis (on referral):

Lesions detected by:
Patient GP GDP
Others (Specify):

Diagnosed by:

First visit to OM:
Last visit to OM:
Provisional diagnosis:
Final diagnosis:

Method of Diagnosis:
Blood Clinical
Histopath. (date):

……

Smoking: Yes No Past smoker

Start: Stop:

Duration of smoking Yrs

Type: Cig. Cigar Chew
Pipe

Cig/ Day:

Alcohol: Yes No Past user

Start Stop

Units/week:

Other Habits:

Pt discharge from OM:
Yes No

Reason for discharge:

APPENDIX 2

Clinical Features:

1. Oral lichen planus:

Extra-oral signs and symptoms:

Are there any lesions other than oral lesions? Yes No In Past

Site: Type: Duration:

Which involved first? Oral Skin (Others)

How long it takes to involve the second site:

Date		Yes	Note
Cervical lymphadenopathy	Right Anterior Triangle		
	Right Post Triangle		
	Left Anterior triangle		
	Left Post Triangle		
	Tender		
	Not specify		
Skin			
Nails			
Genitals			
Other			

Intra-oral signs and symptoms:

Type of OLP Reticular Papular Plaque-like
Erosive Bullous Ulcerative

Site		Yes	Note
General distribution	Right		
	Left		
	Bilateral		
Lips	Upper		
	Lower		
Labial mucosa	Upper labial mucosa		
	Lower labial mucosa		
Buccal mucosa	Right buccal mucosa		
	Left buccal mucosa		
Tongue	Dorsum		
	Lateral border		
	Ventral surface		
Gingival involvement (Desquamative gingivitis)	Labial/buccal		
	Lingual/palatel		
	Not specify		
Alveolar ridge			
Soft Palate			
Hard Palate			
Not specify			
Near restoration			

2. Orofacial granulomatosis

Visit		1	2	3	4	5	6	7	8
Date									
Cervical lymphadenopathy									
Oral ulcers									
Desquamative gingivitis									
White/lichenoid lesions									
Atrophy									
Erosion									
Pain	with stimuli								
	without stimuli								
Soreness/burning/ discomfort									

3. Mucous membrane pemphigoid/pemphigus vulgaris

Date																		
Cervical lymphadenopathy																		
U =Ulceration, E =Erosion/Ery., B = Blister			**U**	**E**	**B**	**U**	**E**	**B**	**U**	**E**	**B**	**U**	**E**	**B**	**U**	**E**	**B**
Oral Ulceration/Erosion/Blister	Buccal mucosa	Right															
		Left															
	Lips	Upper															
		Lower															
	Labial mucosa	Upper															
		Lower															
	Tongue	Dorsum															
		Lateral borders															
		Ventral															
	Desquamative gingivitis	Labial/buccal															
		Lingual/palatel															
		Not specify															
	Alveolar ridge/other gingival problems																
	Soft palate																
	Hard Palate																
	Floor of the mouth																
	Not specify																
Asymptomatic/Pain/Soreness/ Burning/ Discomfort/Same/Improved/worse																	
Others																	

P = Present **I = Improved** **W = Worse**
N = Not recorded **A = Absent**

APPENDIX 3

Past medical and social histories

Medical	Operations		
	Serious illnesses		
	Hospital admissions		
	Allergies eg: penicillin, aspirin, plaster, other		
	Corticosteroids: current or within 1 year		
CVS	Heart disease		
	Hypertension		
	Cardiac surgery		
	Endocaraditis		
	Rheumatic carditis		
	Other		
Resp.	Asthma		
	Bronchitis		
	TB		
	Other		
Haem.	Bleeding disorders		
	Sickle cell disease		
	Leukemia		
	Other		
Endo.	Diabetes		
	Thyroid		
	Other		
GIT	Hepatitis		
	Jaundice		
	Peptic ulcer		
	Celiac disease		
	Crohn's disease		
	Ulcerative colitis		
	Other		
CNS	Sight or hearing problems		
	Epilepsy		
	Strokes		
	Parkinson's		
	Psychiatric problems		
	Dementia		
	Spasticity		
	Learning disability		
	Other		
GU/ Immu.	Renal		
	Urinary		
	Sexually transmitted disease		
	HIV		
	Other		
Social	Family history		
Derm./other	Skin disease		
	Other conditions		

APPENDIX 4

Past drug history

Drugs at first visit	Date	Comments

Therapeutic agents prescribed by other health care professionals to control disease

Drug	Specialty	Effectiveness	Comment

Therapeutic agents prescribed for present cohort of patients

TOPICAL MEDICATIONS	1	Fluticasone Propio. (Cutivate)														
		Clobetasol (Dermovate)														
		Fluticasone propionate 400														
		Fluticasone propio. (flixonase) 50 mcg														
		Flixotide Nebules														
		Betamethasone														
		Beclomethasone Diprop. (Bectoide)														
		Adcortyl														
		Tri-adcortyl														
		Hydrocortisone														
		Intralesional triamcin. Aceto.														
		Prednsol MW														
	2	Tacrolimus 0.03%														
		Tacrolimus 0.1%														
	3	Pimecrolimus 1%														
		Ciclosporin														
	O															
Total Topical Med/Pt																

SYSTEMIC MEDICATIONS	4	Prednisolone														
		Deflazacort														
	5	Azathioprine														
		Mycophenolate mofetil														
	6	Dapsone														
		Sulphamethoxypyridazine														
	O															
Total Systemic Med/Pt																
Total Med/Pt																

1. Topical corticosteroids
2. Aminosalicylates
3. Calcineurin Inhibitors
4. Systemic corticosteroids
5. Antiproliferative immunosuppressants
6. Antileprotic drugs

O. Others

APPENDIX 5

Investigations

		Normal Range					
CBC	WBC	(3.0 - 10.0) 10^9/l					
	RBC	(3. 95-5.15) 10^12/l					
	HB	M (13.0-17.0) g/dl F (11.5-15.5) g/dl					
	PLAT.	(150 - 400) 10^9/l					
Lympho. Dif.		(20 – 45) %					
Lympho. Abs.		(1.5 - 4.0) x10^9/l					
RENAL & LIVER PPROFILE	Urea	(1.7 - 8.3) mmol/L					
	Creatinine	(66- 112) umol/L					
	Sodium	(135 -145) mmol					
	Potass.	(3.5 - 5.1) mmol/L					
	Tot. Bili	(0 - 20) umol/L					
	ALT	(10 - 35) IU/L					
	ALP	(35 - 104) IU/L					
	Albumin	(34 - 50) g/L					
	Globulin						
OTHERS	Glucose	(3.9 - 5.8) mmol/L					
	Tacrolimus	< 1.5					

		Normal Range					
CBC	WBC						
	RBC	( ) 10^12/l					
	HB						
	PLAT.						
Lympho. Dif.							
Lympho. Abs.							
RENAL & LIVER PPROFILE	Urea	( ) mmol/L					
	Creat.	( ) umol/L					
	Sodium	( ) mmol					
	Potass.	( ) mmol/L					
	Tot. Bili	( ) umol/L					
	ALT	( ) U/L					
	ALP	( ) U/L					
	Albumin	( ) g/L					
	Globulin						
OTHERS	Glucose	(3. 9- 6) mmol/L					
	Tacro.						

APPENDIX 6

Published papers and meeting presentation from this work

Published papers:

Al Johani K, Moles DR, Hodgson T, Porter SR, Fedele S. (2009) Onset and progression of clinical manifestations of orofacial granulomatosis. Oral Dis.; 15:214-9.

Al Johani KA, Hegarty AM, Porter SR, Fedele S. (2009) Calcineurin inhibitors in oral medicine. J Am Acad Dermatol.; 61:829-40.

Al Johani KA, Moles DR, Hodgson TA, Porter SR, Fedele S. (2010) Orofacial granulomatosis: clinical features and long-term outcome of therapy. J Am Acad Dermatol. 62:611-20.

Meeting presentation:

Clinical features and long-term behaviour of oral pemphigus vulgaris. Pan European Federation (PEF IADR) - London (2008).

Clinical features and long-term behaviour of orofacial granulomatosis. International Association for Dental Research- Toronto (2008).

Clinical features and long-term behaviour of oral mucous membrane pemphigoid. The British Society for oral medicine- Glasgow (2008).

Efficacy and safety of topical tacrolimus in the management of oral lichen planus. The British Society for oral medicine - London (2007).

The safety of treatment of orofacial granulomatosis and related disorders. 8th Biennial Meeting of the European Association of Oral Medicine- Croatia (2006).

Oral Diseases (2009) 15, 214–219. doi:10.1111/j.1601-0825.2009.01512.x

http://www.blackwellmunksgaard.com

ORIGINAL ARTICLE

Onset and progression of clinical manifestations of orofacial granulomatosis

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BACKGROUND: There remain few studies describing in detail the early occurrence and long-term progression of clinical manifestations of orofacial granulomatosis (OFG) in a substantial number of patients.
OBJECTIVES: The aim of this study was to determine the early and late clinical manifestations of a large case series of patients with OFG.
PATIENTS/METHODS: Clinically relevant data of 49 patients with OFG who attended an Oral Medicine unit in the UK were examined retrospectively. The analyzed parameters included occurrence and typology of initial manifestations at onset and with respect to long-term follow-up.
RESULTS: Five major patterns of disease onset were observed. Recurrent facial swelling with/without intra-oral manifestations was the single most common presentation at onset followed by intra-oral ulcers, and other intra-oral and neurological manifestations. The majority of patients later developed a spectrum of additional features.
CONCLUSIONS: OFG results in multiple manifestations at different time points. The disease onset is characterized by manifestations other than facial swelling in about half of affected individuals. However, patients can develop cosmetically unacceptable lip/facial swelling at a later stage. Nearly all affected individuals ultimately develop lip/facial swelling while about half of all patients develop oral ulceration.
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Keywords: orofacial granulomatosis; labial swelling; ulceration; granulomas; facial palsy

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Introduction

Orofacial granulomatosis (OFG) is a granulomatous disorder that typically affects the oro-facial region. It can cause recurrent or chronic persistent swelling of the orofacial tissues and oral mucosal ulceration together with a spectrum of other orofacial features (Leao *et al*, 2004) (Table 1). OFG is often characterized by the presence of granulomas in the sub-epithelial stroma (Hegarty *et al*, 2003).

The aetiopathogenesis of OFG is largely unknown. Current hypotheses have been recently reviewed in detail by Tilakaratne *et al* (2008). The clinical features of OFG are identical to oro-facial manifestations of Crohn's disease, although in contrast to the latter there is no consistent evidence of attendant inflammatory bowel disease. Similar to Crohn's disease, OFG shows several

Table 1 Clinical manifestations of orofacial granulomatosis

Intra-oral manifestations
Aphthous-like flat round-shaped ulceration
Linear ulceration (often with surrounding raised borders, affecting buccal and/or labial vestibules)
Cobblestoning
Gingival enlargement (granulomatous gingivitis)
Mucosal tags
Tongue fissuring
Tongue swelling
Extra-oral manifestations
Lip swelling
Periorbital swelling
Swelling of zygomatic and mental areas
Eyelid swelling
Median and angular cheilitis
Neurological manifestations
Lower motor neuron palsy of the facial nerve
Changes in taste, hearing, or earache
Palsy of glossopharyngeal nerve
Palsy of vagus nerve
Hyperidrosis
Glossodynia
Acroparesthesia
Lacrimation
Sweating
Migraine-like headache
Blepharospasm

similarities with other inflammatory and granulomatous disorders that can affect the head and neck area. Chronic oro-facial swelling, with or without ulceration and inflammation of intra-oral tissues can be found in sarcoidosis, some deep fungal infections, leprosy, tuberculosis, some acquired and hereditary forms of angioedema, foreign body and delayed-hypersensitivity reactions (Neville *et al*, 2002). OFG is believed to be aetiopathologically distinct from these disorders as their major distinctive clinical signs, symptoms and/or laboratory changes are typically lacking in OFG patients (Wiesenfeld *et al*, 1985). It is probable that OFG represents a spectrum of disease that ranges from localized granulomatous inflammation of the lips (granulomatous cheilitis, Miescher's cheilitis), through orofacial swelling with mucosal ulceration to disease with neurological deficit and lingual fissuring (Melkersson-Rosenthal Syndrome) (Mignogna *et al*, 2003; Sciubba and Said-Al-Naief, 2003; El Hakim and Chauvin, 2004; Kauzman *et al*, 2006).

Lip and in general oro-facial swelling is traditionally reported as the most frequent manifestation and common diagnostic feature of OFG (Alawi, 2005). Indeed it is the most common reason for which patients seek medical attention. However, some authors have suggested that the clinical features of OFG can be highly variable and dynamic, especially when early manifestations at disease onset are compared with long-term clinical features (Zimmer *et al*, 1992; Mignogna *et al*, 2003).

There remain however few reports of substantial numbers of patients attending a single centre to allow clear descriptions of the early and late clinical features. The aim of this study was to describe the clinical features of a large group of OFG patients attending a single clinical centre over a period of more than 20 years, and to focus on potential differences between manifestations at onset and during the course of the disease. This study did not include patients with Melkersson-Rosenthal syndrome, and patients with Crohn's disease and sarcoidosis (diagnosed either before or after the onset of oro-facial manifestations) were excluded, hence the present patients represent the largest homogenous group of individuals with OFG reported in the past two decades.

Subjects and method

The study group comprised 49 individuals with OFG who attended the Oral Medicine Unit of UCL Eastman Dental Institute and UCLH Eastman Dental Hospital between 1985 and 2008. Diagnostic criteria included: (i) presence of clinical features belonging to the spectrum of OFG, (ii) histopathological evidence of non-caseating granulomas and (iii) exclusion of other granulomatous disease on the basis of clinical, histopathological and laboratory investigations (Mignogna *et al*, 2003; Leao *et al*, 2004). All patients met at least criteria (i) and (iii). Patients who developed intestinal inflammation of Crohn's disease after the onset of orofacial manifestations were re-categorized as having oral Crohn's disease and were thus excluded from the study.

Data regarding patients' demographics, past medical history, diagnostic features, treatment modalities, short- and long-term outcome, adverse side effects of therapy, and monitoring investigations were systematically extracted from the case file of each patient and are reported in detail elsewhere (K Al Johani, DR Moles, SR Porter, S Fedele, unpublished data). Disease onset was evaluated on the basis of patients' history, referral letter and/or first clinical examination at the Oral Medicine clinic. Long-term clinical manifestations occurring during the course of the disease were evaluated on the basis of clinicians' descriptions in the clinical notes and photographs taken during clinical reviews until January 2008. The impact of therapies on the behavior of clinical manifestations was not considered. The review of clinical notes and comparisons between early and late clinical features were performed independently by two authors (K.A. and S.F.).

Results

The group comprised 27 males (55.0%) and 22 females (45.0%). The mean age at the time of clinical diagnosis by Oral Medicine specialists was 32.4 years (range: 7.4–72.1 years). Considering that the mean reported duration of oral signs/symptoms before definitive diagnosis was 44 months (range: 4–192 months), the mean age of patients at disease onset was estimated to be 28.7 years. The observation period of this cohort of OFG patients varied from 1 to 15 years (mean 2.9, median 1.8).

Clinical features at disease onset

Analysis of data indicated that there were five major patterns of disease onset. These comprised: facial swelling only (group 1), facial swelling with other manifestations (group 2), oral ulceration only (group 3), other intra-oral manifestations without facial swelling (e.g. gingival hyperplasia) (group 4) and neurological manifestations only (e.g. facial palsy) (group 5) (see Table 2 and Figure 1). The most commonly reported abnormality at disease onset was recurrent oro-facial swelling, reported by 26 (53.1%) patients (groups 1 and 2). Twenty-five patients (51.0%) had swelling of one or both lips, and one patient (2.1%) reported bilateral malar swelling. Fifteen (group 1) of these 26 patients reported oro-facial swelling to be their only initial manifestation (upper and/or lower lip in 14 and malar area in one) while in the other 11 patients (group 2) the swelling of the lips co-existed with other extra- and/or intra-oral manifestations including angular cheilitis (one patient), perioral erythema (one), fissuring plus angular cheilitis plus mucosal cobblestoning and tags (one), swelling of the cheek (one), mucosal cobblestoning and gingival enlargement (one), intra-oral ulceration (four), gingival enlargement (one) and lip fissuring (one). Lymph node swelling was never found to be the only presenting manifestation of OFG.

Intra-oral ulcers as the only presenting sign were reported by 14 patients (28.6%) (group 3) consisting of

Table 2 Clinical features of the 49 patients with orofacial granulomatosis at disease onset and during long-term follow-up

Patients	*Manifestation at disease onset*	*Subsequent manifestations*
Group 1		
1	Upper/lower lip swelling	Intra-oral ulceration, cobblestoning, cervical lymphadenopathy.
2	Upper/lower lip swelling	Intra-oral ulceration and cobblestoning.
3	Right cheek swelling	Upper/lower lip swelling
4	Upper lip swelling	Lower lip swelling, cobblestoning and tags
5	Upper lip swelling	Intra-oral ulceration and cobblestoning
6	Upper lip swelling	None
7	Lower lip swelling	Intra-oral ulceration
8	Lower lip swelling	Upper lip swelling, intra-oral ulceration
9	Lower lip swelling	Perioral erythema
10	Lower lip swelling	Upper lip swelling
11	Lower lip swelling	Cervical lymph node swelling
12	Lower lip swelling	None
13	Lower lip swelling	None
14	Lower lip swelling	None
15	Lower lip swelling	None
Group 2		
16	Upper/lower lip swelling and perioral erythema	Intra-oral erythema, mucosal tags and cobblestoning., hypertrophy of palatal mucosa, cervical lymphadenopathy
17	Upper/lower lip swelling, cobblestoning and gingival hyperplasia	Upper/lower lip swelling
18	Upper lip swelling and intra-oral ulceration	Lower lip swelling, cobblestoning., cervical lymph node swelling
19	Upper/lower lip swelling and fissuring	Perioral erythema, cobblestoning.
20	Lower lip swelling and intra-oral ulceration	Gingival hyperplasia
21	Upper lip swelling and angular cheilitis	Lower lip swelling
22	Upper/lower lip swelling and fissuring, angular cheilitis, tags and cobblestoning	Gingival hyperplasia, perioral erythema
23	Upper lip swelling and gingival hyperplasia	Cheek swelling
24	Lower lip swelling and intra-oral ulceration	None
25	Lower lip swelling and intra-oral ulceration	None
26	Upper/lower lip and cheek swelling	None
Group 3		
27	Intra-oral ulceration	Upper/lower lip swelling
28	Intra-oral ulceration	Upper/lower lip and cheek swelling, cobblestoning
29	Intra-oral ulceration	Lower lip swelling
30	Intra-oral ulceration	Upper/lower lip swelling, angular cheilitis
31	Intra-oral ulceration	Lower lip swelling, cobblestoning, tags, cervical lymphadenopathy
32	Intra-oral ulceration	Cobblestoning
33	Intra-oral ulceration	Lower lip and cheek swelling, tags, and cobblestoning.
34	Intra-oral ulceration	Lower lip swelling, cervical lymph node swelling
35	Intra-oral ulceration	Upper/lower lip swelling, lip abscess and mucosal tags
36	Intra-oral ulceration	Lower lip swelling, perioral erythema, cobblestoning, tags, cervical lymph node swelling
37	Intra-oral ulceration	Upper lip swelling
38	Intra-oral ulceration	Lower lip swelling
39	Intra-oral ulceration	Lower lip and cheek swelling, cobblestoning
40	Intra-oral ulceration	Upper lip and cheek swelling, angular cheilitis, cobblestoning, cervical lymph node swelling
Group 4		
41	Tongue swelling	Gingival hyperplasia
42	Gingival hyperplasia	Upper/lower lip swelling and cobblestoning
43	Gingival hyperplasia	Upper lip swelling, cobblestoning
44	Gingival hyperplasia and cobblestoning	Lower lip swelling
45	Cervical lymph node swelling and gingival hyperplasia	Intra-oral erythema and mucosal tags
Group 5		
46	Facial palsy	Upper lip and cheeks swelling, perioral erythema
47	Facial palsy	Upper/lower lip swelling, cobblestoning
48	Chronic paroxysmal hemicrania	Upper/lower lip swelling
49	Facial palsy	Lower lip swelling, gingival hyperplasia, cobblestoning and tags

either superficial aphthous-like ulcers or linear, deep ulcers of the vestibular fold areas.

With regard to other intra-oral manifestations (group 4), gingival enlargement was the presenting sign of OFG in four patients (8.2%), one of whom also had cobblestoning while the other had cervical lymph node swelling. One patient (2.1%) reported swelling of the tongue as the probable initial feature of OFG. Mucosal tags and/

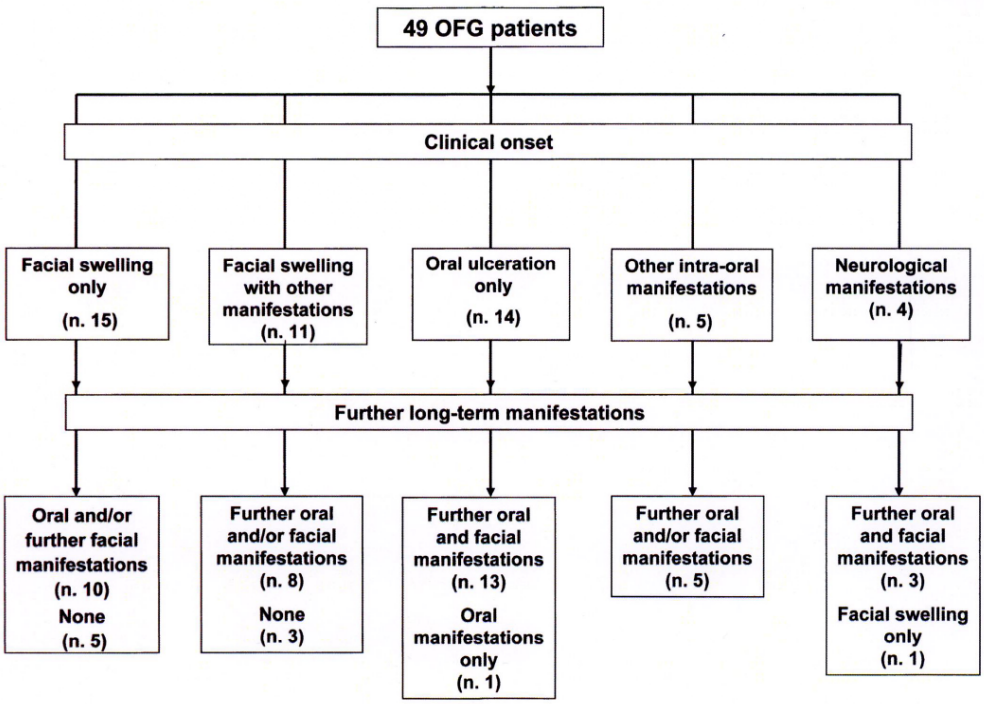

Figure 1 Patterns of disease onset and long-term manifestations in this cohort of 49 patients

or cobblestoning were never found to be the only presenting sign of OFG.

One or more episodes of facial nerve palsy, at disease onset, were reported by three patients (6.1%) and one (2.1%) patient had chronic paroxysmal hemicrania as presenting manifestation of OFG (group 5).

Long-term clinical features

The majority of patients (42/49; 85.7%) developed a variety of different additional features of OFG following its initial manifestation (Table 2 and Figure 1). Ten out of the 15 patients (66.7%) with OFG who initially presented with facial swelling only (group 1) developed other manifestations during the course of the disease including intra-oral ulceration only (one patient), intra-oral ulceration and cobblestoning (two), labial swelling (two), labial swelling and ulceration (one), labial swelling with cobblestoning and tags (one), perioral erythema (one), cervical lymph node swelling (one) and cervical lymphadenopathy with cobblestoning and mucosal ulceration (one).

Eight of the 11 patients (72.7%) who initially had facial swelling co-existing with other clinical features (group 2) developed further signs of OFG including labial and buccal swelling (three patients), labial swelling with cobblestoning and cervical lymphadenopathy (one), intra-oral erythema, tags and cobblestoning, hyperplasia of palatal mucosa and cervical lymph node swelling (one), perioral erythema plus gingival hyperplasia or cobblestoning (two) and gingival enlargement only (one).

Thirteen of the 14 (92.9%) patients who had only intra-oral ulceration at disease onset (group 3) eventually developed facial swelling only (four patients), or swelling associated with cobblestoning (three), angular cheilitis (one), lymph node swelling with or without tags (two), cobblestoning with tags (one), tags with perioral erythema and lymphadenopathy (one) or with angular cheilitis and lymphadenopathy, labial abscess and tags (one). In only one patient intra-oral ulceration was followed by cobblestoning without any labial/facial swelling.

Within group 4, the patient with tongue swelling at disease onset eventually developed gingival enlargement. The patients presenting with gingival enlargement at disease onset without facial swelling (4/49) developed intra-oral erythema and tags (one patient), or labial swelling (one) and labial swelling plus cobblestoning (two) (group 4).

All four patients with neurological manifestations only at disease onset (group 5) later developed labial swelling alone (one patient), labial swelling plus mucosal

cobblestoning (one), labial swelling with gingival hyperplasia, cobblestoning and tags (one) and labial and buccal swelling plus perioral erythema (one).

Twenty of the 23 (87%) patients who had intra-oral (groups 3 and 4) or neurological (group 5) manifestations only at disease onset (individuals presenting without facial swelling) had swelling of one or more facial areas during the following years of clinical monitoring. Similarly, among those patients who only had facial swelling at disease onset (15), the majority (10/15; 66.7%) eventually developed intra-oral manifestations.

In total, 47 of the 49 patients (95.9%) developed facial swelling along the course of their disease whilst mucosal ulceration occurred only in 24 (49%). The lips were affected in 46 of the 47 patients with facial swelling (98%). Labial enlargement affected both lips in 20 patients (43.4%), the lower lip only in 19 (41.3%) cases and the upper lip in 7 (15.2%) patients. Full-blown symptomatic OFG (intra-oral ulceration and facial swelling) occurred in 23 patients (46.9%) during the disease course.

Discussion

Orofacial granulomatosis is a chronic inflammatory disease with the potential to adversely affect the quality of life of patients by virtue of persistent labial and/or facial swelling, painful oral ulcerations and occasionally neurological manifestations (Somech *et al*, 2001). There are no detailed studies of the clinical onset and long-term behavior of this disorder. The present study attempted to clarify these issues by virtue of a retrospective analysis of a group of patients with OFG who were managed at a single centre for more than 20 years. The study represents the largest homogenous group of individuals diagnosed solely with OFG reported in the past two decades. As the majority of previous clinical studies of OFG-like diseases included patients with Crohn's disease and those with hypersensitivity reactions, their findings should be interpreted with caution as these disorders may present and behave differently from OFG (Patton *et al*, 1985; Wiesenfeld *et al*, 1985; James and Ferguson, 1986; Williams *et al*, 1991). Labial swelling is traditionally indicated as the most common clinical feature of OFG. It is also reported as being the most frequent manifestation at disease presentation (Alawi, 2005). However, few authors have reported that clinicians should not focus solely on labial swelling as patients with OFG can in fact present with multiple, temporary and multi-focal clinical features affecting intra-oral mucosa, gingivae, facial tissues and the craniofacial nervous system (Wiesenfeld *et al*, 1985; Mignogna *et al*, 2003). Moreover, different clinical manifestations have been reported to develop at different time points during the course of the disease (Zimmer *et al*, 1992; Mignogna *et al*, 2003). Mignogna *et al* (2003) reported that about half of their 19 OFG patients (9/19) had a disease onset characterized by the absence of labial swelling and occurrence of facial palsy, intra-oral manifestations and swelling of facial areas other than the lips. Seven of these nine patients eventually developed labial swelling. Zimmer *et al* (1992) reported that labial swelling was the initial disease manifestation in only 43% of their 42 patients but this percentage increased to 74% during the course of the disease. Moreover, the overall number of clinical manifestations increased during the years as the percentage of patients with facial swelling increased from 26% to 50% and those with facial palsy from 19% to 33% (Zimmer *et al*, 1992). In partial agreement with these findings, the present study identified five patterns of disease onset (Figure 1) with facial swelling (53.1%) and oral ulceration (28.6%) being the most common initial manifestations. Most patients (85.7%) developed further facial and/or intra-oral manifestations over the years. This confirms the concept that the clinical behavior of OFG is multiform, progressive and highly variable, and that perhaps each patient's disease has a unique pattern of duration and presentation (Mignogna *et al*, 2003). Neurological manifestations are reported to affect between 8.3% and 57.1% of OFG patients (Wiesenfeld *et al*, 1985; Armstrong *et al*, 1997; Mignogna *et al*, 2003; Kanerva *et al*, 2008) and were observed in four patients of our cohort (8.2%). They all occurred at the onset of disease and never as subsequent clinical manifestation, suggesting that patients who do not present neurological involvement at an early stage of their disease are unlikely to develop it afterwards. Details of treatment are not reported in the present study. Nevertheless, it is unlikely that treatment has had any influence on the pattern of occurrence of clinical manifestations as: (i) the patients were homogeneously managed by the same group of clinicians and (ii) subsequent clinical features developed both before and after the start of therapy.

Conclusion

Little is known about clinical onset and early manifestations of OFG. The few data available suggest that early OFG can cause clinical manifestations other than labial swelling that can include transient facial palsy, mucosal ulceration, swelling of other areas of the face, and gingival hyperplasia (Rozen, 2001; Mignogna *et al*, 2003). The results of this study indicate the onset of OFG can be characterized by labial swelling in only half of the patients while in the other half early disease can cause intra-oral or neurological manifestations only. The long-term behavior of OFG can be subsequently characterized by the development of further clinical manifestations. It can be expected that most patients (up to 95.9% in the present study) develop during the course of the disease orofacial swelling and, less frequently (49%), intra-oral ulceration. Clinicians should consider the variable, progressive and multiform nature of OFG when they attempt early diagnosis and long-term management.

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Author contributions

K Al Johani and DR Moles designed the study, analysed the data and prepared manuscript. T. Hodgson assisted in the collection of data. SR Porter performed the plan of study and manuscript preparation. S Fedele performed plan of study, data analysis and manuscript preparation.

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REVIEWS

Calcineurin inhibitors in oral medicine

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Topically applied calcineurin inhibitors have been suggested to be of some benefit in the treatment of immunologically mediated oral mucosal disorders, particularly oral lichen planus. This article reviews the current evidence of the efficacy and safety of topical calcineurin inhibitor agents in the management of different oral conditions. Current evidence suggests that topical tacrolimus and pimecrolimus may be of benefit (at least in the short term) in the treatment of immunologically mediated oral mucosal disease, especially oral lichen planus that has not responded to topical corticosteroids. Both tacrolimus and pimecrolimus are minimally absorbed through the oral mucosa and give rise to few clinically significant local or systemic adverse side effects. There is little evidence to indicate that topical cyclosporine is more effective than topical corticosteroids for the treatment of immunologically mediated oral mucosal disease. Currently, there is no objective evidence suggesting that topical tacrolimus or pimecrolimus increase the risk of oral malignancy associated with oral lichen planus. There is a need for well-designed randomized controlled trials to establish the precise efficacy of topical calcineurin inhibitors for the treatment of immunologically mediated oral mucosal disease. (J Am Acad Dermatol 2009;61:829-40.)

Key words: calcineurin inhibitors; cyclosporine; mucous membrane pemphigoid; oral cancer; oral lichen planus; orofacial granulomatosis; pemphigus vulgaris; pimecrolimus; tacrolimus.

Calcineurin inhibitors are microbially derived immunosuppressive that have been primarily used in transplant medicine and in the treatment of immune-mediated diseases. The principle agents are tacrolimus, pimecrolimus, and cyclosporine. Calcineurin inhibitors bind to different cytoplasmic proteins of T lymphocytes (cyclosporine to cyclophilin; tacrolimus and pimecrolimus to FK506-binding protein) to form complexes that in turn inhibit calcineurin leading to suppression of transcription and production of many cytokines. Calcineurin inhibitors have been suggested to be of clinical benefit in the management of some immunologically mediated oral mucosal disorders. However, there is much debate about their long-term efficacy and safety and their advantage with respect to conventional therapies. The current article reviews current knowledge regarding the management of oral mucosal diseases with this group of agents. The aim is to help clinicians to decide when to use calcineurin inhibitors, which agent is most appropriate, and how to balance risk and benefit.

Abbreviations used:

AD:	atopic dermatitis
FDA:	Food and Drug Administration
GvHD:	graft-versus-host disease
IL:	interleukin
MMP:	mucous membrane pemphigoid
OFG:	orofacial granulomatosis
OLP:	oral lichen planus
SCC:	squamous cell carcinoma

METHODS

MEDLINE (1966-December 2008), EMBASE (1980-December 2008), and the *Cochrane Database of Systematic Reviews* were searched using different combinations of the following key terms: "calcineurin inhibitors," "tacrolimus," "pimecrolimus," "cyclosporine," "ciclosporin," "oral medicine," "oral mucosal diseases," "oral lichen planus" (OLP), "graft-versus-host disease" (GvHD), "mucous membrane pemphigoid" (MMP), "pemphigus vulgaris," "paraneoplastic pemphigus," "orofacial granulomatosis" (OFG), and

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Conflicts of interest: None declared.

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"oral Crohn disease." The abstracts of the articles were retrieved to exclude irrelevant studies and the references hand searched for relevant articles that had not appeared in the main search. A few non-English-language abstracts were included so as to include all the relevant articles reporting adverse side effects of calcineurin inhibitors in the management of oral diseases. Moreover, US Food and Drug Administration (FDA) reports on potential carcinogenic effects of topical tacrolimus and pimecrolimus were included.

CAPSULE SUMMARY:

- Topical application of calcineurin inhibitors, in particular tacrolimus, may be of some clinical benefit with no major adverse effects in the management of immunologically mediated oral mucosal diseases.
- Topical tacrolimus and pimecrolimus can be as effective as topical corticosteroids, and can be used as a second-line therapy, in patients who do not respond to topical corticosteroids.
- There is little evidence to support the use of topical cyclosporine in the management of oral mucosal diseases.
- There is no objective evidence supporting an increased risk of oral malignancy in association with the use of topical tacrolimus or pimecrolimus.

Mechanism of action of the calcineurin inhibitors

In the normal immune response, antigens presented by the major histocompatibility complex to the T-cell receptor cause an elevation of intracytoplasmic calcium that binds to calmodulin, leading to the activation of calcineurin. The free calcium also leads to synthesis of the nuclear factor of activated T cells. Calcineurin (a protein phosphatase) dephosphorylates the cytoplasmic subunit of nuclear factor of activated T cells that eventually binds to the nuclear subunit.[1] This cytoplasmic–nuclear subunit of nuclear factor of activated T cells complex facilitates transcription of many cytokines including interleukin (IL)-2, IL-3, IL-4, tumor necrosis factor-α, interferon-γ, transforming growth factor-β, and granulocyte-macrophage colony-stimulatory factor. Calcineurin inhibitors interfere with this pathway by inhibiting cytosolic calcineurin function hence resulting in suppression of the generation of proinflammatory cytokines.[1-4] Tacrolimus (FK506) and pimecrolimus bind to intracellular FK506-binding protein whereas cyclosporine binds to cytosolic cyclophillin.[5] These intracellular complexes eventually bind to calcineurin, inhibiting its phosphatase activity. Tacrolimus also inhibits histamine release and the de novo synthesis of prostaglandin D2 from mast cells activated by IgE,[6] whereas pimecrolimus can inhibit mast cell cytokine, serotonin, and beta-hexosaminidase release.[2,4]

Tacrolimus

Tacrolimus is a macrolide immunosuppressant derived from *Streptomyces tsukubaensis*. It is a relatively selective inhibitor of calcineurin and was initially developed as a systemic agent to lessen allograft rejection. Formulated for topical application in the management of atopic dermatitis (AD), it was approved in 2000 by the US FDA to be used in moderate to severe AD for patients older than 2 years. Topical tacrolimus has proven to be of benefit in the treatment of other disorders including cutaneous psoriasis, contact allergy, corticosteroid-induced rosacea, pyoderma gangrenosum, alopecia areata, mucocutaneous lichen planus, and GvHD.[1,7-11] Topical tacrolimus is available in different concentrations (0.03%, 0.1%). Systemic tacrolimus is substantially less expensive and 10 to 100 times more potent than cyclosporine,[12,13] even though relative potency of topical preparations has never been evaluated.

With regard to the management of oral mucosal diseases, topical tacrolimus has been reported to be effective in the treatment of symptomatic OLP[13-22] and desquamative gingivitis.[23] Topical tacrolimus has also been reported to be effective in the management of oral mucosal lesions of GvHD,[24-26] MMP,[27-29] pemphigus vulgaris of the lip,[30] and the oral ulceration and labial enlargement of OFG and oral Crohn disease.[31,32]

Oral lichen planus. T-cell activation is central to the pathogenesis of lichen planus (OLP),[33] hence logically a blockage of calcineurin function might be expected to lessen the severity of such disease. There are now numerous reports of the efficacy of tacrolimus in the management of OLP. Effectiveness has been assessed via open-label prospective studies,[13,16,22] randomized trials,[34,35] retrospective studies,[19,36] case series,[17,18] and described in several case reports.[15,20,21] (Table I). Initial studies focused on patients with symptomatic OLP that had not responded to topical corticosteroids or who were at risk of adverse side effects from corticosteroids. Rozycki et al[18] reported retrospectively 13 patients with OLP who had received topical tacrolimus for a mean duration of 6.5 months. Eleven patients had either complete resolution or partial improvement of painful oral mucosal lesions within 4 weeks from the start of the treatment although two patients showed no response. Both 0.1% and 0.3% concentrations of tacrolimus were able to induce complete healing of

Table I. Studies reporting the use of topical tacrolimus in the management of oral lichen planus

Study	Study type	No of patients	Topical tacrolimus formula and regimen	Results (control of symptoms and/or healing of erosion/ulceration)
Corrocher et al,[35] 2008	Controlled, randomized, double-blind	16/32	0.1% Tacrolimus ointment 4 times daily for 4 wk	Tacrolimus more effective than clobetasol
Radfar et al,[34] 2008	Controlled, randomized double-blind	15/30	0.1% Tacrolimus ointment (No. of applications/d reduced from 4 to 1 over 6 wk)	No difference between tacrolimus and clobetasol; both effective
Tavassol et al,[103] 2008	Case series	11	0.1% Tacrolimus ointment twice daily	Effective in 10/11 patients
Erkek et al,[45] 2007	Case series	1	0.1% Tacrolimus ointment	Effective
Chaudhry et al,[37] 2007	Case report	1	0.1% Tacrolimus ointment twice daily	Effective
Rabanal et al,[104] 2007	Case report	1	0.1% Tacrolimus ointment twice daily	Effective
Becker et al,[95] 2006	Case report	1	Tacrolimus 0.1% ointment twice daily	Effective
Lozada-Nur and Sroussi,[22] 2006	Case series	10	0.1% Tacrolimus in Orabase (Colgate-Palmolive Co, New York, NY), 3 times daily for 14 d	Effective
Shichinohe,[21] 2006	Case report	2	0.1% Topical tacrolimus, twice daily	Effective
Laeijendecker et al,[38] 2006	Controlled, randomized	20 /40	0.1% Topical tacrolimus ointment, 4 times daily for 6 wk	Tacrolimus effective in 18/20 whereas triamcinolone in 9/20 patients
Riano Arguelles et al,[105] 2006	Case report	1	0.1% Tacrolimus once daily	Effective
Donovan et al,[86] 2005	Case report	1	0.1% Tacrolimus	Effective
Fricain et al,[39] 2005	Case report	1	1% Topical tacrolimus, twice daily for 8 wk	Effective
Byrd et al,[9] 2004	Retrospective	37	0.03% and/or 0.1% Tacrolimus	Effective
Shen and Pedvis-Leftick,[20] 2004	Case report	1	0.1% Tacrolimus ointment twice daily for 9 mo	Effective
Thomson et al,[36] 2004	Retrospective	23	0.1% Tacrolimus in Orabase (Orabase ConvaTec Limited, Middlesex, UK), once or twice daily	Effective in 21/23 patients
Hodgson et al,[19] 2003	Retrospective	50	0.1% Tacrolimus in paraffin ointment twice daily	Effective in 47/50 patients
Olivier et al,[16] 2002	Case series	8	Tacrolimus mouthwash (0.1 mg/100 mL of distilled water) 4 times daily for 6 mo	Effective in 7/8 patients
Kaliakatsou et al,[13] 2002	Case series	17	0.1% Tacrolimus in a paraffin ointment base	Effective
Morrison et al,[17] 2002	Case series	6	0.1% Tacrolimus ointment or in mineral oil 2-3 times daily for 3 mo	Effective
Lener et al,[15] 2001	Case report	1	0.1% Tacrolimus, twice daily for 3 mo	Effective
Vente et al,[14] 1999	Case series	4	0.1% Tacrolimus ointment, twice daily for 4 wk	Effective

OLP lesions and cause relief of painful symptoms whereas 0.03% formulation led to partial response only. Adverse side effects were uncommon and minimal, but recurrences were observed within 1 to 2 weeks of cessation of tacrolimus therapy.[18]

A retrospective analysis of 50 patients with OLP and erosive/ulcerative OLP recalcitrant to topical corticosteroids demonstrated the long-term (mean: 19.8 months) efficacy and safety of 0.1% topical tacrolimus, 94% of patients having either complete or partial resolution of mucosal erosions.[19] Adverse side effects were uncommon (<25% of treated individuals) and included intraoral burnings sensation and taste disturbance. On the basis of these results, topical tacrolimus was suggested to play a major role in the management of OLP in case of: (1) lesions recalcitrant to topical corticosteroids, (2) patients at risk of oral candidosis, and (3) patients at risk of adverse side effects from systemic immunosuppressant agents.[15,22,37] More recently, the use of topical tacrolimus has been extended to patients with OLP that was not recalcitrant to corticosteroids, to support the use of tacrolimus as an alternative to corticosteroids in the first-line management of OLP.

Two recent randomized trials reported that tacrolimus was more effective than topical corticosteroids (triamcinolone and clobetasol) in controlling painful symptoms of erosive OLP.[35,38] However, another randomized, double-blind study found no significant differences between tacrolimus and clobetasol in the management of symptomatic OLP.[34]

Currently, there remains little strong evidence demonstrating that tacrolimus is notably superior to topical corticosteroids for the treatment of OLP. Moreover, available data should be evaluated with caution as studies often used dissimilar preparations and concentrations of tacrolimus ranging from mouthwash[16] to paraffin- or mineral oil–based ointments.[13,17] Overall, however, tacrolimus can be considered effective in controlling the extent of mucosal lesions and the related symptoms of OLP. It has few adverse side effects but relapses may arise after discontinuation of therapy. Therefore, the maintenance of disease remission necessitates continued intermittent use of topical tacrolimus, the frequency of application being different from one patient to another.[19]

GvHD. Topical tacrolimus has been reported to be an effective agent in the short-term management of oral lesions of chronic GvHD.[24-26,39] In one report, 3 patients had marked subjective and objective improvement after topical application of 0.1% topical tacrolimus[24] for 8 weeks. Complete resolution of symptoms and signs of two patients and partial resolution of 4 patients with oral GvHD treated with topical application of 0.1% tacrolimus ointment was reported in a small study of 6 patients.[26] No significant side effects were reported.

Although topical tacrolimus would seem to offer some benefits in the treatment of the oral mucosal lesions of chronic GvHD, the long-term outcomes of such therapy are unknown. Currently, there are no comparative studies investigating the relative effects of tacrolimus versus other topical therapies for chronic GvHD.

Mucous membrane pemphigoid. Topical tacrolimus has been reported to be effective in the management of MMP of the oral mucosa recalcitrant to conventional treatment.[29] Complete healing of mucosal erosions/ulcerations was achieved after 3-month treatment with topical tacrolimus in 3 patients with long-standing disease who: (1) failed to respond to other treatment modalities (eg, topical corticosteroids, systemic retinoids, or chloroquine), or (2) developed adverse side effects to systemic corticosteroids (eg, osteoporosis).[28] Even though MMP primarily reflects autoantibody-mediated immunologic attack on hemidesmosomes,[40] topical tacrolimus may be effective by blocking local cytokine production that mediates local T-cell–driven response.[27,28] Currently, there are no randomized placebo-controlled trials of the precise efficacy of topical tacrolimus for oral MMP.

Pemphigus vulgaris and paraneoplastic pemphigus. Topical therapy might have a secondary role in the management of oral pemphigus vulgaris as usually complete disease control cannot be obtained without systemic immunosuppression, but there remain few substantive data.

Persistent labial ulceration caused by pemphigus vulgaris that had been recalcitrant to a spectrum of topical and systemic agents resolved when topical tacrolimus (0.1% twice daily) was added to ongoing systemic therapy (mycophenolate mofetil 1 g twice/d).[30] Resolution of oral ulceration of paraneoplastic pemphigus secondary to non-Hodgkin lymphoma was achieved with an oral suspension of 0.03% tacrolimus (3 5-minute rinses/d).[41] The effectiveness of topical tacrolimus in the management of pemphigus may suggest that local T-cell–mediated response plays an important role in B-cell activation and hence the generation of autoantibodies against desmogleins.[42]

OFG/oral Crohn disease. Topical tacrolimus has been suggested to have a role in lessening the labial swelling of granulomatous cheilitis,[43] OFG, and Crohn disease,[32] with the major clinical benefit being observed in individuals with mild lip swelling. Casson et al[31] reported resolution of labial swelling and fissures in 3 young patients with Crohn disease

J Am Acad Dermatol
Volume 61, Number 5

after 4 to 6 weeks of topical application of tacrolimus (0.5 mg/g in Orabase [Colgate-Palmolive Co, New York, NY]). There is a need for additional studies to determine whether topical tacrolimus is consistently effective in lessening the labial ulceration of the aforementioned disorders.

Other disorders. Topical tacrolimus was also reported to be effective in the management of oral lesions of psoriasis,[44] cheilitis glandularis,[45] exfoliative cheilitis,[46] and pyostomatitis vegetans secondary to ulcerative colitis.[47] The evidence that tacrolimus is useful for such disease must, currently, be considered weak.

Topical tacrolimus: Conclusions. There is increasing evidence (albeit of variable quality) to suggest that topical tacrolimus may have a place in the treatment of oral ulceration/erosions secondary to a spectrum of immunologically mediated disorders. Perhaps unsurprisingly, there are substantial data on the possible benefit of tacrolimus for OLP, as this is more common than other aforementioned disorders. Nevertheless, many of the reports (including those of lichen planus) describe only a few patients and used a variety of different topical preparations of tacrolimus. More research is needed to obtain objective evidence of the benefit of topical tacrolimus in the treatment of immunologically mediated oral mucosal diseases.

Pimecrolimus

Pimecrolimus is derived from the macrolide ascomycin isolated from *Streptomyces hygroscopicus* var. *ascomyceticus*.[2] Pimecrolimus shares the same cellular binding protein (FK506-binding protein-12) as tacrolimus and blocks the transcription of cytokines by inhibiting the calcineurin pathway. Topical pimecrolimus is a cream developed specifically for the treatment of AD and approved for the treatment of patients with mild to moderate AD disease in patients older than 2 years.[1,3,48]

There are very limited data of the potential of topical pimecrolimus for the treatment of oral mucosal disease. Pimecrolimus has been suggested to be effective in the management of symptoms and erosions/ulcerations of OLP.[49-53] Swift et al,[53] reported significant pain reduction in patients with erosive OLP treated with pimecrolimus in comparison with placebo. Another study of 12 patients found that 1% pimecrolimus cream was more effective in lessening symptoms and signs of erosive OLP in comparison with vehicle only.[54] The drug was well tolerated with only transient burning sensation arising in two of the 6 patients using pimecrolimus. However, relapse was observed in all patients within 4 weeks of cessation of therapy.[54]

A randomized clinical trial found that pimecrolimus 1% cream was no better than topical triamcinolone acetonide in lessening the symptoms and signs of OLP when applied 4 times daily for 2 months.[55] Moreover, a transient oral burning sensation was reported by 10% of patients who received pimecrolimus.[55] A recent randomized vehicle-controlled small study showed that topical pimecrolimus was effective in controlling pain caused by OLP erosions/ulceration during and up to 30 days after cessation of therapy.[56] Similar results were reported in other studies,[49,50,53] but only one of them included long-term observations of treated individuals (eg, 6 months).[50] Pimecrolimus was also used effectively in association to tacrolimus in a patient with cheilitis glandularis superimposed on OLP.[45]

Pimecrolimus: Conclusions. Current data suggest that topical pimecrolimus may be of some benefit, at least in the short term in the treatment of symptomatic OLP. However, its relative effectiveness and safety when compared with topical tacrolimus or corticosteroids are not known. Further investigations are needed to confirm its suggested prolonged long-term efficacy.

Topical cyclosporine

Cyclosporine is a lipophilic cyclic polypeptide extracted from *Tolypocladium inflatum*. Cyclosporine binds to the cytosolic protein cyclophilin and inhibits the transcription of IL-1, IL-2, and interferon-γ leading to T-lymphocyte inhibition. Systemic cyclosporine remains a widely used immunosuppressant, particularly in transplant medicine.[57] The efficacy of topical cyclosporine in the management of oral mucosal disease dose not seem to be consistent.

Topical cyclosporine has been reported to be effective in the management of a variety of oral mucosal disorders (Table II),[58-65] although it appears to be less effective and more expensive than topical tacrolimus or pimecrolimus for the management of such diseases.[33]

Oral lichen planus. The results of different trials investigating the effectiveness of topical cyclosporine in patients with OLP are not consistent. Several randomized controlled trials,[59,66,67] open trials,[63,68,69] case series,[58,61,70] and case reports[71,72] have described the efficacy of cyclosporine in the management of OLP.

Eisen et al[59] were the first to report, in a double-blind randomized study, that topical cyclosporine (5 mL of 100 mg/mL mouthwash 3 times/d) was significantly more effective than placebo in the treatment of symptomatic OLP in 16 patients.

Table II. Studies reporting the use of topical cyclosporine in the management of oral mucosal disorders

Author	No. of patients	Condition	Formulation and daily dose	Treatment duration, wk	Results	Side effects
Frances et al,[58] 1988	4	OLP	Topical 25 mg	4	CR/PR	None
Balato et al,[106] 1989	7	OLP	Mouthrinse 50-100 mg	8	CR/PR	Not reported
Eisen and Ellis,[88] 1990	16	OLP	Mouthrinse 1500 mg	8	CR/PR	Transient burning sensation
Eisen and Ellis,[70] 1990	6	OLP	Mouthrinse 1500 mg	8	CR	Transient burning sensation
Ho et al,[71] 1990	4	OLP	Mouthrinse 600 mg	8-12	CR	Not reported
Veller Fornasa and Catalano,[77] 1991	2	OLP	Topical 100 mg	12	NR	Not reported
Ho and Conklin,[75] 1991	4	OLP	Mouthrinse 600 mg	8-12	NR	Not reported
Levell et al,[76] 1991	7	OLP	Mouthrinse 1500 mg	4	NR	Not reported
Gombos et al,[73] 1992	6	OLP	Topical 48 mg	8	CR(?)/PR(?)	Not reported
Itin et al,[78] 1992	7	OLP	Topical 126 mg	8	NR/PR	Not reported
Porter et al,[60] 1993	6	OLP	Mouthrinse 1500 mg	8-10	PR	Transient burning sensation Deposits between teeth
Pacor et al,[61] 1994	14	OLP	Mouthrinse 500 mg	12	CR	None
Voute et al,[68] 1994	9	OLP	Topical (unknown)	3	NR	None
Epstein and Reece,[84] 1994	11	GvHD	Mouthrinse 100 mg/mL	4-24	PR	None
Becherel et al,[107] 1995	8	OLP	Topical 50 mg	12	NR/CR	None
Harpenau et al,[62] 1995	7/14	OLP	Mouthrinse 500 mg	4	CR	None
Lopez and Rosello,[66] 1995	?	OLP	Mouthrinse 250 mg	8	CR?	Not reported
Sieg et al,[80] 1995	6/13	OLP	Mouthrinse 100 mg/mL	4	PR	None
Epstein and Truelove,[63] 1996	14	OLP	Topical (unknown)	4	PR/NR	Transient burning sensation
Jungell and Malmstrom,[79] 1996	7	OLP	Mouthrinse 450 mg	4	NR/PR	Not reported
Gooptu and Staughton,[83] 1998	1	PV	Mouthrinse 100 mg/mL	24	PR	None
Demitsu et al,[72] 2000	1	OLP	Mouthrinse 100 mg/mL	4	CR	None
Femiano et al,[69] 2003	10/20	OLP	Mouthrinse 100 mg/ml	4	CR	None
Yoke et al,[67] 2006	68/139	OLP	Mouthrinse 3 times/d	8	PR	Transient burning sensation
Conrotto et al,[81] 2006	20/40	OLP	1.5% Cyclosporine with 4% hydroxyl-cellulose gel	8	PR/CR	Dyspepsia
Thongprasom et al,[74] 2007	6/13	OLP	Mouthrinse 100 mg/mL	8	PR/NR	Transient burning sensation, itching, swelling lips, petechial hemorrhages, sore throat, gastrointestinal discomfort, breast tenderness, and dizziness

CR, Complete remission; *GvHD*, graft-versus-host disease; *NR*, no response; *OLP*, oral lichen planus; *PV*, pemphigus vulgaris; *PR*, partial remission.
Modified from Carrozzo and Gandolfo,[108] 1999, and Lodi et al,[33] 2005.

In comparison with placebo, topical cyclosporine rinse (5 mL [500 mg] for 5 min/d for 4 weeks) also led to a significant improvement in symptoms and signs of OLP.[62] A 50% to 80% improvement of OLP lesions in 6 patients was reported by Gombos et al[73] using topical cyclosporine mixed with a bioadhesive gel (carboxymethylcellulose) (48 mg/d) for 8 weeks. Nevertheless, there remain few comparative studies to support the use of topical cyclosporine as an alternative[66] or a second-line therapy to topical

J Am Acad Dermatol
Volume 61, Number 5

corticosteroids.[74] Moreover, some groups have reported topical cyclosporine to be of little or no benefit for the management of OLP.[68,75-79] For example, one randomized controlled trial found that topical cyclosporine was no better than triamcinolone acetonide in the treatment of symptomatic OLP.[80] A more recent randomized controlled trial of 139 patients concluded that topical cyclosporine is not more effective than triamcinolone acetonide 0.1% in the treatment of OLP.[67] A small randomized controlled trial in patients from Thailand came to the same conclusions.[74] Topical clobetasol may actually be more effective than cyclosporine in the short-term resolution of symptoms of OLP although the latter may give rise to less recurrence than clobetasol.[81] Topical cyclosporine (oral rinse; 1 mL [100 mg/mL] 3 times/d) has been less effective, and more expensive, than sulodexide (heparin-related molecule) (intramuscular 600 U followed by 250 U orally twice daily for 1 month) in the management of erosive/ulcerative OLP,[69] although no significant clinical adverse side effects seem to arise. A systematic review of 11 randomized controlled trials evaluating different topical and systemic agents used in the management of OLP, including topical cyclosporine, concluded that there was a lack of strong evidence supporting the efficacy of any agent, including cyclosporine, in the management of symptomatic OLP.[82]

Pemphigus. There are small numbers of reports of topical cyclosporine being effective for the oral lesions of pemphigus vulgaris.[64,83] Topical cyclosporine (5 mL of oral suspension [500 mg] 3 times/d) was reported to be effective in the treatment of a cohort of 12 patients with oral pemphigus recalcitrant to conventional treatment. After 2 months, a significant improvement in both symptoms and signs was reported.[64]

Oral MMP. The use of topical cyclosporine with other agents (topical and systemic corticosteroids, systemic azathioprine, and tacrolimus) failed to control the oral erosions of one patient with MMP.[65] The disease did, however, respond to mycophenolate mofetil and systemic minocycline.

GvHD. Epstein and Reece[84] reported that 7 of 11 patients with GvHD responded well to the addition of topical cyclosporine to treatment with systemic immunosuppressants and topical dexamethasone.

Topical cyclosporine: Conclusions. There is little evidence that cyclosporine is more than or as affective as topical corticosteroids in the treatment of OLP. Moreover, the cost of cyclosporine usually exceeds the cost of topical corticosteroids or other immunosuppressive agents. There are very few studies and scarce evidence regarding the benefits of topical cyclosporine for the management of other immunologically mediated oral mucosal disorders.

Adverse effects of calcineurin inhibitors

Topical tacrolimus. Adverse effects of systemic tacrolimus include hypertension, nephrotoxicity, and infections secondary to immunosuppressive status of the patients and correlate with the dosage, blood levels, and duration of therapy.[1]

Unlike systemic tacrolimus, topical application for the treatment of oral mucosal disease has, to date, been reported as safe with few adverse effects (Table III). Reported adverse effects include mucosal burning sensation (which may be caused by the vehicle, not to the drug itself), sore throat, transient taste disturbance, and mucosal staining.[16,18,20,22,26] Headaches have been reported by some patients,[19,22] but this does not seem to be dose dependant.[19] Of note, all the reported adverse effects seem to cease as the treatment continues and as the ulcerative or erosive lesions heal.[14]

Systemic absorption of tacrolimus after topical application on the oral mucosa is possible but may be unpredictable. Undetectable (<1.5 ng/mL) or low levels of systemic absorption of tacrolimus after topical oral application have been observed in 4 studies.[13,16,17,36] However, in one retrospective study, blood levels of tacrolimus were detected in 27 of 50 patients, with 5 of them having a concentration greater than 5 μg/L. The clinical significance of systemic absorption of topically applied tacrolimus is probably very limited, as no significant systemic clinical, hematological, or biochemical events have been observed.[19] Indeed in studies of AD, systemic absorption of tacrolimus was not observed in 80% of blood samples.[85] When detected, the hematological presence of tacrolimus was transient and not associated with adverse events.[85] Indeed, topical tacrolimus has been used safely in patients with hepatic disease (active hepatitis C or hepatic cirrhosis).[14,15,86] As observed in patients with AD,[87] absorption of tacrolimus after local application for OLP seems to decrease as disease resolves and mucosal integrity returns.[19]

The absorption associated with OLP seems to be greater than that associated with AD.[19] Indeed, some authors have proposed that a systemic effect of tacrolimus may have a role in resolution of oral lesions.[13] With regard to the safety of tacrolimus in other immunologically mediated oral disease (eg, OFG and oral Crohn disease), the few available data suggest that systemic absorption does not occur.[31] The potential association between topical tacrolimus

Table III. Adverse side effects and systemic absorption related to topical application of tacrolimus in different oral mucosal disorders

Study	No. of patients	Disease	Adverse side effects	Evidence of systemic absorption (blood levels of tacrolimus)
Corrocher et al,[35] 2008	16/32	OLP	Transient (4-5 d) worsening of burning sensation in 9/16 patients	Undetectable (<1.5 ng/mL)
Tavassol et al,[103] 2008	11	OLP	Rare and minor (not specified)	Mean level was 1.30 ng/mL (after 1 wk)
Albert et al,[26] 2007	6	GvHD	Transient burning sensation	Detectable in 4/6 patients
Becker et al,[95] 2006	1	OLP	Development of squamous cell carcinoma at same site of application of tacrolimus	Not reported
Corrocher et al,[23] 2006	12/24	DG	Transient burning sensation in 6/12 patients	Undetectable (<1.5 ng/mL)
Laeijendecker et al,[38] 2006	20/40	OLP	Temporary burning/stinging sensation in 8/20 patients	Not reported
Shichinohe et al,[21] 2006	2	OLP	None	Detectable (>1.5 ng/mL) but never >2.5 ng/mL
Lozada-Nur and Sroussi,[22] 2006	10	OLP	Recurrent headache (1), transient burning sensation (1)	Not reported
Byrd et al,[9] 2004	37	OLP	Local irritation (4), burning (5) and tingling (3) sensation, dysgeusia (2)	Not reported
Fricain et al,[39] 2005	1	OLP	Mucosal pigmentation	Undetectable (<1.5 ng/mL)
Thomson et al,[36] 2004	23	OLP	Paraesthesia and burning sensation (6), dysgeusia (1), dysgeusia and nausea (1)	Detectable in 12/23 patients; plasma levels were 1.5 -2.9 ng/mL in 11 patients and 7.0 ng/mL in 1
Shen and Pedvis-Leftick,[20] 2004	1	OLP	Temporary brown discoloration of oral mucosa	Not reported
Hodgson et al,[30] 2003	1	PV	None	Undetectable (<1.5 ng/mL)
Hodgson et al,[19] 2003	50	OLP	Burning sensation (8), dysgeusia (5), and headache (2)	Detectable in 27/50 patients, ranging from 2.7-11 ng/mL; mean tacrolimus level decreased with duration of therapy from 2.7 μg/L (wk 1) to 0.5 μg/L (wk 32)
Olivier et al,[16] 2002	8	OLP	Transient burning sensation (3), dry mouth (2)	Undetectable (<1.5 ng/mL)
Rozycki et al,[18] 2002	13	OLP	Burning sensation (1), sore throat (1)	Not reported
Kaliakatsou et al,[13] 2002	17	OLP	Tingling sensation (6), burning sensation (1), altered taste sensation (1), slight nausea (1), mild headache (1), and constipation (1)	Detectable in 8/17 patients, ranging from 3-28.6 ng/mL
Morrison et al,[17] 2002	6	OLP	None	Undetectable (3); detectable in 3: 1.6, 1.7, and 9.6-9.9 ng/mL
Vente et al,[14] 1999	4	OLP	Burning sensation (2)	Undetectable (5/6); ectable in 1: 9-15 ng/mL

DG, Desquamative gingivitis; *GvHD*, graft-versus-host disease; *OLP*, oral lichen planus; *PV*, pemphigus vulgaris.

and any increased risk of malignancy is discussed later.

Topical pimecrolimus. To date, no significant adverse reactions as a consequence of topical application of pimecrolimus for OLP have been reported. In one study, transient burning sensation was reported by 33% patients in the initial 2 weeks of therapy, but no patient discontinued treatment as a consequence of this adverse effect,[54] and no other adverse clinical, hematological, or serologic events as a result of systemic absorption were observed.[54]

Topical cyclosporine. Topical cyclosporine can give rise to minor and transient adverse effects including oral mucosal burning sensation, swelling of lips, and mucosal petechiae.[61,63,74,88] Systemic absorption after topical application seems to be infrequent and the efficacy of the drug does not correlate with cyclosporine blood levels.[61,70,74]

J Am Acad Dermatol
Volume 61, Number 5

Carcinogenic potential of topical tacrolimus and pimecrolimus

Systemic immunosuppressants are known to increase the risk of malignancy, notably non-Hodgkin lymphoma[89] and squamous cell carcinoma (SCC).[90] For example, systemic tacrolimus can increase the risk of malignancy (eg, oropharyngeal and skin cancers)[91,92] by suppressing immune surveillance and inhibiting DNA repair and apoptosis.[93] Currently, however, there is no strong evidence that also topical application of tacrolimus is associated with an increased risk of malignancy.

Niwa et al[92] concluded that topical tacrolimus may stimulate the development of cutaneous papillomas and carcinomas in animal models pretreated with the tumor initiator dimethylbenz[alpha]anthracene and thereafter with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate.

In 2004 the US FDA[94] reported that 10 and 19 patients who received topical pimecrolimus and tacrolimus, respectively, developed a malignancy. The 10 malignancies associated with topical pimecrolimus included non-Hodgkin lymphoma, panniculitis-like T-cell lymphoma, granulomatous lymphadenitis with hyperplasia, SCC, intraductal papilloma of the nipple, and basal cell carcinoma. Two of the 10 pimecrolimus-associated malignancies occurred at the same site of local application.

With regard to topical tacrolimus, 9 patients developed lymphomas and 10 developed cutaneous malignancy (mainly SCC, sarcoma, and malignant melanoma). Most of the cutaneous tumors (7/10) developed in the same area as that of tacrolimus application.

Tacrolimus (0.1%) was the suspected causative agent of oral SCC of the tongue in a 56-year-old woman who was given a diagnosis of OLP.[95] The oral SCC developed after 3 years of topical tacrolimus therapy and 6 years after the diagnosis of OLP. Langeland and Engh[96] reported the development of genital SCC in a 57-year-old man with a 2-year history of balanoposthitis. The patient developed the malignancy after 2.5 months of therapy with topical tacrolimus. Both of these mucosal tumors developed at sites of tacrolimus application. These data may suggest that tacrolimus may be a promoter or accelerator of mucocutaneous carcinogenesis.[92,96] However, this should be considered with caution as histopathological description of the mucosal/cutaneous lesions immediately before tacrolimus application was not always provided and hence it is not known whether or not the carcinogenetic process had already commenced before the onset of the therapy.[97,98]

A more recent case-control study did not find any increased risk of lymphoma in patients with AD treated with topical calcineurin inhibitors.[99] In January 2006, the US FDA[100] approved the inclusion of a potential risk of cancer in the labeling of tacrolimus and pimecrolimus cream, and stated that these agents should be used as second-line therapies. In addition, the FDA recommended refraining from using these treatments in children younger than 2 years (FDA, 2006).[100]

There remains little information of the carcinogenic potential of tacrolimus or pimecrolimus, and the new recommendations from the European Medicines Agency state that the benefits of these calcineurin inhibitors outweigh the risks. The European Medicines Agency, however, recommends intermittent use of topical tacrolimus with the lowest strength possible and only for short periods of time. Certainly with regard to OLP, a clear diagnosis should be established before the use of topical tacrolimus as early SCC may clinically mimic lichenoid lesions or develop in the context of lichen planus.[22] In addition, patients must be informed of the potential malignant risk of these agents.[22,97,101,102]

CONCLUSION

Topically applied calcineurin inhibitors, in particular tacrolimus, may be of some clinical benefit in the management of immunologically mediated oral mucosal disease, particularly OLP. Although topical tacrolimus and pimecrolimus are probably safe and likely to be effective for OLP that do not respond to topical corticosteroids, current evidence suggests that these agents will not provide long-term resolution.

There is a need for well-designed randomized controlled trials that truly assess the clinical benefits of topical tacrolimus and pimecrolimus versus potent topical corticosteroids for the short- and long-term management of OLP. Well-planned open studies of the efficacy of these agents for the treatment of other immunologically mediated oral mucosal diseases would help determine whether appropriate randomized controlled trials should be considered.

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Orofacial granulomatosis: Clinical features and long-term outcome of therapy

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Background: Orofacial granulomatosis (OFG) is a chronic inflammatory disorder characterized by persistent or recurrent soft tissue enlargement, oral ulceration, and a variety of other orofacial features. There remain few detailed reports of the clinical features and long-term response to therapy of substantial groups of patients with OFG.

Objective: The aim of this study was to determine retrospectively the clinical, hematologic, and histopathological features of a large case series of patients with OFG. In addition the long-term response to therapy was examined.

Methods: Clinically relevant data of 49 patients with OFG who attended a single oral medicine unit in the United Kingdom were retrospectively examined. The analyzed parameters included diagnostic features, clinical manifestations, and outcomes and adverse side effects of therapy.

Results: Labial swelling was the most common presenting clinical feature at diagnosis (75.5%), followed by intraoral mucosal features other than ulceration such as cobblestoning and gingival enlargement (73.5%). Mucosal ulceration was observed in 36.7% of patients whereas extraoral facial manifestations such as cutaneous erythema and swelling were present in 40.8% of patients. Of the 45 patients who required treatment, 24 (53.3%) were treated with topical corticosteroids/immunosuppressants only, whereas 21 (46.7%) received a combined therapy (topical plus systemic corticosteroids/immunosuppressants and/or intralesional corticosteroids). The long-term outcome analysis showed complete/partial resolution of tissue swelling and oral ulceration in 78.8% and 70% of patients, respectively.

Limitations: The main limitation of the current study was its retrospective design and methodology including differences in reporting clinical features and outcome.

Conclusions: OFG can show multiple facial and mucosal clinical features. Long-term treatment with topical and/or combined therapy is needed in the majority of patients. Response to therapy is highly variable even though in the long-term complete/partial disease resolution can be obtained in the majority of patients. Mucosal ulceration tends to be more recalcitrant than orofacial swelling. Adverse side effects of therapy are rare. (J Am Acad Dermatol 2010;62:611-20.)

Key words: clinical features; long-term outcome; orofacial granulomatosis.

Orofacial granulomatosis (OFG) is an uncommon immunologically mediated disorder clinically characterized by recurrent or persistent swelling of the orofacial tissues and oral mucosal ulceration together with a spectrum of other orofacial features.[1] The chronic inflammation of OFG is often characterized by the presence of granulomas in the subepithelial stroma, however,

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noncaseating granulomas are not always detected.[2,3]

The clinical features of OFG are identical to orofacial manifestations of Crohn disease, although in contrast to the latter there is no consistent evidence of attendant inflammatory bowel disease. The clinical features of OFG may also mimic orofacial manifestations of sarcoidosis.[4] It is probable that OFG represent a spectrum of disease that ranges from localized granulomatous inflammation of the lips (granulomatous cheilitis, Miescher cheilitis), through orofacial swelling with mucosal ulceration to disease with neurologic deficit and lingual fissuring (Melkersson-Rosenthal syndrome).[5-9]

The increasing number of reports of small numbers of patients with OFG may suggest that the prevalence of this disorder may be rising, and certainly clinical experience in the current study center would indicate that this change in prevalence is real. There remain, however, few reports of substantial numbers of patients attending a single center to allow clear descriptions of the clinical features, long-term behavior, and likely successful therapeutic regimens of OFG. The aim of this study was to describe the clinical, hematologic, serologic, and histopathological features of OFG and the long-term response to therapy of a substantial group of affected individuals. Patients with Crohn disease and sarcoidosis (given a diagnosis either before or after the onset of orofacial manifestations) were excluded. Hence the current patients represent the largest homogenous group of individuals with OFG reported in the past two decades.

CAPSULE SUMMARY

- Lip swelling was the most common, but rarely the sole presenting clinical feature of orofacial granulomatosis at diagnosis.
- Other intraoral and extraoral manifestations occurred in the majority of patients.
- About half of the patients with orofacial granulomatosis benefited from topical therapies. The remaining patients needed the addition of either intralesional or systemic therapies.
- Complete/partial resolution of clinical signs could be obtained in the majority of affected individuals in the long term.

METHODS

Patients

The study group compromised 49 individuals with OFG who attended the Oral Medicine Unit of University College London Eastman Dental Institute and University College London Hospital Eastman Dental Hospital between 1985 and 2007. Details of the diagnostic criteria used are indicated in Table I.[1,6] From the initial cohort of 52 individuals, 3 patients, who developed intestinal inflammation of Crohn disease after the onset of orofacial manifestations, were recategorized as having oral Crohn disease and were thus not considered for data collection and analysis.

Methods

Details of the demographics, medical history, extraoral and intraoral clinical features, treatment modalities, response to therapy, adverse side effects of therapy, short- and long-term outcomes, and diagnostic and monitoring investigations were systematically extracted from the case file of each patient. Representative incisional biopsy was performed during initial consultations wherever possible and relevant histopathology obtained. Hematological and serological data were evaluated in some of the studied patients as they were required: (1) for diagnostic purposes; (2) to evaluate potential gastrointestinal involvement; and (3) to monitor therapy. These include full blood cell count, differential white cell count, hepatic and renal biochemistry, erythrocyte sedimentation rate, C-reactive protein, and serum angiotensin-converting enzyme levels. The number of patients tested varied from 16 to 34 on the basis of which types of investigations were undertaken.

Single hematologic investigations were considered for the calculation of abnormal results. Analyses were performed with regard to the total number of investigations, the total number of patients tested, and any association with pharmacologic therapies.

The response to therapy was evaluated separately for intraoral and facial manifestations on the basis of observation at 6 monthly reviews recorded in clinical notes. The therapeutic effectiveness was estimated using a 4-point scoring system: 0 (initial status), −1 (worsening), +1 (partial resolution), +2 (complete resolution). Evaluation of response was based on clinicians' judgments during clinical examination, clinical photographs, and the patients' opinions as reported in clinical notes. Clinical notes were reviewed independently by two authors (K. A. and S. F.) and subsequently compared and discussed to agree on a final score. Initial status defined the size of orofacial swelling and number/dimension of intraoral ulceration at pretherapy stage. Partial resolution was defined as a 30% to 70% dimensional reduction of swelling in case of facial manifestations and 30% to

J Am Acad Dermatol
Volume 62, Number 4

Table I. Diagnostic investigations and criteria of orofacial granulomatosis

Investigations	Results
Full blood cell count	Should be normal
Hemoglobin	Should be normal
Serum angiotensin converting enzyme levels*	Should be normal
C-1 esterase inhibitor levels†	Should be normal
Serum iron and transferrin	Should be normal
Tuberculin skin test (when clinically justified)	Should be negative
Chest radiography (when clinically justified)	Should be normal
GI endoscopy/histopathology‡	Should be normal; if inflammatory changes are present, Crohn disease should be excluded
Histopathology I: dilated lymphatics, edema of corium, slight fibrosis, with/without multiple noncaseating granulomas with Langerhans giant cell and lymphocytes	Should be present§
Histopathology II: PAS reaction and Ziehl-Neelsen stain (when clinically justified)	Should be negative
Polarized light microscopy: identification of birefringent foreign-body material (when clinically justified)	Should be negative

GI, Gastrointestinal; *PAS*, periodic acid–Schiff.
*To be performed when there are clinical features compatible with potential diagnosis of sarcoidosis.
†To be performed when orofacial swelling is recurrent and edematous without signs of persistent tissue fibrosis.
‡To be performed when clinical or laboratory features increase suggestion of GI inflammatory disease.
§Absence of histopathological features does not exclude orofacial granulomatosis diagnosis if clinical features are compatible.

70% reduction in number or size of intraoral ulcerative disease. The 30% to 70% range was arbitrarily chosen as a practical mean to measure clinically significant albeit not complete resolution of the disease: a reduction of less then 30% is in fact hardly recognizable on clinical examination and photographs and a reduction of more than 70% is very close to complete resolution. Complete resolution was defined as 70% or more swelling reduction or complete return to normal dimension/shape of affected facial tissues and complete resolution (or >70% reduction) of intraoral ulcerative disease. Worsening was defined as dimensional increase of any facial swelling and/or an increase in number and/or size of intraoral ulcerative disease. Analysis of treatment outcome was based on: (1) the comparison between disease status before therapy and last review in 2007; and (2) the serial measurements of disease status at 6-month reviews. The Kaplan-Meier cumulative incidence curve was constructed to assess the proportions of patients having a complete resolution of soft tissue swelling over time.

RESULTS

Patient demographics

The group comprised 27 (55.0%) male and 22 (45.0%) female patients. The mean age at time of clinical diagnosis by oral medicine specialists was 32.4 years (SD 19.1) although this ranged from 7.4 to 72.1 years. The mean age at OFG diagnosis was statistically significantly lower in male (23.3 years) than female (43.6 years) patients ($P < .001$). The duration of oral signs/symptoms before definitive diagnosis varied from 4 to 192 months, with a mean of 44 months (SD 44.6). The group principally comprised white-British (36 of 49; 73.5%), although some individuals were white-other (6 of 49; 12.2%), Asian (3 of 49; 6.1%), or Black (4 of 49; 8.2%). The observation period of patients with OFG varied from 1 to 15 years (mean 2.9, median 1.8). It was less than 3 years for 30 patients, 3 to 4 years for 10 patients, and 5 years or greater for 9 patients.

General medical history and social history

The patients had a history of a wide variety of medical problems, the most common of which were: allergies (14/49; 28.6%), eczema or atopic dermatitis (13/49; 26.5%), respiratory (10/49; 20.4%), and central nervous system disease other than cranial nerve neuropathies and migraine (10/49; 20.4%). Gastrointestinal symptoms and serologic abnormalities necessitated referral to a gastroenterology unit where endoscopic investigations failed to show any gastrointestinal inflammatory disease.

Clinical manifestations at presentation

In all, 37 patients (37 of 49; 75.5%) had labial swelling at the time of initial specialist examination, whereas 12 individuals (12 of 49; 24.5%) had solely intraoral manifestations. Both lips were affected in 9 (18.4) patients whereas 9 and 19 patients had swelling of upper and lower lip, respectively. Eighteen

Table II. Presenting clinical features of 49 patients with orofacial granulomatosis

Signs and symptoms	No. (%)
Lip enlargement	37 (75.5)
Both lips	9 (18.4)
Upper lip	9 (18.4)
Lower lip	19 (38.8)
Other intraoral	36 (73.5)
Cobblestoning	15 (30.6)
Gingival enlargement	13 (26.5)
Fissure tongue	7 (14.3)
Swelling of tongue	1 (2.0)
Mucosal tags	4 (8.2)
Other facial	20 (40.8)
Median lip fissure	7 (14.3)
Angular cheilitis and fissure of lip	7 (14.3)
Facial swelling, erythema, or both	6 (12.2)
Oral ulceration	18 (36.7)
Aphthous-like ulcers	17 (34.7)
Linear, deep ulcers	2 (4.1)
Cervical lymphadenopathy	10 (20.4)
Neurologic	2 (4.1)
Facial nerve palsy	2 (4.1)

(36.7%) patients had oral ulceration at time of initial examination. Seventeen (94.4%) of the 18 patients had superficial aphthous-like ulcers whereas two (4.1%) patients had linear, deep ulcers of the vestibular fold areas. Ten (20.4%) patients had cervical lymphadenopathy, usually comprising multiple small (<1 cm diameter) rubbery mobile nodes of the front and/or back triangle of the neck. Two patients had facial nerve palsy and no further neurologic manifestations were observed at presentation. Additional details about presenting clinical features are provided in Table II.

Histopathology

Details of histopathological examination were available for 37 (75.5%) patients. In the remaining 12 (24.5%) cases biopsy was refused by the patient, or undertaken in other hospitals/units (with the results unavailable for review) or considered not necessary by the attending specialist. According to literature, absence of noncaseating granulomas does not exclude a diagnosis of OFG if clinical features are compatible and other investigations ruled out disorders that can mimic orofacial manifestations of OFG.[2] Noncaseating granulomas were observed in only 43.2% (16 of 37) of the examined specimens. The granulomas were usually small, loose, and poorly defined consisting of epithelioid histiocytes surrounded usually by lymphocytes. Moreover, multinucleate giant cells were present and were sometimes of the Langhans type. Features of edema of the corium with dilated lymphatic and blood vessels and nonspecific inflammatory infiltrate were observed in all specimens, regardless of the presence or absence of granulomas.

Therapy

The aims of OFG management were to lessen and hopefully resolve intraoral painful lesions, orofacial swelling, and other features of the disease (eg, lip fissures, angular cheilitis). Hence the presence of painful symptoms, aesthetic concerns, or both was used as criteria to offer and initiate therapy. Selection of treatment method was initially based on severity of clinical manifestations. Ulceration of the oral mucosa, mucosal tags, and cobblestoning were usually managed with topical corticosteroids[6] and only rarely were they severe enough to require systemic therapies. Mild orofacial swelling was managed with topical corticosteroid, tacrolimus, or both. Mild swellings that were nonresponsive to topical agents and moderate to severe swellings were usually managed with short courses (1-2 weeks) of moderate doses of systemic corticosteroids (25-50 mg of prednisolone) and/or, when required, with intralesional corticosteroids injections (triamcinolone acetonide 40 mg/mL) as described by Mignogna et al[10]; long-term systemic immunosuppressants (eg, azathioprine); or anti–tumor necrosis factor-α agents (thalidomide) (Fig 1). Choice among these different therapies and agents was based on patient's systemic conditions, patient's preference, and expertise/experience of attending clinician. A list of the medications prescribed is provided in Table III.

Overall 45 (91.8%) of 49 required medical treatment whereas 4 experienced spontaneous remission. In all, 24 (53.3%) of 45 patients were treated with topical therapy only, whereas 21 (46.7%) received combined therapy (topical plus systemic, intralesional, or both). Different topical and/or systemic agents were used during the long-term management of OFG because of: (1) development of new manifestations; (2) lack of response; or (3) adverse side effects. The duration of treatment of OFG (from commencement of therapy until end of data collection) differed greatly among patients (1-15 years; median 1.8).

Details of treatment outcome after a minimum of 3, 5, and 10 years of therapy were available for 38 (77.6%), 26 (53.1%), and 9 (18.4%) patients, respectively.

Clinical outcome (orofacial swelling)–disease status before therapy versus last review

Of the 49 patients with OFG, 47 (95.9%) in this cohort had orofacial swelling and 44 needed medical

J Am Acad Dermatol
Volume 62, Number 4

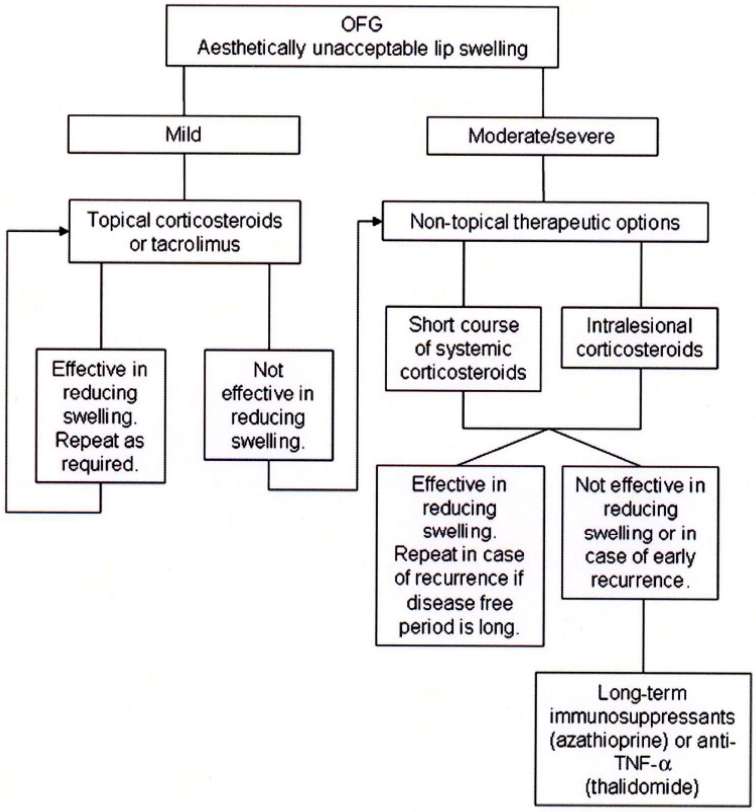

Fig 1. Therapeutic ladder of lip swelling of orofacial granulomatosis (*OFG*). *TNF*, Tumor necrosis factor.

therapy to control their disease. Analysis of the overall outcome (based on the comparison between disease status before therapy and last review in 2007) indicated 19 (40.4%) patients had complete resolution of disease whereas 18 (38.3%) had partial resolution. The disease status on last review was the same as that observed at the commencement of treatment in 6 (12.8%) patients. Only one (2.1%) patient had a worsening of disease (Table IV). Three (6.4%) patients presented with complete resolution at their last review but were classified as being spontaneous remission cases as resolution was not associated with any ongoing therapy.

The 19 patients with complete resolution of the swelling had been treated with topical agents only in 8 cases and with combined therapy (topical and systemic/intralesional therapy) in 11 cases. The 18 patients with partial resolution of the swelling had been treated with topical agents only in 4 cases and with combined therapy in 14 cases. The 6 patients whose disease status on last review was the same as that observed at the commencement of treatment had been treated with topical agents only in 5 cases and with combined therapy in one case. The patient who had worsening of the disease had been treated with topical therapy only.

Clinical outcome (orofacial swelling)—serial measurements of disease status

Analysis of the typical progress during the treatment (calculated on serial measurements of disease status during 6-month reviews) showed a typical remitting behavior. It permitted classification of patients into 4 distinct groups on the basis of the most common (>50%) disease status during reviews: complete resolution (17 patients; 36.2%), partial resolution (17 patients; 36.2%), worsening (one

Table III. Different topical and systemic agents used to control orofacial granulomatosis lesions in these patients

Agent	No of patients (%)
Topical	
Fluticasone propionate 0.05% cream—Cutivate	23 (47.0)
Clobetasol propionate 0.05% cream—Dermovate	7 (14.3)
Fluticasone propionate, 400 μg in 15 mL of water as mouthwash	2 (4.1)
Fluticasone propionate, 50-μg spray	15 (30.6)
Fluticasone propionate inhaler—Flixotide	2 (4.1)
Betamethasone sodium phosphate mouthwash	10 (20.4)
Triamcinolone acetonide in 0.1% carmellose paste	6 (12.2)
Hydrocortisone hemisuccinate pellets	2 (4.1)
Tacrolimus 0.03%	5 (10.2)
Tacrolimus 0.1%	22 (44.9)
Pimecrolimus 1%	1 (2.0)
Intralesional	
Triamcinolone acetonide (40 mg/mL)	6 (12.2)
Systemic	
Prednisolone	13 (26.5)
Deflazacort	8 (16.3)
Azathioprine	7 (14.3)
Mycophenolate mofetil	2 (4.1)
Clofazimine	1 (2.0)
Dapsone	1 (2.0)
Thalidomide	7 (14.3)
Pentoxifylline	3 (6.1)
Systemic tacrolimus	1 (2.0)

patient; 2.0%), and same disease status as that before therapy (12 patients; 25.5%) (Table IV).

The 17 patients who showed complete resolution in the majority (>50%) of reviews had been treated with combined therapy in 9 cases, and with topical agents only 5 cases. Three patients had spontaneous resolution.

The 17 patients who showed partial resolution in the majority (>50%) of reviews during therapy were treated with topical agents only in 5 cases and with combined topical/systemic agents in 12 cases.

The 12 patients whose disease status was mainly the same as that at initial pretherapy were treated with topical therapy (8 patients) or combined topical and systemic agents (4 patients). The patient with worsening disease status was treated with topical agents only. A subanalysis of 3 patients treated with long-term systemic thalidomide showed that the most frequent disease status during therapy was equally distributed between partial resolution (one patient), complete resolution (one patient), and initial status (one patient). Table IV summarizes the clinical outcome of orofacial swelling in these patients with OFG.

The Kaplan-Meier analysis of 46 patients showed that 23 (50%) of them had complete resolution of the orofacial swelling within 3 years of treatment (ie, the median time to complete resolution was 36 months). Also, about a quarter of patients had complete resolution of swelling within the first year of therapy. However, there were still 6 patients who did not have complete resolution of swelling during the follow-up period (Fig 2).

Clinical outcome (intraoral ulceration)—disease status before therapy versus last review

A total of 24 (49%) patients had symptomatic intraoral ulceration that required medical therapy. Analysis of the overall outcome (based on the comparison between disease status before therapy and the last review in 2007) demonstrated that complete resolution occurred in 7 (29.2%) patients, whereas partial resolution occurred in 10 (41.7%). The disease status on last review was the same as that observed at treatment start in 6 (25%) patients, and in only one (4.2%) case had the disease worsened.

The 7 patients who showed complete resolution of intraoral ulceration were treated with topical agents only in 5 cases and combined topical/systemic agents in two cases. The 10 patients who showed partial resolution of intraoral ulceration were treated with topical agents only in 4 cases and combined therapies in 6 cases.

The 6 patients whose disease status on last review was the same as that observed at the commencement of treatment were treated with topical agents only in 4 cases and with combined therapy in two cases. The patient who had worsening of the disease was treated with topical therapy only.

Clinical outcome (intraoral ulceration)—serial measurements of disease status

Analysis of the typical progress during the treatment (calculated on serial measurement of disease status during 6-month reviews) was undertaken based on the aforementioned classification. One group of 10 (41.7%) patients showed partial resolution in the majority of reviews. Another 5 (20.8%) patients presented complete resolution in the majority of reviews. Disease status was the same as the initial pretherapy status during the majority of the reviews in a third group of 8 (33.3%) patients. Only one (4.2%) patient showed a worsening of disease status in the majority of reviews.

J Am Acad Dermatol
Volume 62, Number 4

Table IV. Status of facial swelling and intraoral ulceration before and during treatment, and at last review

	Disease status before therapy	Disease status during therapy (>50% of reviews)	Disease status at last review
Facial swelling	Initial status (47 patients)	Complete resolution (17; 36.2% of patients)	Complete resolution (22; 46.8% of patients)
		Partial resolution (17; 36.2% of patients)	Partial resolution (18; 38.3% of patients)
		Same status as that before therapy (12; 25.5% of patients)	Same status as that before therapy (6; 12.8% of patients)
		Worsening (1; 2.0% of patients)	Worsening (1; 2.0% of patients)
Intraoral ulceration	Initial status (24 patients)	Complete resolution (5; 20.8% of patients)	Complete resolution (7; 29.2%; of patients)
		Partial resolution (10; 41.7% of patients)	Partial resolution (10; 41.7% of patients)
		Same status as that before therapy (8; 33.3% of patients)	Same status as that before therapy (6; 25.0% of patients)
		Worsening (1; 4.2% of patients)	Worsening (1; 4.2% of patients)

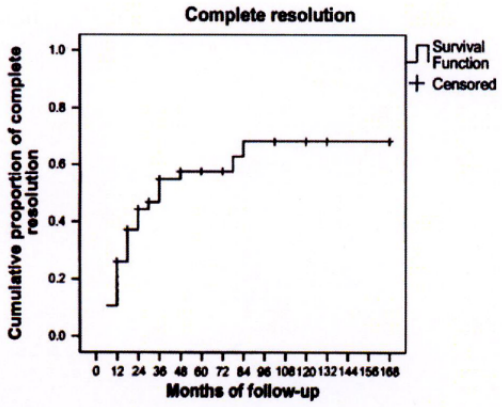

Fig 2. Kaplan-Meier plot of clinical outcome of soft tissue swelling. Graph shows that 23 (50%) of patients had complete resolution of orofacial swelling within 3 years of treatment. Also, about a quarter of patients had complete resolution of swelling within first year of therapy. However, there were still 6 patients who did not have complete resolution of swelling during follow-up period.

The 10 patients who showed partial resolution in the majority of reviews during therapy were treated with topical agents only in 5 cases and combined topical/systemic agents in 5 cases. The 5 patients who presented complete resolution in the majority of reviews were treated with topical agents only (3 patients) and topical and systemic therapy (two patients). The 8 patients whose disease status was mainly the same as initial pretherapy status were treated with topical therapy only in 5 cases and combined topical and systemic agents in the remaining 3 cases. The patient with worsening disease status was treated with topical agents only. A summary of the clinical outcome of therapy of oral ulceration is provided in Table IV.

Hematologic and serologic assessments

Overall 12.2% (mean value; range 0%-41.4%) of the total number of investigations showed abnormal results and these were mainly associated with combined therapy. Overall 20% of the total number of patients showed abnormal results and these were mainly associated with combined therapy.

Abnormal results consisted of mild reduction/elevation with respect to normal values and were thus considered of little clinical significance.

Adverse drug reactions

Six patients had adverse drug reactions (ADRs) such as gastrointestinal upset, nausea, vomiting, diarrhea, rash, and sensory neuropathy. Five patients had one ADR and one had 3 ADRs. All patients who developed an ADR were on systemic agents, mainly long-term azathioprine or thalidomide. Azathioprine was prescribed to 7 patients; adverse effects developed in 3 patients and included rash (one patient), nausea and headache (one patient), and cardiac arrhythmia (one patient). Thalidomide was prescribed to 7 patients; adverse effects developed in 4 patients and included rash (3 patients) and fatigue (one patient). Systemic prednisolone was prescribed to 13 patients; it caused gastrointestinal upset in one patient. Gastrointestinal upset developed in the only patient who was on systemic tacrolimus. Oral candidosis was the most common adverse side effect from topical therapy.

DISCUSSION

OFG is a chronic inflammatory disease with the potential to adversely affect the quality of life of patients by virtue of persistent labial and/or facial swelling, painful oral ulcerations, and occasionally neurologic manifestations.[8]

There are few detailed studies on the clinical features of OFG in large groups of patients and there

is no clear information regarding the long-term outcomes of different therapies and disease behavior during long-term treatment. The current study attempted to clarify these issues by virtue of a retrospective analysis of a group of patients with OFG who were treated at a single center during more than 20 years. The study represents the largest homogenous group of individuals given a diagnosis of OFG reported in the past two decades, as individuals with likely Crohn and sarcoidosis were excluded. As the majority of previous clinical studies of OFG-like diseases included Crohn disease and those with hypersensitivity reactions, their findings should be interpreted with caution as these disorders may behave and respond to therapy differently from OFG.[4,5,7,9]

With regard to epidemiologic findings, our case series had a male:female ratio of 1.2:1, which accords with the majority of previous reports.[4,9,11-14] These studies also suggest that OFG may develop at any age and only one study reported that young individuals are more frequently affected than adults.[5] Our results are in accordance with the latter as we found that the majority of patients (26 of 49; 53.1%) in our series were younger than 30 years and about two-thirds (32 of 49; 65.3%) were younger than 40 years at diagnosis. It remains difficult to explain why more women than men were given a diagnosis at an older age. We can speculate that individual and gender-related factors able to modulate the onset and manifestations of the disease are likely to exist.

White-British and white-other were the most common reported ethnic group (85.7%) with Asian, black-Caribbean, and black-African representing 14.3% of our patients. This ethnic distribution parallels that of general population of London as indicated by the United Kingdom 2001 census[15] and indeed OFG had been reported in patients from many parts of the world.[6,16-25] The clinical features of OFG are known to be multiple and multifocal, potentially affecting intraoral mucosa, gingivae, facial tissues, and the craniofacial nervous system.[4,6] In agreement with these reports,[4,6,11,13] OFG in the current series of patients typically gave rise to recurrent/persistent painless facial (mainly of the lips) swelling (75.5%) and long-standing painful ulceration (36.7%). Cervical lymphadenopathy has not been frequently described in association with OFG, but was found in 10 (20.4%) of the current patients. It can cause facial/submandibular swelling and may reflect, at least in some individuals, granulomatous lymphadenitis, as observed in the mesenteric lymph node of Crohn disease.[26]

Gingival inflammation and/or enlargement unrelated to plaque or a drug were observed in 26.5% of the current group of patients. This is a similar prevalence to that reported in a previous group of United Kingdom residents with OFG[4] but twice as common as that reported in a group of patients' resident in Italy.[6]

Neurologic manifestations are reported to affect up to 33% of patients with OFG,[4,6,27,28] and were observed in two (4.1%) of our patients at presentation and in the medical history of another two (4.1%) patients. In the current study the neurologic manifestations all occurred at the early stage of disease suggesting that patients who do not present neurologic involvement at early stage are unlikely to develop it afterward. OFG does not seem to be associated with any significant hematologic abnormalities or serologic evidence of systemic inflammation (C-reactive protein, erythrocyte sedimentation rate), other granulomatous disorders (eg, serum angiotensin-converting enzyme), or gastroenterological involvement (eg, iron or folic acid anemia). All these parameters were normal in this group of patients, which in part reflects the inclusion criteria applied. These findings appear consistent with other reports that found no consistent hematologic and/or serologic abnormalities in patients with OFG.[13] OFG is considered to be a granulomatous disorder[4]; however, few studies have determined the exact frequency of granulomas in a large cohort of homogenous patients with OFG.[13] In the current study histopathological results were available for 37 (75.5%) patients. In general, the reports revealed a range of features and typical noncaseating granulomas were observed in only 43.2% (16) of the specimens, which is similar to the prevalence (46.4%) reported before by Williams et al.[9] Other studies reported that granulomas were found in 81% to 100% of affected patients.[4,13,29] It should be noted that two of these included patients with oral Crohn disease.[4,29] As reported earlier,[4,13] other histopathological features such as edema of the corium with dilated lymphatic and blood vessels and unspecific inflammatory infiltrate can characterize OFG and these were present in the histopathological lesional tissues examined in our study.

This analysis of OFG treatment showed that combined therapy (topical plus intralesional corticosteroids or systemic agents) was more frequently associated with partial/complete control of the facial manifestations of OFG than topical therapy alone. Even though the behavior of OFG was typically remittent, almost half of the patients showed complete resolution of facial swelling at last review. About a third of the patients responded only partially to therapy and in 12.8% of cases the treatment could only prevent further increase in facial swelling.

J Am Acad Dermatol
Volume 62, Number 4

Resistance to therapy, with worsening of the disease, was extremely uncommon (1/49; 2.0%).

Comparison of long-term clinical outcomes (as recorded at last review) with serial outcomes recorded during 6-month reviews demonstrated that facial swelling of OFG tends to improve slowly over time as long as therapy is provided. The percentage of patients with complete resolution of swelling increased from 36.2% during the course of therapy to 46.8% at last review whereas the percentage of patients with no significant improvement decreased from 25.5% to 12.8%. This means that a considerable number of patients who had not benefited from treatment in the short to medium term eventually showed partial and complete resolution in the long term.

With regard to the time needed to achieve clinical effectiveness, the results of the current study suggest that OFG responds slowly to treatment with 50% of the patients achieving complete resolution of the orofacial swelling within 3 years of treatment and only 25% of them doing so within the first year of therapy (Fig 2). However, a subanalysis of clinical outcome data suggests that intralesional corticosteroids are usually effective in the first weeks of treatment (data not shown). Intraoral ulceration was typically less responsive to treatment than facial swelling. Only a third of patients achieved complete resolution of intraoral ulceration whereas in the majority of cases treatment led to partial resolution only (41.7%) or prevention of further worsening (25%) of the mucosal disease. Comparison of long-term clinical outcomes (as recorded at last review) with serial outcomes recorded during 6-month reviews showed that intraoral ulceration of OFG uncommonly improves over time. The outcomes observed in the short/medium term overlapped those recorded in the long term (Table IV). Despite the wide range and longtime use of topical and/or systemic therapies used in the treatment of these patients with OFG, no consistent hematologic and/or serologic abnormalities were observed. A few patients undergoing long-term topical therapy developed oral candidosis that was managed by appropriate antimycotic agents such as nystatin. The other clinical ADRs were minor and were mostly observed in patients on systemic therapy. The main limitation of the current study relies in its retrospective design and associated methodological inadequacies including differences in reporting clinical features and outcome, lack of a control group, and variations in diagnostic and monitoring procedures.

The results of this study indicated that OFG is a disease of young adults whose ethnicity reflects that of the general population. Lip/facial swelling is the most common clinical manifestation of OFG leading the patients to seek medical attention. Among intraoral manifestations, the prevalence of cobblestoning, gingival enlargement, and mucosal changes exceeds that of oral ulceration. A wide range of topical, intralesional, and systemic agents can be used to control signs and symptoms. The improvement of tissue swelling and oral ulceration can be achieved in 78.8% and 70% of patients, respectively. Complete remission of facial swelling is possible in about half of patients within 3 years of therapy but may be achieved quicker when intralesional corticosteroids are used. A significant number of patients showing little response during the first months/years of therapy can eventually show significant improvement of facial swelling as long as the treatment is maintained. Intraoral ulceration is less responsive and short-term outcomes are usually maintained in the long term. Significant adverse side effects of therapy are rarely observed and spontaneous remission may rarely occur.

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