ORAL DISEASES

Oral Diseases (2014) 20, 35–54 doi:10.1111/odi.12193

www.wiley.com

ORAL MYTH SERIES

# Urban legend series: mucous membrane pemphigoid

**G Di Zenzo[1], M Carrozzo[2], LS Chan[3]**

[1]*Molecular and Cell Biology Laboratory, Istituto Dermopatico dell'Immacolata, IDI-IRCCS, Rome, Italy;* [2]*Department of Oral Medicine, Centre for Oral Health Research, Newcastle University, Newcastle upon Tyne, UK;* [3]*Department of Dermatology and Immunology/Microbiology, University of Illinois College of Medicine, Chicago, IL, USA*

**Mucous membrane pemphigoid (MMP) is a heterogeneous group of autoimmune subepithelial blistering diseases affecting primarily mucous membranes showing marked degree of clinical and immunological variability. We investigated four controversial topics: (i) Does oral pemphigoid (OP) really exist as a separate entity? (ii) Is mucous membrane pemphigoid curable? (iii) What is the best therapeutic option for MMP? (iv) Does exclusive oral IgA dermatitis exist as a distinct entity from MMP? Results from extensive literature searches suggested that (i) it is still unclear whether patients with OP could be considered as a distinct subset of MMP with specific clinical and immunological features; (ii) it is uncertain whether treatment regimens that get MMP under control can be eliminated to allow patients to be in drug-free remission or they should be continuously administered in some capacities; (iii) there is a concerning paucity of good-quality trials on MMP and available recommendations are solely based on generally small patients' cohorts or case series. Some of the 2002 consensus experts' opinions should be possibly updated, particularly regarding the safety of sulfa drugs; (iv) we did not find any strong evidence to support an exclusive oral (and perhaps also mucosal) form of LAD as a separate entity.**

*Oral Diseases* (2014) **20**, 35–54

**Keywords:** mucous membrane pemphigoid; oral pemphigoid; treatment; mucosal IgA linear dermatitis

## Introduction

Broadly defined, mucous membrane pemphigoid (MMP) is a heterogeneous group of putative autoimmune subepithelial blistering diseases affecting primarily mucous membranes, with or without some degrees of skin involvement (Chan *et al*, 2002). Scarring is the clinical hallmark; however, this is not always obvious, particularly in the oral mucosa (Chan *et al*, 2002). As a heterogeneous group of diseases, patients affected by MMP can develop autoantibodies that target a variety of known epithelial basement membrane structure components, bullous pemphigoid antigen 2 (BP180), alpha6 integrin, beta4 integrin, laminin-332, laminin-331, and type VII collagen (Bernard *et al*, 1992; Domloge-Hultsch *et al*, 1992; Chan *et al*, 1997; Chan *et al*, 1999; Bhol *et al*, 2000; Bhol *et al*, 2001; Chan *et al*, 2002; Malik *et al*, 2007; Letko *et al*, 2007). In some patients, the antigens of their autoantibodies targeted are not defined (Chan *et al*, 1991, 1993). The relative frequency of mucous membrane location affected is estimated to be oral > ocular > nasal > nasopharyngeal > anogenital > laryngeal > esophageal (Chan *et al*, 2002). The first consensus supported by 26 international experts in the field recommended that the diagnosis of MMP should be established by both clinical morphology and a direct immunofluorescence (DIF) finding of linear deposition of IgG, IgA, or C3 at the epithelial basement membrane zone (Chan *et al*, 2002). In this chapter of the Urban Legends series on controversial topics in oral medicine (Carrozzo, 2011), we focused on four questions about MMP: (i) Does oral pemphigoid really exist as a separate entity? (ii) Is mucous membrane pemphigoid curable? (iii) What is the best therapeutic option? (iv) Does exclusive oral IgA dermatitis exist as a distinct entity from MMP?

All along the text, the terms 'oral pemphigoid' (OP) and 'ocular pemphigoid' (OCP) have been used to indicate patients with exclusive lesions in the oral cavity and the eyes, respectively. The term 'MMP' has been used to define patients with predominant involvement of any mucosal areas either with or without any skin lesions.

## Does oral pemphigoid really exist as a separate entity?

As yet said, there is a marked degree of variability in the clinical and immunological features of MMP, suggesting the existence of several phenotypic variants. From a

Correspondence: Marco Carrozzo, MD, DSM (Turin 1995), Professor of Oral Medicine, School of Dental Sciences, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne NE2 4BW, UK.
Tel: +0044 191 222 7818, Fax: +0044 191 222 6137,
E-mail: marco.carrozzo@ncl.ac.uk
Received 17 July 2013; revised 17 September 2013; accepted 2 October 2013

diagnostic and therapeutic perspective, it might be of significant benefit to attempt to distinguish whether a clinical subset of MMP termed oral pemphigoid (OP) in which the disease is limited to the oral cavity really exists, mainly because it has been suggested that OP has a better prognosis compared to other MMP variants (Chan *et al*, 2002).

*From a therapeutic point of view*

In patients with MMP, scarring and the associated loss of function are the major complications, except usually for some patients in whom the disease is restricted to the oral mucosa. Interestingly, both IL-4 and IL-13 are thought to be involved in cicatricial scarring process in MMP (Bhogal *et al*, 2005; Giomi *et al*, 2005). Very recently, it has been suggested that the interleukin-4 receptor A (IL-4RA)-1902 A/A, a genotype that has been found in 90% of patients with OP, is associated with a reduced response to IL-4 and thus may explain a better clinical outcome for this group of patients (Carrozzo *et al*, 2013).

OP was originally reported to be associated with a better prognosis and to be more amenable to medical treatments (Chan *et al*, 2002). However, there is a paucity of long-term follow-up studies on MMP, and several case reports and cohort series report the difficult treatment for OP (Bohn *et al*, 1999; Ahmed and Colón, 2001; Sacher *et al*, 2002; Canizares *et al*, 2006; Segura *et al*, 2007; Carrozzo *et al*, 2008; Kasperkiewicz *et al*, 2011; Le Roux-Villet *et al*, 2011). At least 21 cases of OP recalcitrant to even doses such as 100 mg per daily of prednisolone (Pred) and other immunosuppressive/immunomodulant drugs, including intravenous cyclophosphamide (CYC), have been published (Table 1). In those patients, modalities such as plasma exchange, tumor necrosis factor alpha antagonists, intravenous immunoglobulins (IVIg), and even rituximab (RTX) were used to control, sometimes only temporarily, the oral lesions (Table 1). Because the limited number of reports existed in the literature, at the present time it is not possible to definitively determine whether the exclusive oral involvement may account for a significant difference in the response to therapy and more research is needed to identify the most effective treatment options.

*From a clinical presentation point of view*

Because MMP is not a single entity, it does not have a unified and predictable natural history. In some patient, the disease is localized and has a slowly progressive course without complications; in others, it is devastating, with severe morbidity. At the present time, it is clear that only in a subset of the total MMP patients studied, the disease remains localized to the oral cavity. An important point to address is whether the exclusive oral involvement is only a stage of MMP course, often presents at disease onset, or represents the phenotype of a distinct clinical entity.

Mobini and co-workers have studied 29 MMP patients with disease confined to the oral cavity in which a long-term follow-up study showed that no other mucosae or the skin was involved (mean length of follow-up was 6.7 $\pm$ 2 years) (Mobini *et al*, 1998). Furthermore, a

**Table 1** Treatment for recalcitrant oral mucous membrane pemphigoid (OP)

| *Author (year)* | *Country* | *Patients* | *Treatment* | *Duration of treatment (months)* | *Previous treatment* | *Response* |
|---|---|---|---|---|---|---|
| Bohn *et al* (1999) | Germany | 1 | Plasmapheresis plus CYC IV (12 mg $kg^{-1}$) followed by oral CYC (150–200 mg $day^{-1}$) | NA | DDS, Pred, topical steroids | CR |
| Ahmed and Colón (2001) | USA | 8 | IVIg 1–2 mg $kg^{-1}$ per cycle | Mean: 32.9 (range: 26–42) | DDS, topical steroids | 100% CR |
| Ahmed and Colón (2001) | USA | 3 | Pred (40–80 mg $day^{-1}$) plus MTX (25 mg $week^{-1}$) or AZA (150 mg $day^{-1}$) or AZA plus MTX (20 mg $day^{-1}$) plus CYC (150 mg $day^{-1}$) | Mean: 38.8 (range: 33–45) | DDS, topical steroids | 67% CR |
| Sacher *et al* (2002) | Germany | 1 | Etanercept 25 mg per subcutaneously per twice weekly plus Pred (60 mg $day^{-1}$ | NA | Pred, AZA, MMF | CR |
| Canizares *et al* (2006) | USA | 1 | Etanercept 25 mg per subcutaneously per twice weekly | NA | Topical steroids | CR |
| Segura *et al* (2007) | Spain | 2 | IVIg 2 mg $kg^{-1}$ per cycle alone or plus Pred and CYC | NA | DDS, Pred, AZA, CYC | PR |
| Carrozzo *et al* (2008) | Italy | 1 | MMF (2 g $day^{-1}$) plus Mino (200 mg $day^{-1}$) | 6 | Pred, AZA, topical steroids, topical tacrolimus | CR |
| Kasperkiewicz *et al* (2011) | Germany | 1 | RTX (375 mg $m^{-2}$ per week for 4 consecutive weeks) | NA | DDS, Pred | CR |
| Le Roux-Villet *et al* (2011) | France | 3 | RTX (375 mg $m^{-2}$ per week for 4 consecutive weeks | NA | DDS, CYC, IVIg, Pred, Aza, MMF | 100% CR |

CYC, cyclophosphamide; NA, not available; DDS, dapsone; CR, complete response; PR, partial response; IVIg, intravenous immunoglobulin; MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate mofetil; Mino, minocycline; RTX, rituximab.

long-term follow-up study of a large cohort of 70 patients with OP (comprising 51 patients already analyzed in previous studies) showed that no other mucosae or the skin was involved during the course of the disease (mean length of follow-up was 9.1 years) (Malik *et al*, 2007).

By contrast, two independent groups reported that MMP patients with exclusive oral involvement at disease onset could later on develop ocular lesions with an incidence ranging from 0.03 to 0.07 per person-year over 5 years of follow-up (Thorne *et al*, 2004; Higgins *et al*, 2006).

Recently, 20 patients with OP followed up for almost 3 years were immunologically characterized. All patients included in this study had had exclusively oral lesions without scarring during the entire follow-up period (Calabresi *et al*, 2007).

Notably, a recent research suggests that patients with OP, with antibodies to integrin alpha6 (see below), may have a possible reduced relative risk for developing cancer compared to anti-laminin 332-positive patients (Egan *et al*, 2001; Matsushima *et al*, 2004; Malik *et al*, 2007).

Although in several long-term follow-up studies, MMP with exclusive oral involvement does not develop lesions in other sites during the course of the disease and also seems to be often associated with a good prognosis, the categorization of OP as a separate entity should be restricted on the homogeneous immunological and immunopathological features of a specific MMP subset. Notably, the identical genetic predisposition of having HLA-DQB1*03:01 allele (formerly known as DQB1*0301) could lead to OP phenotype as well as ocular MMP (OCP) and other MMP (Delgado *et al*, 1996; Carrozzo *et al*, 2001; Carrozzo *et al*, 2013).

*From an immunological point of view*

Circulating autoantibodies (IgG and rarely IgA) can be detected in MMP by indirect immunofluorescence (IIF) on normal or salt-split human skin. Patients with MMP confined to the oral cavity often do not have circulating IgG antibodies (Scully *et al*, 1999; Chan *et al*, 2002). Immunostaining results assessed by DIF and IIF appeared similar between MMP with the involvement of multiple sites and those with exclusive oral involvement (Carrozzo *et al*, 2004).

Immunoblotting (IB) and enzyme-linked immunosorbent assay (ELISA) have simplified the diagnostic process and have identified novel protein targets recognized by autoantibodies of MMP (Zillikens *et al*, 1997; Schumann *et al*, 2000; Bhol *et al*, 2001; Lee *et al*, 2003; Mariotti *et al*, 2004). However, the characterization of target antigens of humoral immune response in OP has showed some discordant results.

A first study in a group of six MMP patients with disease limited to the oral cavity (not in all) showed circulating autoantibodies reacting against a 168-kDa oral mucosal protein (Ghohestani *et al*, 1996). Further studies neither confirmed this finding nor characterized the unknown target antigen.

Several recent studies, all performed in the same laboratory, subsequently demonstrated that OP circulating autoantibodies target the α6 integrin subunit in a region between fibrinogen repeats III and IV and are capable of inducing a separation of the epithelium from the basement membrane of normal human buccal mucosa in organ culture (Bhol *et al*, 2001; Rashid *et al*, 2006a,b; Mignogna *et al*, 2006). Absorption studies showed that OP sera reacted exclusively against α6 integrin subunit and from bovine or human gingiva. The OP autoantibody anti-α6 integrin was absent in patients in a prolonged remission and not detected in the sera of patients with MMP involving multiple mucosal membranes. In addition, no serologic reactivity to BP antigens or to other currently recognized MMP antigens has been reported (Chan *et al*, 1993; Mobini *et al*, 1998; Rashid *et al*, 2006b). A further follow-up study indicates that the extent and severity of the oral disease correlates with the titer of antibody against α6 integrin (Sami *et al*, 2002b). Finally, an important limitation of all these studies remains the lack of *in vivo* functional data in inducing blisters in living animals.

In contrast to these results, two independent studies on MMP and OP show that their sera contain IgG antibodies to the two major BP antigens, BP180 and BP230, regardless of their distinct clinical presentations (Egan *et al*, 1999; Carrozzo *et al*, 2004). In addition, a more recent study showed that 75% of a cohort of 20 OP patients without scarring phenotype had circulating autoantibodies against BP180 antigen, supporting the notion that this molecule represents a major target antigen in patients with OP (Calabresi *et al*, 2007). Similar results were also obtained in a study on a large cohort of MMP with scarring phenotype and involvement of various mucosal sites (Oyama *et al*, 2006). Most of the autoantibodies from OP patients were directed against epitopes in the BP180 ectodomain, similarly to what reported for MMP with multiple mucosal sites (Balding *et al*, 1996; Bedane *et al*, 1997; Murakami *et al*, 1998). In addition, OP sera displayed a low frequency of reactivity against the immune-dominant region of BP180 termed NC16A (45%), as previously reported for patients with MMP (Murakami *et al*, 1998; Schmidt *et al*, 2001). In contrast with previously reported data, none of OP sera reacted against a 120-kDa protein by immunoblotting on keratinocyte extract, suggesting the absence of autoantibodies against the α6 integrin subunit (Carrozzo *et al*, 2004; Egan *et al*, 1999; Calabresi *et al*, 2007). However, the lack of correlation analysis between disease severity and anti-BP180 reactivity during the course of OP disease and experiments on mouse model to establish the possible pathogenic role of these specific autoantibodies are the major limitations of these studies.

Altogether these data show that the IgG reactivity against α6 integrin in oral mucosa could be a key immunological feature of patients with OP never detected in other MMP clinical subsets. However, the reactivity against BP180 is shared by both OP and MMP patients, regardless of whether they have the cicatricial phenotype. In this context, a possible role of anti-α6 integrin autoantibodies in the pathogenesis of OP has been postulated. Because integrin α6β4 interacts with laminin through the binding in the region between fibrinogen repeats III and IV to stabilize skin BMZ (Kikkawa *et al*, 2000), autoantibodies from patients with OP may perturb this binding possibly leading to BMZ separation.

Some controversial points of these studies remain to clarify. Firstly, although in both oral mucosa and skin there is the same variant of integrin subunit (alfa6A), OP sera reactivity against α6 integrin subunit was always detected by IB on extracts from a human prostate cancer cell line (DU145), human and bovine gingival, while it was never detected on keratinocyte extracts. Secondly, because α6 integrin is a hemidesmosomal component of mucosa and skin, autoantibodies against integrin could induce lesions both in mucosa and in skin. In fact, α6β4 gene-knockout mice die shortly after birth having an extensive blistering of the skin and other stratified squamous epithelium (Georges-Labouesse *et al*, 1996), and patients with junctional epidermolysis bullosa carrying mutations in the integrin α6β4 genes manifest cutaneous blistering and pyloric atresia (Ashton *et al*, 2001). Contrary to what is expected for a humoral response against α6 integrin, patients with OP possess mucosal lesions without skin involvement and organ culture model shows that OP sera were able to separate basement membrane zone in normal buccal mucosa showing no effect on cultured human skin.

Last but not least, the results on integrin α6 have to be duplicated by other independent groups.

*Conclusion*

In conclusion, it is still unclear whether patients with OP could be considered as a distinct subset of MMP with specific clinical and immunological features such as (i) exclusive involvement of oral mucosa even after a long-term follow-up study, rarely scarring and typically associated with a good prognosis, and (ii) specific recognition of α6 integrin subunit. As discussed above and also below, long-term follow-up and therapeutic studies are scarce and available evidence seems controversial. Moreover, the lack of well-verified serologic markers and the absence of *in vivo* studies to definitively assess pathogenic activity of OP autoantibodies do not lead to an unequivocal answer to the original question, and further studies are warranted.

## Is mucous membrane pemphigoid curable?

If curability is defined as the patient will be in total remission without the need for continuous treatment, the answer should be possibly no. Theoretically, MMP, as an autoimmune disease, cannot be cured, as autoreactive T cells can be persisted in the patients' lymphoid system for indefinite period of time and can always activate B cells to produce autoantibodies that cause the disease.

However, it has been shown that complete and long-lasting remission without treatment can be induced in a more serious than MMP blistering disease such as pemphigus vulgaris (PV), in up to 75% of patients after 10 years (Herbst and Bystryn, 2000). Thus, a comparable control of the disease could be likely achieved in MMP. Indeed, several studies report complete response of patients with MMP to treatment (see below Table 4). However, available evidence provides information on remission at only a single point and they do generally not allow to determine how often remissions occur, how long it takes to achieve those, and how long remissions last. Only 4 small studies with an average follow-up of 67 months (Table 2) show long-term outcome of patients with MMP, and three of them are from the same center (Ahmed and Colón, 2001; Sami *et al*, 2002a,b); thus, a single-center bias cannot be excluded.

In at least one of these trials, 15 MMP patients with multiple mucosal involvement experienced complete remission off therapy for an average of only 24 months (Sami *et al*, 2002a).

Thus, it is still uncertain whether treatment regimens that get MMP under control can be eliminated to allow patients to be in drug-free remission or they should be continuously administered in some capacities. Well-controlled, long-term studies, enrolling larger cohort of patients, are clearly warranted to better clarify the actual prognosis of MMP and to ascertain the pattern of remission, if any, for this group of diseases.

## What is the best therapeutic option for MMP?

*Introduction*

Because of the rarity of the disease (Bernard *et al*, 1995; Zillikens *et al*, 1995; Rauz *et al*, 2005; Bertram *et al*, 2009), clinical trials of treatments for MMP are scarce and often enroll only a limited number of patients with heterogeneous entities. Indeed, MMP is highly variable and does not have a predictable natural history. In some patients, the disease is localized and has a slowly progressive course without complications; in others, it causes severe morbidity (Scully *et al*, 1999).

A wide range of treatment modalities has been employed in MMP (Table 3), but randomized controlled trials are scarce (Kirtschig *et al*, 2003).

In 2002, an international consensus statement on treatment for MMP developed by a group of experts, mainly from dermatology field, issued its opinion on therapeutic approaches (Chan *et al*, 2002). If the mucosal lesions are localized to oral cavity, topical corticosteroid and dapsone (DDS) should be the first line of medications. If more control is needed, a low dose of systemic corticosteroid or immunosuppressive agent (such as azathioprine [AZA] or mycophenolate mofetil [MMF]) could be added. If other mucosae are affected, more aggressive treatment options are needed, including immunosuppressive agents such as cyclophosphamide (CYC), AZA, and MMF (Chan *et al*, 2002). In cases of rapidly progressed diseases, particularly ocular disease, CYC was considered the best choice (Chan *et al*, 2002; Thorne *et al*, 2008). However, a Cochrane systematic review on MMP treatment, first published in 2003 (Kirtschig *et al*, 2003) and lastly updated in April 2005, found only limited evidence that MMP involving the eyes responds best to treatment with CYC combined with corticosteroids.

To address the above cited question, we have conducted a review of studies reporting medical intervention for MMP from the date of last update of the Cochrane review.

*Methods*

A search of the pertinent literature was performed by two authors (L.S.C and M.C.) using Medline/PubMed, limiting

**Table 2** Long-term remission in mucous membrane pemphigoid (MMP)

| *Author (year)* | N | *Sites of involvement* | *Treatment* | *Mean duration of treatment (months)* | *Duration of remission (months)* | *Total duration of follow-up (months)* | *Maintenance treatment* |
|---|---|---|---|---|---|---|---|
| Ahmed and Colón (2001) | 10 | Mouth ($N = 10$) | IVIg, MTX, Pred, AZA | 33 | Mean: 14 (range: 11–18) | 61 (range: 51–74) | Unclear |
| Sami *et al* (2002a) | 15 | Mouth ($N = 14$); eyes ($N = 13$); nose ($N = 7$); esophagus ($N = 6$); pharynx ($N = 3$); vagina ($N = 2$), larynx ($N = 2$); anal ($N = 1$) | Pred, DDS, AZA, MTX, CYC, Doxy, Tacro, Tetra, IVIg | 103 | Mean: 24 (range: 12–72) | 127 (range: 50–248) | None |
| Sami *et al* (2002b) | 7 | Mouth ($N = 7$) | IVIg, Triamc | 27 | Mean: 22 (range: 15–36) | 59 (range:48–80) | Unclear |
| Le Roux-Villet *et al* (2011) | 13 | Unclear | RTX, DDS, SAZ, MMF, Pred | 3 | Mean: 17 (range: 3–46) | 22 (range: 5–49) | DDS, SAZ |

CYC, cyclophosphamide; DDS, dapsone; IVig, intravenous immunoglobulin; MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate mofetil; Doxy, doxycycline; SAZ, sulfasalazine; Tacro, tacrolimus; Tetra, tetracycline; Triamc, triamcinolone acetonide; RTX, rituximab.

the search to human clinical trials published in any language from May 1, 2005, to March 23, 2013, using the following terms: 'mucous membrane pemphigoid OR cicatricial pemphigoid AND treatment OR Therapy'. Eligible studies were randomized controlled trials (RCTs) and uncontrolled and controlled, not randomized, therapeutic studies of MMP involving 5 or more participants who received medical intervention for MMP. The diagnosis should be confirmed in all cases by immunofluorescence study findings. The studies included in the last published version of the Cochrane review were also checked, as well as the reference lists from identified studies. When selective reporting was evident, studies were excluded. When possible, the studies were then rated based on quality and potential for bias according to Richards (2009).

*Results*

Three RCTs (Foster, 1986; El-Darouti *et al*, 2011), all of uncertain quality (Richards, 2009), and 42 non-randomized trials on the treatment for MMP were identified (Tables 4 and 5). Sixteen of these 45 studies, including all the 3 RCTs, investigated patients with predominantly OCP, 10 patients with predominantly OP, and the other 19 mixed patients. Sixteen of these studies, including one RCT (Foster, 1986) commented on sulfa drugs (DDS, sulfapyridine, sulfamethoxypyridazine, sulfasalazine), sometimes associated with other medications. Whereas most of the patients benefited from these medications to some extent, complete and permanent remissions were rare, the patients experienced commonly adverse effects (AE), and up to 33% discontinued the drug due to those AE.

Sixteen trials, including a RCT (Foster, 1986), employed different modalities of prednisolone, whereas another RCT (El-Darouti *et al*, 2011) used intravenous methylprednisolone. Generally, systemic corticosteroids were successful, mainly with various adjuvant drugs, although some studies reported the lack of efficacy of prednisolone alone (Nisengard and Rogers, 1987; Nayar and Wojnarowska, 1993). Systemic corticosteroids can commonly cause side effects but they are generally manageable and rarely need complete drug discontinuation.

Nine studies, including 2 RCTs (Foster, 1986; El-Darouti *et al*, 2011), used oral or intravenous cyclophosphamide (CYC) in various dosages and with several other drugs. CYC seems particularly effective for aggressive OCP or recalcitrant MMP, particularly associated with prednisolone, but it causes AE in up to 77% of patients and leads to high rates of discontinuation.

Eight trials commented on azathioprine (AZA). In all but two (Bialasiewicz *et al*, 1994; Pasadhika *et al*, 2009), AZA was used as steroid-sparring agent and the results were usually positive. There is a scarcity of data on AE of AZA for MMP, but according to a large study on ocular inflammatory diseases (Pasadhika *et al*, 2009), the drug was discontinued for AE at a rate of 0.16 per person-year (95% CI, 0.11–0.22).

Seven trials assessed intravenous immunoglobulins (IVIg) also as a monotherapy, and the overall response rate was 100%. Impressively, IVIg were apparently never

**Table 3** Treatment modalities for mucous membrane pemphigoid (MMP)

| *Surgical* | *Topical* | *Systemic* | |
|---|---|---|---|
| Low-energy | *Corticosteroids* | *Corticosteroids* | *Sulfonamides* |
| laser phototherapy Amniotic | Triamcinolone acetonide | Methylprednisolone | Dapsone |
| membrane transplantation | Betamethasone valerato | Prednisolone | Sulfapyridine |
| Cryotherapy | Beclomethasone dipropionate | *Other immunosuppressants* | Sulfamethoxypyridazine |
| Cultivated oral mucosal | Budesonide | Azathioprine | Sulfasalazine |
| epithelial transplantation (COMET) | Clobetasol propionate | Cyclophosphamide | *Tetracyclines* |
| Keratoprosthesis | Fluocinolone acetonide | Cyclosporine | Tetracycline |
| | Fluocinonide | Leflunomide | Doxycycline |
| | *Calcineurin inhibitors* | Methotrexate | Minocycline |
| | Tacrolimus | Mycophenolate mofetil | Other |
| | Cyclosporine | *Biologics* | Colchicine |
| | *Antibiotics* | Etanercept/ | Interferon α-2b |
| | Mitomycin C | infliximab | Intravenous Ig |
| | | Daclizumab | Nicotinamide |
| | | Rituximab | Immunoadsorption |
| | | | Pentoxifylline |
| | | | Plasmapheresis |
| | | | Thalidomide |

discontinued due to side effects and they could control MMP better than other conventional therapies (Letko *et al*, 2004).

Various topical corticosteroids (clobetasol propionate, fluocinonide, fluocinolone acetonide) have been primarily used in five studies, mostly involving patients with OP, and with apparently very positive results and virtually no drop-out (Table 4).

Five studies (Nayar and Wojnarowska, 1993; Poskitt and Wojnarowska, 1995; Reiche *et al*, 1998; Carrozzo *et al*, 2009; Chaidemenos *et al*, 2011) commented on cycline family of drugs (mainly minocycline) with and without nicotinamide, the results of which are controversial with a discontinuation rate up to 67%.

Five trials analyzed mycophenolate mofetil (MMF) efficacy with general positive results. MMF has also been used without concurrent systemic corticosteroids in OCP and OP (Zurdel *et al*, 2001; Ingen-Housz-Oro *et al*, 2005; Carrozzo *et al*, 2008) with promising results, and it is apparently safer than CYC.

Two trials used rituximab (RTX) in particular recalcitrant MMP cases, and this drug showed encouraging results. It should, however, be emphasized that two patient died as a result of RTX treatment (Le Roux-Villet *et al*, 2011).

Treatment with colchicine (Chaidemenos *et al*, 2011), cyclosporine (Kaçmaz *et al*, 2010), and methotrexate (Gangaputra *et al*, 2009) has been described in single trials (Table 4).

*Discussion*

Comparing to the latest version of the Cochrane review on treatment for MMP, we found 9 more studies but the amount of evidence to determine the best treatment for this disease remains scarce. Only three small RCTs were found, and in all of them, allocation concealment was unclear. Many of the non-randomized studies are small, retrospective case series combining a wide range of medications at different dosages. The lack of uniform outcome measures was another drawback. The largest cohorts are from ophthalmologists but these are mainly focused on ocular effects and commonly exclude other mucosal or skin lesions, thus making the applicability very limited.

*Anti-inflammatories*

Some medications such as tetracycline or sulfa drugs that were deemed promising (Kirtschig *et al*, 2003) are now under serious scrutiny for their safety profile (Wertheim *et al*, 2006; Hegarty *et al*, 2010; Carrozzo *et al*, 2009). Cycline group of medications can rarely cause clinical remission, have little effect on ocular disease, and can cause serious and frequent adverse effects, particularly minocycline (Carrozzo *et al*, 2010). Sulfa drugs, particularly dapsone (DDS), have been widely employed in MMP, but still their efficacy is unclear because of the lack of good-quality RCTs. DDS therapy may cause a variety of adverse effects, which may be categorized as pharmacologic, dose dependent, and allergic, or idiosyncratic reactions (Gürcan and Ahmed, 2009). Some degree of anemia is common using DDS but also severe adverse effects such as meta-hemoglobinemia (Kirtschig *et al*, 1998), agranulocytosis (Raizman *et al*, 1994), DDS hypersensitivity syndrome (Risse *et al*, 1994), and peripheral neuropathy (Foster, 1986) have been reported in patients with MMP. AE are supposed to be dose related and mostly not serious at daily dose below 100 mg, but the evidences are controversial (Table 3). In a recent comprehensive review on DDS in bullous disorders, 41% of the patients with MMP experience AE and overall 14% of the treated patients discontinued DDS due to AE (Gürcan and Ahmed, 2009). Other sulfa drugs such as sulfamethoxypyridazine (SMXP) have been reported to be of value and better tolerated than DDS in the treatment for MMP, but they also can cause potentially fatal AE such as allergic alveolitis (Steinfort *et al*, 1989; McFadden *et al*, 1989).

**Table 4** MMP: non-randomized studies

| *Author (year)* | N | *Treatments* | *Trial duration* | *Outcome and adverse events (AE)* | *Comments* |
|---|---|---|---|---|---|
| Rogers *et al* (1982) | 24 (oral [OP]and ocular [OCP]) | 75–200 mg day$^{-1}$ DDS *plus* Pred/Aza/CYC at various dosages in 14 patients | NA | 20 (83%) responded; 2 (8%) in prolonged remission but 1 recurred and treated with Pred + AZA AE in 9 (37.5%); discontinued in 4 (16.7%) | In 4 patients, DDS was not effective and they responded to Pred + Aza |
| Foster *et al* (1982) | 26 OCP | 1–2 mg kg day$^{-1}$ CYC + 20–80 mg day$^{-1}$ Pred (Group 1) *vs* Pred (Group 2) *vs* topicals (Group 3) | 3 months | 14 (78%) in Group 1 responded; all patients in Groups 2–3 had progression of the disease. AE in 3/18 (17%) discontinued because of gastrointestinal upset | No randomized controlled study |
| Nisengard and Rogers (1987) | 44 OP (all with desquamative gingivitis) | Fluo 0.05% or Fluo 0.01% ($N$ = 17); DDS (25–150 mg day$^{-1}$) or Sulfa (0.5–1.5 g day$^{-1}$) ($N$ = 16); Pred (unclear dosage) ($N$ = 3); no treatment ($N$ = 8) | NA | 31 (70%) responded: 15 (88%) on topical steroids, 15 (94%) on Dap or sulfapyridine, and 1 (12%) with no treatment. No response with Pred AE: NA | Not stated Pred dosage |
| Rogers and Mehregan (1988) | 77 (16 OP, 30 OCP, and 31 MMP) | 150 mg day$^{-1}$ DDS or 1.5–3 g day$^{-1}$ Sulfa | 12 weeks (minimum) | 15 OP (94%), 21 MMP (68%), and 26 (87%) improved; unclear if on remission AE: NA | Follow-up of Rogers *et al* (1982) |
| McFadden *et al* (1989) | 15 OP, MMP | 500–1500 mg SMXP | 3 months | 10 (67%) responded 1 (7%) in remission AE: 1 (allergic alveolitis) | Allergic alveolitis can be life-threatening and has been reported before as a result of SMXP therapy in MMP |
| Mondino (1990) | 139 OCP | 1.5 mg kg day$^{-1}$ CYC ($N$ = 13); 1.5 mg kg day$^{-1}$ CYC + 20 mg day$^{-1}$ Pred ($N$ = 17); 1.5 mg kg day$^{-1}$ Aza ($N$ = 10); 60–80 mg day$^{-1}$ Pred ($N$ = 11); combined treatment ($N$ = 51); no treatment ($N$ = 35) | NA | Pred better option for stages 1–2 disease; Pred + CYC overall better than other modalities. Non-treated seems to have more progression AE: NA | Unclear difference between several modalities |
| Tauber *et al* (1991) | 117 OCP | 2 mg kg day$^{-1}$ DDS ($N$ = 59) plus Pred ($N$ = 8) *vs* 2 mg kg day$^{-1}$ CYC ($N$ = 25, additional Pred in 23?) *vs* 2 mg kg day$^{-1}$ Aza ($N$ = 23, additional Pred in 2?) | NA | DDS was the most effective initial agent for modestly active OCP; Cyclo was the most effective initial choice for highly active cases AE: NA | No significant differences were found comparing progression rates |
| Lamey *et al* (1992) | 50 (40 OP, 9 OCP, and 1 MMP) | Fluo ($N$ = 19) *vs* Fluo + other topicals *vs* systemics including Pred 40 mg day$^{-1}$ + topicals ($N$ = 14) *vs* Pred + Aza 50 mg day$^{-1}$ ($N$ = 3) *vs* DDS 100 mg day$^{-1}$ ($N$ = 2) *vs* Pred + CYC 50 mg day$^{-1}$ ($N$ = 1) | 1–48 weeks | All (100%) responded to Fluo, Fluo+other topicals, Aza and Pred + Cyclo; all but one responded to Pred + topicals (93%) and half (50%) to DDS + topicals. Unclear remission rates as just mentioned 'asymptomatic' AE: NA | Patients treated in 2 different countries (UK and USA). No further details provided |
| Fern *et al* (1992) | 5 OCP (2 with oral lesions) | 50–150 mg day$^{-1}$ DDS | NA | All (100%) responded and underwent remission but relapsed off DDS AE in 2 (40%) (jaundice and hemolysis) | One patient needed systemic steroids when severe corneal and scleral involvement occurred. Some patients had also topical antibiotic and corticosteroids |

(continued)

**Table 4** (continued)

| *Author (year)* | N | *Treatments* | *Trial duration* | *Outcome and adverse events (AE)* | *Comments* |
|---|---|---|---|---|---|
| Nayar and Wojnarowska (1993) | 48 MMP | 40–60 mg day$^{-1}$ Pred ($N$ = 15); 50–150 mg day$^{-1}$ DDS ($N$ = 14); 100–150 mg day$^{-1}$ Aza ($N$ = 9); 50–100 mg day$^{-1}$ Mino ($N$ = 10); 0.5–1 g day$^{-1}$ SMXP ($N$ = 1) | NA | 5(30%) on Pred, 7(50%) on DDS/SMXP, and 2 (20%) on Mino responded AE: unclear; 6 (43%) discontinued DDS; many discontinued Aza | In all groups, additional topical or low-dose oral corticosteroids may have been used |
| Bialasiewicz *et al* (1994) | 9 OCP | 120–150 mg day$^{-1}$ Aza + nasal mucosal graft | NA | 9 (100%) responded; unclear if in remission AE: NA | Recurrence of symblepharon in 2 when AZA stopped |
| Poskitt and Wojnarowska (1995) | 7 (6 with oral lesions; 5 MMP and 2 OP) | 50–100 mg day$^{-1}$ Mino | 3–39 months (average: 10 months) | 6 (86%) responded (symptomatic improvement); none in remission AE: 6 (86%), mainly pigmentation | Patients were also taking topical and systemic steroids |
| Carrozzo *et al* (1997) | 11 (all with oral lesions; 9 OP and 2 MMP) | Clob 0.05% in 4% hydroxyethyl cellulose gel ($N$ = 8); Clob + prednisone 25–100 mg day$^{-1}$ ($N$ = 3) | 2–27 months | All (100%) responded; 6 (54%) complete remission after 5.7 months on average AE:4 (36%);none discontinued | Patients taking Clob were also given chlorhexidine 0.12% and miconazole gel |
| Reiche *et al* (1998) | 8 MMP (1 OP) | 100 mg day$^{-1}$ Mino + nicotinamide 2.5–3 g day$^{-1}$ | NA | 7 (87%) responded; no complete remission AE in 3 (37%); 1 (12.5%) discontinued | One patient used oxytetracycline 1 g day$^{-1}$. Duration of tetracycline treatment unclear |
| Carbone *et al* (1998) | 6 (all with oral lesions; 3 OP and 3 MMP) | 50–100 mg Pred | 20–80 days | All (100%) responded; 2 (33%) complete remission AE: 4 (67%); none discontinued | Two complete remissions were achieved using Pred 100 mg day$^{-1}$ |
| Ciarrocca and Greenberg (1999) | 20 MMP (15 OP) | Fluo 0.05%($N$ = 9); Fluo + 50–175 mg day$^{-1}$ DDS ($N$ = 11) | NA | 20 (100%) responded; 9 (45%) complete remission: 2 (10%) on Fluo alone and 7 (35%) on DDS + Fluo AE: unclear; 2 (10%) discontinued DDS | 11 patients who fail to be controlled by topical steroids were successfully treated adding DDS |
| Foster and Ahmed (1999) | 10 (6 OCP, 4 MMP, 3 with oral lesions) | IVIg 2–3 g kg$^{-1}$ per cycle over 3 days, every 2–6 weeks, increased by response (mean of 19 cycles) | 18 months | All (100%) responded; 9 (90%) in remission but under treatment AE: none | All patients did not respond to DDS, Pred, Aza, Cyclo, MTX, topicals. All continue to take Pred + immunosuppressives during trial |
| Thornhill *et al* (2000) | 25 MMP (8 OP) | 1 g day$^{-1}$ SMXP | 0.1–26 months | 22(88%) responded; 5 (20%) complete remission AE in 6 (24%), 3 (12% discontinued SMXP) | No intention-to-treat analysis. Three patients were also taking Pred or Pred + Aza |
| Ahmed and Colón (2001) | 20 OP | IVIg 1–2 mg kg$^{-1}$ per cycle over 3 days every 3–4 weeks, increased to 6, 8, 10, 12, 14, 16 weeks (mean: 18 cycles) (Group 1, $N$ = 8) *vs* Pred 0.5–1 mg kg day$^{-1}$ plus immunosuppressants (Group 2, $N$ = 12) | 26–42 months (Group 1) 33–51 months (Group 2) | All eight patients in Group 1 (100%) complete remission *vs* 6 (50%) in Group 2 AE: 3(37%) Group 1; 12 (100%) in Group 2; none discontinued in both groups | All patients were unresponsive to DDS and topical corticosteroids |
| Doan *et al* (2001) | 9 OCP (3 with oral and 1 with skin lesions) | Sulfa 1–4 g day$^{-1}$ | NA | 6 (66%) responded; none on remission AE: 3 (33%), all discontinued | All with DDS-related AE 2 patients had also CYC |

(continued)

**Table 4** (continued)

| *Author (year)* | N | *Treatments* | *Trial duration* | *Outcome and adverse events (AE)* | *Comments* |
|---|---|---|---|---|---|
| Zurdel *et al* (2001) | 5 OCP | MMF 2 g $day^{-1}$ | NA | All (100%) responded. None in remission. In one eye, the inflammatory process restarted after surgery due to symblepharon AE: unclear | Four of the five patients had been treated before with Cyclo ($n$ = 1), DDS ($n$ = 1), AZA ($N$ = 1), AZA + cyclosporine ($N$ = 1). The treatment had been ineffective or had to be stopped due to AE |
| Musette *et al* (2001) | 9 MMP (7 with oral lesions) | IV CYC 20 mg $kg^{-1}$ per month; if unresponsive after 4 boluses, CYC given every 3 weeks, and the dose was increased 25% every three boluses (mean: 11 cycles) | NA | All (100%) responded; 7 (78%) complete remission, but in only 3 medication stopped AE: 6 (67%), none discontinued | All patients took other drugs, Pred ($N$ = 1), Pred + DDS ($N$ = 1), Pred + Sulfa ($N$ = 2), DDS($N$ = 2), DDS + Sulfa($N$ = 3) that failed to control the disease |
| Sami *et al* (2002a,b) | 15 MMP | IVIg 1–2 mg $kg^{-1}$ per cycle over 3 days every 3–4 weeks, increased to 6, 8, 10, 12, 14, 16 weeks (mean of 25 cycles) | 13–39 months | All (100%) responded; all (100%) into remission after 24 months since stopping IVIg AE:NA | 12 patients were previously treated with Pred + immunosuppressive drugs (12) or Pred alone (3) and they were not in control Topical medications were also provided and for the mouth also 15–20 mg $ml^{-1}$ of intralesional triamcinolone acetonide (TA) |
| Gonzalez-Moles *et al* (2003) | 22 OP | Clob 0.05% plus nystatin 100 000 IU $ml^{-1}$ in orabase 3 day in gingival trays | 2 months | All (100%) responded; unclear how many went into remission AE: none | Results were grouped together with oral lichen planus |
| Letko *et al* (2004) | 14 OCP | IVIg 2 g $kg^{-1}$ at 2–4-week intervals (Group 1) *vs* various immunosuppressive drugs (including Pred, CYC, DDS, tacrolimus) (Group 2) | 16–30 months (Group 1) 21–90 months (Group 2) | Median time for clinical remission in Group 1 and Group 2 was 4 and 8.5 months, respectively ($P < 0.01$). All 8 patients in Group 1 did not progress *vs* 2/6 in Group 2 AE: 4 (50%) in Group 1, all (100%) in Group 2; none discontinued | Unclear dosages of immunosuppressive drugs |
| España *et al* (2005) | 5 MMP (1 OP) | Triamcinolone acetonide 0.1% + 100 mg $day^{-1}$ DDS ($N$ = 1); 20–30 mg $day^{-1}$ Pred + 100 mg $day^{-1}$ DDS + 750–1000 mg $m^{-2}$ IV CYC ($N$ = 3); Pred + DDDS + CYC + plasmapheresis ($N$ = 1) | NA | All (100%) responded; all (100%) into remission but one patient still taking Dap AE:NA | One patient required several sessions of plasmapheresis |
| Ingen-Housz-Oro *et al* (2005) | 14 MMP | 1.5–2 mg kg $day^{-1}$ MMF | NA | 10 (71%) responded; 5 (36%) complete remission AE: 1 (7%) pancytopenia and gastrointestinal effects | All the patients received other drugs (i.v. CYC or DDS/Sulfa) before or jointly MMF |

(continued)

**Table 4** (continued)

| *Author (year)* | N | *Treatments* | *Trial duration* | *Outcome and adverse events (AE)* | *Comments* |
|---|---|---|---|---|---|
| Thorne *et al* (2008) | 78 MMP (70 OCP) | 1 mg kg day$^{-1}$ Pred+ 2 mg kg day$^{-1}$ CYC ($N$ = 63); CYC ($N$ = 5); Pred ($n$ = 5); Pred+ other immunosuppressive drugs (including MMF, DDS, clorambucil, $N$ = 5); 100–150 mg day$^{-1}$, DDS ($N$ = 1); DDS + CYC ($N$ = 1) | 3–204 months | 58 (83%) of 70 OCP had achieved complete control of the inflammation after 1 year; 50 (71%) had complete remission of ocular inflammation. Initial treatment with Pred+Cyclo was more likely to produce an ocular remission AE: unclear overall number 34 (49%) infections; 8 (12%) malignancy; 16 (23%) discontinued | Cross-sectional retrospective study; reports data just for eyes; AE only reported for CYC |
| Mignogna *et al* (2008) | 6 MMP | IVIg 2 g kg$^{-1}$ per over 3–5 days at 4-week intervals (mean of 16 cycles)+Pred and immunosuppressive drugs | 8–20 months | All (100%) responded and in complete remission AE: unclear | Unclear dosage of Pred and immunosuppressive drugs |
| Gangaputra *et al* (2009) | 58 OCP | 12.5–22.5 mg week$^{-1}$ MTX | NA | 38 (66%) complete remission AE: unclear; overall 52% discontinued MTX (but also other diseases counted) | Likely many patients also taking Pred at unknown dosage. Most of the patients still taking Pred |
| Pasadhika *et al* (2009) | 33 OCP | ≤125 mg day$^{-1}$ Aza ($N$ = 20); Aza+other immunosuppressive drugs ($N$ = 13) | NA | 21 (64%) responded; 15 (45%) complete remissionAE: unclear as data pooled together with other diseases | 24% of the 145 patients with various ocular inflammatory diseases stopped Aza because of AE |
| Carrozzo *et al* (2010) | 9 MMP (7 OP) | 100–200 mg day$^{-1}$ Mino | 4–16 months | 6 (67%) responded; 1 (11%) complete remission AE: 6 (67%), all discontinued Mino | 5 patients were also taking clobetasol propionate |
| Foster *et al* (2010) | 12 OCP | RTX 375 mg m$^{-2}$ (once weekly) and IVIg (2 g kg$^{-1}$) (Group 1) *vs* other immunosuppressive drugs (Group 2) | 2 months | All six patients in Group 1 had not disease progression, 6 patients in Group 2 became blind in both eyes AE: none | 10 patients were blind in one eye |
| Daniel *et al* (2010) | 18 OCP | MMF dosage unclear (≤2 g day$^{-1}$) | NA | 13 (72%) complete remission AE: unclear as the data on OCP were grouped with other disorders | Likely all patients also taking Pred at unknown dosage Only ocular effectiveness considered |
| Pujari *et al* (2010 | 98 OCP | CYC 75–150 mg day$^{-1}$ | NA | 69 (70%) effective; 60 (61%) complete remission AE: unclear; overall 33% discontinued Cyclo (but also other diseases counted) | Likely many patients also taking Pred at unknown dosage Only ocular effectiveness considered |
| Hegarty *et al* (2010) | 20 (all oral lesions; 9 OP) | 50–150 mg day$^{-1}$ DDS | 1–46 months | 8 (40%) responded AE: 11 (55%). Discontinued in all 11 | All patients took also topical betamethasone or fluticasone |
| Kaçmaz *et al* (2010) | 6 OCP | Cyclosporine dosage unclear (≤2–3.5 mg kg day$^{-1}$) | NA | All (100%) responded; unclear remission rate AE: unclear; unclear discontinuation rate | Likely many patients also taking Pred at unknown dosage Only ocular effectiveness considered |
| Doycheva *et al* (2011) | 10 OCP | 2 g day$^{-1}$ MMF ($N$ = 4); MMF+Pred 1 mg kg day$^{-1}$ | NA | All (100%) responded; 6 (60%) complete response but still in treatment AE: 7 (70%); 1 (10%) discontinued | All patients received also topical cyclosporine and 2 were given topical dexamethasone |

(continued)

**Table 4** (continued)

| *Author (year)* | N | *Treatments* | *Trial duration* | *Outcome and adverse events (AE)* | *Comments* |
|---|---|---|---|---|---|
| Chaidemenos *et al* (2011) | 15 MMP (all with oral lesions) | 1–1.5 mg $day^{-1}$ colchicine +Pred 40 mg $day^{-1}$ ($N = 12$); DDS 100 mg $day^{-1}$ + Pred ($N = 10$); Aza unclear dosage + Pred ($N = 2$); 1 g $day^{-1}$ CYC + Pred ($N = 4$); MMF unclear dosage + Pred ($N = 1$); cyclosporine + Pred ($N = 1$); tetracycline–nicotinamide + Pred ($N = 2$) | NA | 8 (67%) Colchicine-treated patients responded, 3 (25%) in complete remission; 3 (30%) responded and in remission with DDS; 50% responded with Aza and CYC, 1 (25%) in remission with CYC; none responded with the others AE: 2 (20%) discontinued DDS and 1 (8%) colchicine | Colchicine best steroid-sparing drug but unclear if effective in severe cases |
| Le Roux-Villet *et al* (2011) | 25 MMP | 375 mg $m^{-2}$ weekly for 4 weeks RTX, 1–2 cycles jointly with DDS (1 mg kg $day^{-1}$) and/or sulfasalazine (1–3 g $day^{-1}$) and/or topical steroids | 1.5–6 months | 22 (88%) had a complete remission but 10 experienced relapse AE: 3 severe infectious complications, 2 (8%) died | All patients had recalcitrant MMP (21 to DDS and/or sulfasalazine, 10 to Pred, 3 to IVIg and 20 to several immunosuppressants) |
| Staines and Hampton (2012) | 6 MMP (all oral lesions) | 500–1500 mg $day^{-1}$ MMF + 25–100 mg $day^{-1}$ DDS + 30–80 mg $day^{-1}$ Pred | | All (100%) responded and in remission but all patients still under medication AE: 3 (50%) all from DDS; 2 (33%) discontinued DDS | 1 patient took also minocycline/doxycycline, and all used topical corticosteroids MMF and DDS given at different times in all patients |
| Munyangango *et al* (2013) | 13 MMP | CYC (2 mg kg $day^{-1}$) | ½–4.3 months | 9 (63%) responded, 7 (54%) had complete remission AE: 10 (77%), 6 (46%) discontinued | 10 patients took also DDS; 2 sulfasalazine |

NA, not available; CYC, cyclophosphamide; Pred, prednisolone; DDS, dapsone; Fluo, fluocinolone acetonide; Sulfa, sulfapyridine; SMXP, sulfamethoxypyridazine; Minocycline, Mino; Clob, clobetasol propionate; Sulfa, sulfasalazine; IVIg, intravenous immunoglobulin; MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate mofetil; Doxy, doxycycline; SAZ, sulfasalazine; Tacro, tacrolimus; Tetra, tetracycline; Triam, triamcinolone acetonide; RTX, rituximab.

**Table 5** MMP: randomized studies

| *Author (year)* | N | *Treatments* | *Trial duration* | *Methods* | *Outcome and adverse events (AE)* | *OCEBM quality rating/source of bias* |
|---|---|---|---|---|---|---|
| Foster (1986) | 24 (14 OCP; 10 with extra-ocular lesions; 6 with oral lesions) | CYC (2 mg kg day$^{-1}$) plus Pred (1 mg kg day$^{-1}$) (Group A, $N = 12$) *vs* Pred alone (Group B, $N = 12$) plus placebo (dextrose) | 6 months | Double-blind; randomized (table of random numbers, 'incomplete block design', were placed in sequentially numbered sealed envelopes) | All (100%) improved in Group A *vs* 5 (42%) in Group B; unclear if in remission AE: All (100%) in Group A and Group B; none discontinued | 2B/small sample; doubt about the concealment of allocation; lack of clarity on the drug regimen in the follow-up period |
| Foster (1986) | 40 (21 OCP, 19 with extra-ocular lesions; unclear oral involvement) | DDS 2 mg kg day$^{-1}$ (Group A, $N = 20$) *vs* CYC (2 mg kg day$^{-1}$) (Group B, $N = 20$) | 3 months | Double-blind; randomized: table of random numbers, 'incomplete block design', were placed in sequentially numbered sealed envelopes | All (100%) improved in Group B *vs* 14 (70%) in Group A; unclear if in remission AE: unclear | 2B/small sample, doubt about the concealment of allocation; lack of clarity on the drug regimen in the follow-up period; unclear if the tablets were exactly the same |
| El-Darouti *et al* (2011) | 30 OCP | 500 mg day$^{-1}$ IV MethylPred for 5 days and 500 mg day$^{-1}$ IV CYC therapy on the first day of pulse steroid (Group A, $N = 15$) *vs* 1.2 g for 3 days I.V pentoxifylline plus pulse steroid and CYC therapy (Group B, $N = 15$) | 6 months | Single-blinded (?); randomized: computer-generated random sequence; sequence was kept in the pharmacy | Nine patients (60%) in Group A and 12 (80%) in Group B responded; unclear if in remission. All patients in Group B did not progress, whereas 2 (13%) in Group A did. AE: NA | 2B/; small sample; unclear how the blind design was achieved; unclear allocation, unclear duration of treatment |

CYC, cyclophosphamide; Pred, prednisolone; MethylPred, methylprednisolone; DDS, dapsone.

*Corticosteroids*

Contrarily, topical corticosteroids have an excellent compliance and seem effective, particularly clobetasol propionate used for OP, and they can also lead to remission (Carrozzo *et al*, 1997; Gonzalez-Moles *et al*, 2003). RCTs are needed in order to evaluate the true value in the treatment of topical corticosteroids. Systemic glucocorticoids have traditionally a central role in the management of blistering diseases, but the data for MMP, essentially of prednisolone, are rather patchy. Many trials have used these medications, mostly together with other immunosuppressive drugs (Table 4-5). It is well known that glucocorticoids at high dose and for prolonged courses are associated with significant adverse effects. Although the main long-term complication of systemic corticosteroids, which is osteoporosis, can be now efficiently prevented (Tee *et al*, 2012), the overall safety and optimal dosage regimen are still an issue.

*Immunosuppressives*

Diverse drugs such as CYC, AZA, and MMF have been proposed as systemic immunomodulatory agents for MMP in more than one study. Two small RCTs (Foster, 1986) have suggested that CYC and prednisolone are more effective than the latter alone in suppressing ocular MMP progression and that CYC is better than DDS. Given the above highlighted risk of bias, these results need to be interpreted with caution and it is unclear whether CYC also works for other MMP variants or whether it is of significant benefit without corticosteroids. A very recent open trial suggests that oral CYC (2 g per daily) without corticosteroids has a rapid efficacy in refractory MMP. However, almost half of the patients discontinued CYC due to the AE of lymphopenia (Munyangango *et al*, 2013).

Similarly, AZA and MMF appear to work as adjuvant agents, but they have been rarely used without corticosteroids and they are generally considered less toxic but also no so beneficial as CYC (Ingen-Housz-Oro *et al*, 2005). However, a direct comparison is lacking and there are not enough data for a reliable safety comparison of these immunosuppressive drugs.

*Intravenous Immunoglobulin (IVIg)*

IVIg is a blood product prepared by cold ethanol fractionation from the pooled plasma of 10 000 $\pm$ 20 000 donors per batch (Jolles, 2001). The use of IVIg in MMP seems promising not only to improve clinical status and reduce systemic corticosteroids but also to prevent disease progression and relapse. The majority of patients were treated with 2–3 gm kg$^{-1}$ per cycle every 2 weeks concurrently with systemic immunosuppressive agents. This frequency of IVIg cycling is considerably greater than that used to treat other autoimmune bullous diseases. IVIg is a relatively safe and well-tolerated therapy, but serious adverse effects requiring discontinuation have been reported in MMP (Segura *et al*, 2007). This treatment modality often requires patients' hospitalization and is an expensive biological product. However, according to a recent study, when the cost of treating the side effects caused by the conventional immunosuppressive therapy is included, IVIg is statistically more cost-effective (Daoud and Amin,

**Table 6** Reported cases of linear IgA disease with predominant mucosal involvement

| *Author (year)* | *Setting* | *Gender; Age* | *Lesions location* | *Histopathology* | *DIF* | *IIF* | *IB* | *Treatment/Course* |
|---|---|---|---|---|---|---|---|---|
| Kumar *et al* (1980) | Dermatology | F; 69 | Oral, ocular | Liquefaction degeneration of basal layer and lymphoplasmacytic dermal infiltrate | IgA | Neg | NA | Sulfones; corticosteroids/PR |
| Leonard *et al* (1984)[a] | Dermatology | M; 65 | Oral (gingival) | NA | IgA | NA | NA | NA |
| Leonard *et al* (1984)[a] | Dermatology | M; 59 | NA | NA | IgA | NA | NA | NA |
| Hietanen *et al* (1985)[a] | Dentistry | F; 61 | Oral, ocular, nasal, genital, skin | NA | IgA | NA | NA | Dapsone 50 mg day$^{-1}$ per PR with evidence of scarring |
| Chan *et al* (1990) | Dermatology | F; 76 | Oral, laryngeal, vaginal, skin | | IgA | | | |
| Porter *et al* (1990) | Dentistry | M; 69 | Oral (gingival) | Subepithelial split | IgA, C3 | NA | NA | |
| Porter *et al* (1992) | Dentistry | M; 29 | Oral (gingival) | Subepithelial split | IgA | NA | NA | Sulfapyridine/CR |
| Kirtschig *et al* (1998)[a] | Dermatology | M; 38 | Oral (gingival) | NA | IgA | Neg | Neg | Dapsone 50–100 mg day$^{-1}$; sulfamethoxypyridazine 1500 mg day$^{-1}$; prednisone 20 mg day$^{-1}$; topical hydrocortisone/PR with scarring |
| Lazzaro and Lazzaro (1999) | Ophthalmology | M; 59 | Oral (buccal mucosa), ocular | NA | IgA | NA | NA | NA/scarring |
| Cohen *et al* (1999) | Dentistry | F; 78 | Oral (gingival) | Subepithelial split, lichenoid infiltrate | IgA | NA | NA | Topical clobetasol propionate; clotrimazole troches and chlorhexidine; dapsone 25 mg day$^{-1}$ per CR |
| Cohen *et al* (1999) | Dentistry | F; 58 | Oral (gingival and buccal mucosa) | Lichen planus; ulceration with chronic inflammation | IgA | NA | NA | Tetracycline and niacinamide; sulfapyridine; dapsone/PR |
| Egan *et al* (1999) | Dermatology | NA | Oral | NA | IgA | IgA | IgA to LABD-97 | NA |
| Smith *et al* (1999) | Ophthalmology | F; 65 | Oral (gingival, palatal), ocular, skin (leg) | Stromal fibrosis with a lymphocytic inflammatory infiltrate | IgA, IgG, C3 | Neg | NA | Dapsone 200 mg day$^{-1}$; sulfapyridine 1.5 g day$^{-1}$; prednisolone 1 mg kg day$^{-1}$; cyclophosphamide 100 mg day$^{-1}$ per PR with evidence of scarring |
| Letko *et al* (2000) | Ophthalmology | M; 67 | Ocular | NA | IgA | IgA | IgA to LABD-97 | Prednisolone 60 mg day$^{-1}$; intravenous Ig 4 g kg$^{-1}$ per month per CR |
| Eguia del Valle *et al* (2003) | Dentistry | F; 72 | Oral (gingival) | Subepithelial split, lymphoplasmacytic dermal infiltrate | IgA, fibrinogen | NA | NA | Topical triamcinolone acetonide; clobetasol propionate; dapsone 50–100 mg day$^{-1}$ per PR |
| Eguia del Valle *et al* (2003) | Dentistry | M; 43 | Oral (gingival) | Subepithelial split, lymphoplasmacytic dermal infiltrate | IgA, fibrinogen | *NA* | *NA* | Topical clobetasol propionate; prednisolone 100 mg day$^{-1}$; doxycycline 50 mg day$^{-1}$; dapsone 50–150 mg day$^{-1}$ per PR |
| O'Regan *et al* (2004) | Dentistry | M; 50 | Oral (gingiva and buccal mucosa); laryngeal; pharyngeal; esophageal; skin (foot) | Subepithelial split containing abundant eosinophils | IgA | Neg | NA | Dapsone (50 mg day$^{-1}$), corticosteroids/CR |
| Sato *et al* (2005) | Otorynolaryngology | M;50 | Laryngeal; nasal; skin | NA | IgA | NA | NA | Corticosteroids; surgery/PR found dead at home probably because of accidental occlusion of the tracheostomy tube |

(continued)

**Table 6** (continued)

| *Author (year)* | *Setting* | *Gender; Age* | *Lesions location* | *Histopathology* | *DIF* | *IIF* | *IB* | *Treatment/Course* |
|---|---|---|---|---|---|---|---|---|
| Sato *et al* (2005) | Otorynolaryngology | M;67 | Pharynx; oral; skin | NA | IgA | NA | NA | Corticosteroids; PR (diagnosis of LAD made after resection of a malignant mesopharyngeal tumor) |
| Talhari *et al* (2006) | Ophthalmology | M;75 | Ocular | Subepithelial split, mixed infiltrate | IgA | Neg | NA | NA/blindness |
| Lewis *et al* (2007) | Dentistry | F;79 | Oral (palatal) | Subepithelial split, mixed infiltrate with prevalence of eosinophils | IgA | Neg | NA | Prednisolone 20 mg $day^{-1}$; azathioprine 100 mg $day^{-1}$; mycophenolate mofetil 1 g $day^{-1}$ per CR |
| Angiero *et al* (2007) | Dentistry | F;57 | Oral (gingival) | Subepithelial split, chronic infiltrate | IgA | NA | NA | Triamcinolone acetonide cream; methylprednisolone 32 mg $day^{-1}$ per CR |
| Leao *et al* (2008) | Dentistry | M;33 | Oral (gingival) | Subepithelial split | IgA | NA | NA | NA |
| Betts *et al* (2009) | Dentistry | M;44 | Oral (gingiva and buccal mucosae) | Subepithelial bulla filled with neutrophils and occasional eosinophils | IgA | NA | NA | Betamethasone mouthwash/NA |
| Sertznig and Megahed (2010) | Dermatology | M;69 | Oral, pharyngeal, esophageal | Subepithelial split, mixed infiltrate | IgA | Neg | NA | Mycophenolate mofetil; IV Ig |
| Dan *et al* (2011) | Dentistry | F;38 | Oral (gingival) | Subepithelial split | IgA | NA | NA | Triamcinolone acetonide injections; topical dexamethasone |
| Carbone *et al* (2012) | Dentistry | M;83 | Oral (gingival) | Subepithelial split | IgA | Neg | IgG to PBAg 1 and PBAg2 [b] | Clobetasol propionate |
| Carbone *et al* (2012) | Dentistry | F;47 | Oral (gingival); skin | Subepithelial split | IgA | Neg | IgA to BPAg2[b] | Topical clobetasol propionate; prednisolone 50 mg $day^{-1}$ per PR |
| Suresh and Neiders (2012) | Dentistry | M;56 | Oral (gingival) | NA | IgA | NA | NA | NA |
| Suresh and Neiders (2012) | Dentistry | F;81 | Oral (gingival) | NA | IgA | NA | NA | NA |

NA, not available.
aPublished as mucous membrane pemphigoid.
[b]Personal data not shown on Carbone *et al* (2012): both the patients were HLA-DQB*03:01 positive.

2006). RCTs are certainly warranted to confirm the above encouraging results on IVIg and determine the optimal protocol.

*Rituximab (RTX)*

RTX is a chimeric monoclonal anti-CD20 antibody that targets pre-B cells and mature B cells and has been increasingly used in blistering diseases (Cirillo *et al*, 2012). Since now, it has been used in 28 severe and recalcitrant MMP patients, almost always in association with immunosuppressive and anti-inflammatory drugs (Shetty and Ahmed, 2013). Although 96% of the patients went in complete remission, major attention should focus also on the immediate or delayed adverse effects of RTX treatment, as two patients died as a result of severe bacterial infections (Hertl *et al*, 2011). RTX might help to avoid major devastating complications of MMP, but the optimal protocol and safety issues need to be elucidated in more detail.

*Conclusion*

There is a concerning paucity of good-quality trials on MMP, and available recommendations are solely based on generally small patients' cohorts or case series. Some of the 2002 consensus experts' opinions (Chan *et al*, 2002) should be possibly updated, particularly regarding the safety of sulfa drugs. A number of therapeutic modalities, namely very high-potency topical corticosteroids, MMF, and IVIg, should be urgently examined in RCTs given the promising preliminary results. Those studies should conduct a more comprehensive assessment of the mucocutaneous involvement of patients with MMP. It would seem important that the future research focus on the prevention and reversal of the fibrotic/scarring process that would eventually lead to major functional impairment. However, these trials will likely be possible through a multidisciplinary approach of several international groups of clinicians (oral medicine specialists, dermatologists, ophthalmologist, and otorhinolaryngologists) interested in improving the outcome of MMP. Given the present state of knowledge, the first step in MMP management is establishing the diagnosis based upon both clinical features and immunological findings; this is to be followed, according to the signs and symptoms, by variable topical and/or systemic modalities/drugs mainly based upon clinician experience.

## Does exclusive oral IgA dermatitis exist as a distinct entity from MMP?

*Introduction*

Linear immunoglobulin A (IgA) bullous dermatitis (LABD) or linear IgA disease (LAD) is a unique immunobullous disease that was first recognized as an entity distinct from dermatitis herpetiformis (DH) or bullous pemphigoid (BP) on the basis of the immunopathological finding of linear IgA deposits in the basement membrane zone (BMZ) on direct immunofluorescence (DIF) by Chorzelski *et al* (1979). In addition, histologically, prominent neutrophilic infiltration is characteristic of this disease.

There is also a childhood variant of LAD termed chronic bullous dermatosis of childhood (CBDC). Currently, these disorders are widely recognized as a single entity with two variants: adult-onset LAD and childhood-onset LAD, with slightly different clinical features and different peaks of onset. CBDC occurs in children with a peak incidence of about 4.5 years, while LABD is a disease of adults mainly aged 60–65 years with a slight female predominance. Cutaneous manifestations of patients with LAD are serum- or blood-filled blisters that have risen out of normal skin, sometimes with an erythematous or urticarial base (Fortuna and Marinkovich, 2012). The blisters of LAD are generally tense and may be somewhat linear or 'sausage' like in shape and frequently tend to form annular or polycyclic plaques due to the coalescence of lesions. In CBDC, there is a typical localization on the lower abdomen and perineum, and the lesions can appear as 'cluster of jewels'. In adult LAD, the torso and limbs are most frequently involved, the latter on both flexural and extensor surfaces. Mucosal involvement, particularly in the mouth and the eyes, is common in both adult and childhood LAD (Kelly *et al*, 1988). Occasionally, eosinophils may be admixed among the predominantly neutrophilic infiltrate (Egan and Zone, 1999). The *conditio sine qua* non for the diagnosis of LAD is the presence of BMZ-specific IgA class antibody in a linear distribution on DIF of perilesional skin in the absence of other immunoglobulins (Egan and Zone, 1999). However, cases with occasional IgG and complement at the BMZ have been reported (Chan *et al*, 1995). LAD may be diagnosed based on the following three criteria: (i) the presence of a vesicular or bullous eruption, usually confined to the skin, but which may involve the mucous membranes; (ii) the presence of a subepidermal vesicle with a predominantly neutrophilic infiltrate on histology of lesional skin; and (iii) the presence of BMZ-specific IgA antibody deposited in a linear pattern in the absence of other immunoglobulins on DIF of perilesional skin (Egan and Zone, 1999; Fortuna and Marinkovich, 2012).

Most LAD patients develop IgA against 97-kDa (LABD-97) and 120-kDa (LAD-1) (Zone *et al*, 1990; Marinkovich *et al*, 1996) antigens. It now appears that both of these antigens are generated as proteolytic cleavage products of the BP180 ectodomain (Hirako *et al*, 1998; Zone *et al*, 1998).

LAD is described as being associated with the HLA alleles B8, DR3, and Cw7 (Collier *et al*, 1999), and despite the lack of RCTs, the best options for systemic therapy of LAD are sulfones (DDS) and sulfonamides (sulfapyridine or SMXP) (Fortuna and Marinkovich, 2012).

*Methods*

A PubMed search was performed using as a search strategy the Mesh terms 'oral OR mucosal linear IgA disease or dermatosis' with a time limit, March 2013. The reviewers further identified additional studies from citations in the reviewed literature.

*Results*

The literature search retrieved 29 cases of suspicious predominantly mucosal LAD (Table 6). All 29 patients were adults (mean age: 62 years, range: 29–83); males/females ratio was 16:12.

Since the publication of the consensus in 2002 (Chan *et al*, 2002), 15 cases have been published and the large majority of them (73%) by oral medicine specialists (Table 6). Four of the cases included in Table were diagnosed and published as cases of MMP (Leonard *et al*, 1984; Hietanen *et al*, 1985; Kirtschig *et al*, 1998). Twenty-five of 29 (86%) had oral lesions and 18 (62%) had exclusive oral, in most of the cases, gingival lesions. When clinical pictures were provided, almost all the oral lesions had the appearances suggestive of MMP. The main histologic features were a subepithelial split and a dermal inflammatory infiltrate, but just in one patient (Betts *et al*, 2009) with predominance of neutrophils. All but three cases had exclusive linear IgA staining at BMZ. Target antigen search was performed in five patients and showed IgA against 97-kD antigen (LAD-1) in two cases and against BPAg2 in another, IgG against BPAg 1 and 2 in the fourth and no antigen in the last one (Table 6). Notably, the two patients reported by Carbone *et al* (2012) were both HLA-DQB*03:01 positive (personal data not shown in the paper).

The course of the cases was mixed and not always reported but mostly with partial remission of the lesions. Different combinations of medications have been employed and the response to DDS/sulfones was variable. In six patients (21%), cicatricial lesions were observed leading to blindness in one case and requiring tracheostomy in another.

*Discussion*

Very rarely predominantly or exclusively mucosal LAD cases have been published. Moreover, in 2002, an international consensus proposed that subepithelial blistering disorders with predominant mucosal involvement previously classified as LAD or epidermolysis bullosa acquisita should be comprised under the same term of MMP because this disease can no longer be defined by a specific target antigen as multiple antigens have been identified by the autoantibodies of this group of patients (Chan *et al*, 2002). According to the consensus, direct methods of immunofluorescence microscopy or immunohistochemistry examinations on perilesional mucosa and/or skin biopsies showing continuous deposits at the BMZ of IgG, IgA, or C3 or combination are diagnostic of MMP (Chan *et al*, 2002).

These recommendations have been widely accepted in dermatology, but not always in dentistry (Torchia *et al*, 2008; Betts *et al*, 2009; Dan *et al*, 2011), as confirmed by our analysis of reported cases. More importantly, almost all the published cases of oral LAD did not show any common features clinically, histologically, and/or immunologically to justify a diagnosis different from MMP. According to two recent reviews, none but possibly two of the cases (only one with exclusive oral involvement, Table 1) might be considered LAD (Egan and Zone, 1999; Fortuna and Marinkovich, 2012).

Even if we agree that the results of immunopathological examinations can be sometimes ambiguous in LAD (Jin *et al*, 2012), target antigen search was not performed in most cases and immunogenetic analysis was almost never performed in the cases reported in Table 1. Indeed, further tests such as salt-split skin indirect immunofluorescence, immunoblot/immunoprecipitation, and ELISAs are sometimes needed to achieve a proper diagnosis and an effective treatment for subepithelial blistering disease (Calabresi *et al*, 2007; Carrozzo *et al*, 2008), but they are rarely used in the dental setting. As a result, misclassification of MMP is not uncommon in dentistry (Torchia *et al*, 2007; Carrozzo, 2009).

It should be indeed remarked that contrary to LAD, MMP is strongly associated with HLA-DQB* 03:01 regardless of the clinical phenotype, whereas existing evidence suggests that MMP sera commonly recognize BPAg 1 and 2, integrin $\alpha 6$ and $\beta 4$ and laminin 332, but not LAD antigens (LABD97 or LAD-1). Of note, two of the reported patients with predominantly oral LAD had IgA or IgG against BPAg 1 and 2 and were both associated with the typical MMP HLA-DQB* 03:01 allele (Table 6), supporting MMP as the final diagnosis.

*Conclusion*

We did not find any strong evidence to support an exclusive oral (and perhaps also mucosal) form of LAD as a separate entity. It is highly recommended to verify the presence of IgA autoantibodies using one or more of the above cited immunopathological tests (Fortuna and Marinkovich, 2012). Furthermore, we urge to investigate target antigens and typical HLA allele's link in every case suggestive of MMP. Moreover, we would suggest that future reports follow the 2002 consensus proposal (Chan *et al*, 2002) as a standard reporting method.

## Author contributions

M Carrozzo led the review team. Di Zenzo G and Chan L and Carrozzo M reviewed the literature, wrote sections, revised the full text and approved the submitted version.

## References

Ahmed AR, Colón JE (2001). Comparison between intravenous immunoglobulin and conventional immunosuppressive therapy regimens in patients with severe oral pemphigoid: effects on disease progression in patients nonresponsive to dapsone therapy. *Arch Dermatol* **137**: 1181–1189.

Angiero F, Benedicenti S, Crippa R, Magistro S, Farronato D, Stefani M (2007). A rare case of desquamative gingivitis due to linear IgA disease: morphological and immunofluorescence features. *In Vivo* **21**: 1093–1098.

Ashton GH, Sorelli P, Mellerio JE, Keane FM, Eady RA, McGrath JA (2001). $\alpha 6\beta 4$ integrin abnormalities in junctional epidermolysis bullosa with pyloric atresia. *Br J Dermatol* **144**: 408–414.

Balding SD, Prost C, Diaz LA *et al* (1996). Cicatricial pemphigoid autoantibodies react with multiple sites on the BP180 extracellular domain. *J Invest Dermatol* **106**: 141–146.

Bedane C, McMillan JR, Balding SD *et al* (1997). Bullous pemphigoid and cicatricial pemphigoid autoantibodies react with

ultrastructurally separable epitopes on the BP180 ectodomain: evidence that BP180 spans the lamina lucida. *J Invest Dermatol* **108**: 901–907.

Bernard P, Prost C, Durepaire N, Basset-Seguin N, Didierjean L, Saurat JH (1992). The major cicatricial pemphigoid antigen is a 180-kD protein that shows immunologic crossreactivities with the bullous pemphigoid antigen. *J Invest Dermatol* **99**: 174–179.

Bernard P, Vaillant L, Labeille B *et al* (1995). Incidence and distribution of sub-epidermal autoimmune bullous skin diseases in three French regions. *Arch Dermatol* **131**: 48–52.

Bertram F, Bröcker EB, Zillikens D, Schmidt E (2009). Prospective analysis of the incidence of autoimmune bullous disorders in Lower Franconia, Germany. *J Dtsch Dermatol Ges* **7**: 434–440.

Betts A, Yeoman CM, Farthing PM (2009). Oral mucosal involvement as the sole or main manifestation of linear IgA disease: case report and review of the literature. *Oral Surgery* **2**: 198–204.

Bhogal RK, Stoica CM, McGaha TL, Bona CA (2005). Molecular aspects of regulation of collagen gene expression in fibrosis. *J Clin Immunol* **25**: 592–603.

Bhol KC, Dans MJ, Simmons RK, Foster CS, Giancotti FG, Ahmed AR (2000). The autoantibodies to alpha 6 beta 4 integrin of patients affected by ocular cicatricial pemphigoid recognize predominantly epitopes within the large cytoplasmic domain of human beta 4. *J Immunol* **165**: 2824–2829.

Bhol KC, Goss L, Kumari S, Colon JE, Ahmed AR (2001). Autoantibodies to human alpha6 integrin in patients with oral pemphigoid. *J Dent Res* **80**: 1711–1715.

Bialasiewicz AA, Forster W, Radig H, Hüttenbrink KB, Grewe S, Busse H (1994). Syngeneic transplantation of nasal mucosa and azathioprine medication for therapy of cicatricial ocular mucous membrane pemphigoid. Study of 9 patients with 11 eyes. *Ophthalmologe* **91**: 244–250.

Bohn J, Jonsson S, Holst R (1999). Successful treatment of recalcitrant cicatricial pemphigoid with a combination of plasma exchange and cyclophosphamide. *Br J Dermatol* **141**: 536–540.

Calabresi V, Carrozzo M, Cozzani E *et al* (2007). Oral pemphigoid autoantibodies preferentially target BP180 ectodomain. *Clin Immunol* **122**: 207–213.

Canizares MJ, Smith DI, Conners MS, Maverick KJ, Heffernan MP (2006). Successful treatment of mucous membrane pemphigoid with etanercept in 3 patients. *Arch Dermatol* **142**: 1457–1461.

Carbone M, Carrozzo M, Castellano S, Conrotto D, Broccoletti R, Gandolfo S (1998). Systemic corticosteroid therapy of oral vesiculoerosive diseases (OVED). An open trial. *Minerva Stomatol* **47**: 479–487.

Carbone M, Broccoletti R, Gambino A *et al* (2012). Clinical and histological features of gingival lesions: a 17-year retrospective analysis in a northern Italian population. *Med Oral Patol Oral Cir Bucal* **17**: e555–e561.

Carrozzo M (2009). A reappraisal of diagnostic criteria for mucous membrane pemphigoid. *J Oral Pathol Med* **38**: 160.

Carrozzo M (2011). Urban legends. *Oral Dis* **17**: 753–754.

Carrozzo M, Carbone M, Broccoletti R, Garzino-Demo P, Gandolfo S (1997). Therapeutic management of mucous membrane pemphigoid. Report of 11 cases. *Minerva Stomatol* **46**: 553–559.

Carrozzo M, Fasano ME, Broccoletti R *et al* (2001). HLA-DQB1 alleles in Italian patients with mucous membrane pemphigoid predominantly affecting the oral cavity. *Br J Dermatol* **145**: 805–808.

Carrozzo M, Cozzani E, Broccoletti R *et al* (2004). Analysis of antigens targeted by circulating IgG and IgA antibodies in patients with mucous membrane pemphigoid predominantly affecting the oral cavity. *J Periodontol* **75**: 1302–1308.

Carrozzo M, Arduino PG, Baldovino S *et al* (2008). Minocycline in combination with mycophenolate mofetil in oral mucous membrane pemphigoid. *Eur J Dermatol* **18**: 198–200.

Carrozzo M, Arduino P, Bertolusso G, Cozzani E, Parodi A (2009). Systemic minocycline as a therapeutic option in predominantly oral mucous membrane pemphigoid: a cautionary report. *Int J Oral Maxillofac Surg* **38**: 1071–1076.

Carrozzo M, Dametto E, Fasano M *et al* (2013). Interleukin-4RA gene polymorphism is associated with oral mucous membrane pemphigoid. *Oral Dis* 10.1111/odi.12106. [Epub ahead of print].

Chaidemenos G, Sidiropoulos T, Katsioula P, Koussidou-Eremondi T (2011). Colchicine in the management of mucous membrane pemphigoid. *Dermatol Ther* **24**: 443–445.

Chan LS, Regezi JA, Cooper KD (1990). Oral manifestations of linear IgA disease. *J Am Acad Dermatol* **22**: 362–365.

Chan LS, Soong HK, Foster CS, Hammerberg C, Cooper KD (1991). Ocular cicatricial pemphigoid occurring as a sequela of Stevens-Johnson syndrome. *JAMA* **266**: 1543–1546.

Chan LS, Yancey KB, Hammerberg C *et al* (1993). Immune-mediated subepithelial blistering diseases of mucous membranes. Pure ocular cicatricial pemphigoid is a unique clinical and immunopathological entity distinct from bullous pemphigoid and other subsets identified by antigenic specificity of autoantibodies. *Arch Dermatol* **129**: 448–455.

Chan LS, Traczyk T, Taylor TB *et al* (1995). Characterization of a subset of patients with concurrent IgA and IgG anti-basement membrane autoantibodies. *Arch Dermatol* **131**: 1432–1437.

Chan LS, Majmudar AA, Tran HH *et al* (1997). Laminin-6 and laminin-5 are recognized by autoantibodies in a subset of cicatricial pemphigoid. *J Invest Dermatol* **108**: 848–853.

Chan RY, Bhol K, Tesavibul N *et al* (1999). The role of antibody to human beta4 integrin in conjunctival basement membrane separation: possible *in vitro* model for ocular cicatricial pemphigoid. *Invest Ophthalmol Vis Sci* **40**: 2283–2290.

Chan LS, Ahmed AR, Anhalt GJ *et al* (2002). The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* **138**: 370–379.

Chorzelski TP, Jablonska S, Beutner EH (1979). Linear IgA bullous dermatosis. Adult form of linear IgA bullous dermatosis. In: Beutner EH, Chorzelski TP, Bean SF, eds. *Immunopathology of the skin*. Wiley: New York, NY, pp. 315–319.

Ciarrocca KN, Greenberg MS (1999). A retrospective study of the management of oral mucous membrane pemphigoid with dapsone. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **88**: 159–163.

Cirillo N, Cozzani E, Carrozzo M, Grando SA (2012). Urban legends: pemphigus vulgaris. *Oral Dis* **18**: 442–458.

Cohen DM, Bhattacharyya I, Zunt SL, Tomich CE (1999). Linear IgA disease histopathologically and clinically masquerading as lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **88**: 196–201.

Collier PM, Wojnarowska F, Welsh K *et al* (1999). Adult linear IgA disease and chronic bullous disease of childhood: the association with human lymphocyte antigens Cw7, B8, DR3 and tumour necrosis factor influences disease expression. *Br J Dermatol* **141**: 867–875.

Dan H, Lu R, Li W, Chen Q, Zeng X (2011). Linear IgA disease limited to the oral mucosa. *J Am Acad Dermatol* **65**: 677–679.

Daniel E, Thorne JE, Newcomb CW *et al* (2010). Mycophenolate mofetil for ocular inflammation. *Am J Ophthalmol* **149**: 423–32.e1-2.

Daoud YJ, Amin KG (2006). Comparison of cost of immune globulin intravenous therapy to conventional immunosuppressive therapy in treating patients with autoimmune mucocutaneous blistering diseases. *Int Immunopharmacol* **6**: 600–606.

Delgado JC, Turbay D, Yunis EJ *et al* (1996). Common major histocompatibility complex class II allele HLA-DQB1* 0301 is present in clinical variants of pemphigoid. *Proc Natl Acad Sci USA* **93**: 8569–8571.

Doan S, Lerouic JF, Robin H, Prost C, Savoldelli M, Hoang-Xuan T (2001). Treatment of ocular cicatricial pemphigoid with sulfasalazine. *Ophthalmology* **108**: 1565–1568.

Domloge-Hultsch N, Gammon WR, Briggaman RA, Gil SG, Carter WG, Yancey KB (1992). Epiligrin, the major human keratinocyte integrin ligand, is a target in both an acquired autoimmune and an inherited subepidermal blistering skin disease. *J Clin Invest* **90**: 1628–1633.

Doycheva D, Deuter C, Blumenstock G, Stuebiger N, Zierhut M (2011). Long-term results of therapy with mycophenolate mofetil in ocular mucous membrane pemphigoid. *Ocul Immunol Inflamm* **19**: 431–438.

Egan CA, Zone JJ (1999). Linear IgA bullous dermatosis. *Int J Dermatol* **38**: 818–827.

Egan CA, Taylor TB, Meyer LJ, Petersen MJ, Zone JJ (1999). The immunoglobulin A antibody response in clinical subsets of mucous membrane pemphigoid. *Dermatology* **198**: 330–335.

Egan CA, Lazarova Z, Darling TN, Yee C, Coté T, Yancey KB (2001). Anti-epiligrin cicatricial pemphigoid and relative risk for cancer. *Lancet* **357**: 1850–1851.

Eguia del Valle A, Martinez-Sahuquillo A, Padrón JR, Urizar JM (2003). Two cases of linear IgA disease with clinical manifestations limited to the gingiva. *J Periodontol* **74**: 879–882.

El-Darouti MA, Fakhry Khattab MA, Hegazy RA, Hafez DA, Gawdat HI (2011). Pentoxifylline (anti-tumor necrosis factor drug): effective adjuvant therapy in the control of ocular cicatricial pemphigoid. *Eur J Ophthalmol* **21**: 529–537.

España A, del Olmo J, Marquina M, Fernández S, Panizo C, Maldonado M (2005). Mucous membrane pemphigoid: clinical manifestations and treatment with corticosteroids, dapsone and cyclophosphamide in 5 patients. *Actas Dermosifiliogr* **96**: 357–364.

Fern AI, Jay JL, Young H, MacKie R (1992). Dapsone therapy for the acute inflammatory phase of ocular pemphigoid. *Br J Ophthalmol* **76**: 332–335.

Fortuna G, Marinkovich MP (2012). Linear immunoglobulin A bullous dermatosis. *Clin Dermatol* **30**: 38–50.

Foster S (1986). Cicatricial pemphigoid. *Trans Am Ophthalmol Soc* **84**: 527–663 (pp 619–638).

Foster CS, Ahmed AR (1999). Intravenous immunoglobulin therapy for ocular cicatricial pemphigoid: a preliminary study. *Ophthalmology* **106**: 2136–2143.

Foster CS, Wilson LA, Ekins MB (1982). Immunosuppressive therapy for progressive ocular cicatricial pemphigoid. *Ophthalmology* **89**: 340–353.

Foster CS, Chang PY, Ahmed AR (2010). Combination of rituximab and intravenous immunoglobulin for recalcitrant ocular cicatricial pemphigoid: a preliminary report. *Ophthalmology* **117**: 861–869.

Gangaputra S, Newcomb CW, Liesegang TL *et al* (2009). Methotrexate for ocular inflammatory diseases. *Ophthalmology* **116**: 2188–2198.

Georges-Labouesse E, Messaddeq N, Yehia G, Cadalbert L, Dierich A, Le Meur M (1996). Absence of the $\alpha$6 integrin leads to epidermolysis bullosa and neonatal death in mice. *Nat Genet* **13**: 370–373.

Ghohestani RF, Nicolas JF, Rousselle P, Claudy AL (1996). Identification of a 168-kDa mucosal antigen in a subset of patients with cicatricial pemphigoid. *J Invest Dermatol* **107**: 136–139.

Giomi B, Caproni M, Fabbri P (2005). IL-4 and cellular adhesion molecule (CAM) pathway are involved in cicatricial pemphigoid scarring process. *J Dermatol Sci* **38**: 57–59.

Gonzalez-Moles MA, Ruiz-Avila I, Rodriguez-Archilla A *et al* (2003). Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays. *Oral Surg OralMed Oral Pathol Oral Radiol Endod* **95**: 688–692.

Gürcan HM, Ahmed AR (2009). Efficacy of dapsone in the treatment of pemphigus and pemphigoid: analysis of current data. *Am J Clin Dermatol* **10**: 383–396.

Hegarty AM, Ormond M, Sweeney M, Hodgson T (2010). Dapsone efficacy and adverse events in the management of mucous membrane pemphigoid. *Eur J Dermatol* **20**: 223–224.

Herbst A, Bystryn JC (2000). Patterns of remission in pemphigus vulgaris. *J Am Acad Dermatol* **42**: 422–427.

Hertl M, Bernard P, Borradori L (2011). Rituximab for severe mucous membrane pemphigoid: safe enough to be drug of first choice? *Arch Dermatol* **147**: 855–856.

Hietanen J, Rantala I, Reunala T (1985). Benign mucous membrane pemphigoid with linear IgA deposits in oral mucosa. *Scand J Dent Res* **93**: 46–51.

Higgins GT, Allan RB, Hall R, Field EA, Kaye SB (2006). Development of ocular disease in patients with mucous membrane pemphigoid involving the oral mucosa. *Br J Ophthalmol* **90**: 964–967.

Hirako Y, Usukura J, Uematsu J *et al* (1998). Cleavage of BP180, a 180-kDa bullous pemphigoid antigen, yields a 120-kDa collagenous extracellular polypeptide. *J Biol Chem* **273**: 9711–9717.

Ingen-Housz-Oro S, Prost-Squarcioni C, Pascal F *et al* (2005). Cicatricial pemphigoid: treatment with mycophenolate mofetil. *Ann Dermatol Venereol* **132**: 13–16.

Jin X, Wang L, Zeng X, Dan H (2012). Diagnosis of linear IgA disease: the results of immunopathologic examinations can be ambiguous. *J Am Acad Dermatol* **67**: 156–157.

Jolles SA (2001). Review of high-dose intravenous immunoglobulin (hdIVIg) in the treatment of the autoimmune blistering disorders. *Clin Exp Dermatol* **26**: 127–1231.

Kaçmaz RO, Kempen JH, Newcomb C *et al* (2010). Cyclosporine for ocular inflammatory diseases. *Ophthalmology* **117**: 576–784.

Kasperkiewicz M, Shimanovich I, Ludwig RJ, Rose C, Zillikens D, Schmidt E (2011). Rituximab for treatment-refractory pemphigus and pemphigoid: a case series of 17 patients. *J Am Acad Dermatol* **65**: 552–558.

Kelly SE, Frith PA, Millard PR *et al* (1988). A clinicopathological study of mucosal involvement in linear IgA disease. *Br J Dermatol* **119**: 161–170.

Kikkawa Y, Sanzen N, Fujiwara H, Sonnenberg A, Sekiguchi K (2000). Integrin binding specificity of laminin-10/11: laminin-10/11 are recognized by $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, integrins. *J Cell Sci* **113**: 869–876.

Kirtschig G, Mengel R, Mittag H, Flores-De-Jacoby L, Happle R (1998). Desquamative gingivitis and balanitis – linear IgA disease or cicatricial pemphigoid? *Clin Exp Dermatol* **23**: 173–177.

Kirtschig G, Murrell D, Wojnarowska F, Khumalo N (2003). Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. *Cochrane Database Syst Rev* **1**: CD004056.

Kumar V, Rogozinski T, Yarbrough C, Beutner EH, Chorzelski TP (1980). A case of cicatricial pemphigoid or cicatricial linear IgA bullous dermatosis. *J Am Acad Dermatol* **2**: 327–331.

Lamey PJ, Rees TD, Binnie WH, Rankin KV (1992). Mucous membrane pemphigoid. Treatment experience at two institutions. *Oral Surg Oral Med Oral Pathol* **74**: 50–53.

Lazzaro DR, Lazzaro EC (1999). Linear IgA dermatosis mimicking ocular cicatricial pemphigoid. *CLAO J* **25**: 197–199.

Le Roux-Villet C, Prost-Squarcioni C, Alexandre M *et al* (2011). Rituximab for patients with refractory mucous membrane pemphigoid. *Arch Dermatol* **147**: 843–849.

Leao JC, Ingafou M, Khan A, Scully C, Porter S (2008). Desquamative gingivitis: retrospective analysis of disease associations of a large cohort. *Oral Dis* **14**: 556–560.

Lee JB, Liu Y, Hashimoto T (2003). Cicatricial pemphigoid sera specifically react with the most C-terminal portion of BP180. *J Dermatol Sci* **32**: 59–64.

Leonard JN, Wright P, Williams DM *et al* (1984). The relationship between linear IgA disease and benign mucous membrane pemphigoid. *Br J Dermatol* **110**: 307–314.

Letko E, Bhol K, Foster S, Ahmed AR (2000). Linear IgA bullous disease limited to the eye: a diagnostic dilemma. Response to intravenous immunoglobulin therapy. *Ophthalmology* **107**: 1524–1528.

Letko E, Miserocchi E, Daoud YJ, Christen W, Foster CS, Ahmed AR (2004). A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies. *Clin Immunol* **111**: 303–310.

Letko E, Gürcan HM, Papaliodis GN, Christen W, Foster CS, Ahmed AR (2007). Relative risk for cancer in mucous membrane pemphigoid associated with antibodies to the beta4 integrin subunit. *Clin Exp Dermatol* **32**: 637–641.

Lewis MA, Yaqoob NA, Emanuel C, Potts AJ (2007). Successful treatment of oral linear IgA disease using mycophenolate. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **103**: 483–486.

Malik M, Gürcan HM, Christen W, Ahmed AR (2007). Relationship between cancer and oral pemphigoid patients with antibodies to alpha6-integrin. *J Oral Pathol Med* **36**: 1–5.

Marinkovich MP, Taylor TB, Keene DR *et al* (1996). LAD-1, the linear IgA bullous dermatosis autoantigen, is a novel 120-kDa anchoring filament protein synthesized by epidermal cells. *J Invest Dermatol* **106**: 734–748.

Mariotti F, Grosso F, Terracina M *et al* (2004). Development of a novel ELISA system for detection of anti-BP180 IgG and characterization of autoantibody profile in bullous pemphigoid patients. *Br J Dermatol* **151**: 1004–1010.

Matsushima S, Horiguchi Y, Honda T, Fujii S *et al* (2004). A case of anti-epiligrin cicatricial pemphigoid associated with lung carcinoma and severe laryngeal stenosis: review of Japanese cases and evaluation of risk for internal malignancy. *J Dermatol* **31**: 10–15.

McFadden JP, Leonard JN, Powles AV, Rutman AJ, Fry L (1989). Sulphamethoxypyridazine for dermatitis herpetiformis, linear IgA disease and cicatricial pemphigoid. *Br J Dermatol* **6**: 759–762.

Mignogna M, Lanza A, Rossiello L, Ruocco V, Ahmed AR (2006). Comparison of reactivity and epitope recognition between sera from American and Italian patients with oral pemphigoid. *Clin Exp Immunol* **145**: 28–35.

Mignogna MD, Leuci S, Piscopo R, Bonovolontà G (2008). Intravenous immunoglobulins and mucous membrane pemphigoid. *Ophthalmology* **115**: 752–752.e1.

Mobini N, Nagarwalla N, Ahmed AR (1998). Oral pemphigoid. Subset of cicatricial pemphigoid *Oral Surg Oral Med Oral Pathol Oral Radiol Endo* **85**: 37–43.

Mondino BJ (1990). Cicatricial pemphigoid and erythema multiforme. *Ophthalmology* **97**: 939–952.

Munyangango EM, Le Roux-Villet C, Doan S *et al* (2013). Oral cyclophosphamide without corticosteroids to treat mucous membrane pemphigoid. *Br J Dermatol* **168**: 381–390.

Murakami H, Nishioka S, Setterfield J *et al* (1998). Analysis of antigens targeted by circulating IgG and IgA autoantibodies in 50 patients with cicatricial pemphigoid. *J Dermatol Sci* **17**: 39–44.

Musette P, Pascal F, Hoang-Xuan T *et al* (2001). Treatment of cicatricial pemphigoid with pulse intravenous cyclophosphamide. *Arch Dermatol* **1**: 101–102.

Nayar M, Wojnarowska F (1993). Cicatricial pemphigoid: a re-evaluation of therapy. *J Dermatol Treat* **4**: 89–93.

Nisengard RJ, Rogers RS III (1987). The treatment of desquamative gingival lesions. *J Periodontol* **58**: 167–172.

O'Regan E, Bane A, Flint S, Timon C, Toner M (2004). Linear IgA disease presenting as desquamative gingivitis: a pattern poorly recognized in medicine. *Arch Otolaryngol Head Neck Surg* **130**: 469–472.

Oyama N, Setterfield JF, Powell AM *et al* (2006). Bullous pemphigoid antigen II (BP180) and its soluble extracellular domains are major autoantigens in mucous membrane pemphigoid: the pathogenic relevance to HLA class II alleles and disease severity. *Br J Dermatol* **154**: 90–98.

Pasadhika S, Kempen JH, Newcomb CW *et al* (2009). Azathioprine for ocular inflammatory diseases. *Am J Ophthalmol* **148**: 500–509.

Porter SR, Scully CM, Midda M, Eveson JW (1990). Adult linear immunoglobulin A disease manifesting as desquamative gingivitis. *Oral Surg Oral Med Oral Pathol* **70**: 450–453.

Porter SR, Bain SE, Scully CM (1992). Linear IgA disease manifesting as recalcitrant desquamative gingivitis. *Oral Surg Oral Med Oral Pathol* **74**: 179–182.

Poskitt L, Wojnarowska F (1995). Minimizing cicatricial pemphigoid orodynia with minocycline. *Br J Dermatol* **132**: 784–789.

Pujari SS, Kempen JH, Newcomb CW *et al* (2010). Cyclophosphamide for ocular inflammatory diseases. *Ophthalmology* **117**: 356–365.

Raizman MB, Fay AM, Weiss JS (1994). Dapsone-induced neutropenia in patients treated for ocular cicatricial pemphigoid. *Ophthalmology* **101**: 1805–1807.

Rashid KA, Stern JN, Ahmed AR (2006a). Identification of an epitope within human integrin alpha 6 subunit for the binding of autoantibody and its role in basement membrane separation in oral pemphigoid. *J Immunol* **176**: 1968–1977.

Rashid KA, Gürcan HM, Ahmed AR (2006b). Antigen specificity in subsets of mucous membrane pemphigoid. *J Invest Dermatol* **126**: 2631–2636.

Rauz S, Maddison PG, Dart JKG (2005). Evaluation of mucous membrane pemphigoid with ocular involvement in young patients. *Ophthalmology* **112**: 1268–1274.

Reiche L, Wojnarowska F, Mallon E (1998). Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy. *Clin Exp Dermatol* **23**: 254–257.

Richards D (2009). GRADING–levels of evidence. *Evid Based Dent* **10**: 24–25.

Risse L, Bernard P, Brosset A, Enginger V, Bedane C, Bonnetblanc JM (1994). Disulone hypersensitivity syndrome. *Ann Dermatol Venereol* **121**: 242–244.

Rogers RS III, Mehregan DA (1988). Dapsone therapy of cicatricial pemphigoid. *Semin Dermatol* **7**: 201–205.

Rogers RS III, Seehafer JR, Perry HO (1982). Treatment of cicatricial (benign mucous membrane) pemphigoid with dapsone. *J Am Acad Dermatol* **6**: 215–223.

Sacher C, Rubbert A, König C, Scharffetter-Kochanek K, Krieg T, Hunzelmann N (2002). Treatment of recalcitrant cicatricial pemphigoid with the tumor necrosis factor alpha antagonist etanercept. *J Am Acad Dermatol* **46**: 113–115.

Sami N, Bhol KC, Razzaque Ahmed A (2002a). Intravenous immunoglobulin therapy in patients with multiple mucosal involvement in mucous membrane pemphigoid. *Clin Immunol* **102**: 59–67.

Sami N, Bhol KC, Ahmed AR (2002b). Treatment of oral pemphigoid with intravenous immunoglobulin as monotherapy. Long-term follow-up: influence of treatment on antibody titres to human alpha6 integrin. *Clin Exp Immunol* **129**: 533–540.

Sato K, Hanazawa H, Sato Y, Watanabe J (2005). Initial presentation and fatal complications of linear IgA bullous dermatosis in the larynx and pharynx. *J Laryngol Otol* **119**: 314–318.

Schmidt E, Skrobek C, Kromminga A *et al* (2001). Cicatricial pemphigoid: IgA and IgG autoantibodies target epitopes on both intra- and extracellular domains of bullous pemphigoid antigen 180. *Br J Dermatol* **145**: 778–783.

Schumann H, Baetge J, Tasanen K *et al* (2000). The shed ectodomain of collagen XVII/BP180 is targeted by autoantibodies in different blistering skin diseases. *Am J Pathol* **156**: 685–695.

Scully C, Carrozzo M, Gandolfo S, Puiatti P, Monteil R (1999). Update on mucous membrane pemphigoid: a heterogeneous immune-mediated subepithelial blistering entity. *Oral Surg Oral Med Oral Pathol Oral Radiol Endo* **88**: 56–68.

Segura S, Iranzo P, Martínez-de Pablo I *et al* (2007). High-dose intravenous immunoglobulins for the treatment of autoimmune mucocutaneous blistering diseases: evaluation of its use in 19 cases. *J Am Acad Dermatol* **56**: 960–967.

Sertznig P, Megahed M (2010). Linear IgA disease of the oral mucosa with pharyngeal and esophageal involvement. *Hautarzt* **61**: 924–927.

Shetty S, Ahmed AR (2013). Critical analysis of the use of rituximab in mucous membrane pemphigoid: a review of the literature. *J Am Acad Dermatol* **68**: 499–506.

Smith JR, Kupa A, Coster DJ (1999). Linear IgA disease. *Aust N Z J Ophthalmol* **27**: 443–446.

Staines K, Hampton PJ (2012). Treatment of mucous membrane pemphigoid with the combination of mycophenolate mofetil, dapsone, and prednisolone: a case series. *Oral Surg Oral Med Oral Pathol Oral Radiol* **114**: e49–e56.

Steinfort CL, Wiggins J, Sheffield EA, Keal EE (1989). Alveolitis associated with sulphamethoxypyridazine. *Thorax* **44**: 310–311.

Suresh L, Neiders ME (2012). Definitive and differential diagnosis of desquamative gingivitis through direct immunofluorescence studies. *J Periodontol* **83**: 1270–1278.

Talhari C, Althaus C, Megahed M (2006). Ocular linear IgA disease resulting in blindness. *Arch Dermatol* **142**: 786–787.

Tauber J, Saniz de la Maza M, Foster CS (1991). Systemic chemotherapy for ocular cicatricial pemphigoid. *Cornea* **10**: 185–195.

Tee SI, Yosipovitch G, Chan YC *et al* (2012). Prevention of glucocorticoid-induced osteoporosis in immunobullous diseases with alendronate: a randomized, double-blind, placebo-controlled study. *Arch Dermatol* **148**: 307–314.

Thorne JE, Anhalt GJ, Jabs DA (2004). Mucous membrane pemphigoid and pseudopemphigoid. *Ophthalmology* **111**: 45–52.

Thorne JE, Woreta FA, Jabs DA, Anhalt GJ (2008). Treatment of ocular mucous membrane pemphigoid with immunosuppressive drug therapy. *Ophthalmology* **115**: 2146–2152.

Thornhill M, Pemberton M, Buchanan J, Theaker E (2000). An open clinical trial of sulphamethoxypyridazine in the treatment of mucous membrane pemphigoid. *Br J Dermatol* **143**: 117–126.

Torchia D, Caproni M, Fabbri P (2007). Linear IgA dermatosis with exclusive mucosal involvement or mucous membrane pemphigoid? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **104**: 151–152.

Torchia D, Caproni M, Fabbri P (2008). Linear IgA disease and desquamative gingivitis: time for inclusion in mucous membrane pemphigoid. *Oral Dis* **14**: 768–789.

Wertheim MS, Males JJ, Cook SD, Tole DM (2006). Dapsone induced haemolytic anaemia in patients treated for ocular cicatricial pemphigoid. *Br J Ophthalmol* **90**: 516.

Zillikens D, Wever S, Roth A, Weidenthaler-Barth B, Hashimoto T, Brocker EB (1995). Incidence of autoimmune subepidermal blistering dermatoses in a region in central Germany. *Arch Dermatol* **131**: 957–958.

Zillikens D, Mascaro JM, Rose PA *et al* (1997). A highly sensitive enzyme-linked immunosorbent assay for the detection of circulating anti-BP180 autoantibodies in patients with bullous pemphigoid. *J Invest Dermatol* **109**: 679–683.

Zone JJ, Taylor TB, Kadunce DP *et al* (1990). Identification of the cutaneous basement membrane zone antigen and isolation of antibody in linear immunoglobulin A bullous dermatosis. *J Clin Invest* **85**: 812–820.

Zone JJ, Taylor TB, Meyer LJ *et al* (1998). The 97 kDa linear IgA bullous disease antigen is identical to a portion of the extracellular domain of the 180 kDa bullous pemphigoid antigen, BPAg2. *J Invest Dermatol* **110**: 207–210.

Zurdel J, Aboalchamat B, Zierhut M, Stübiger N, Bialasiewicz A, Engelmann K (2001). Early clinical results with mycophenolate mofetil in immunosuppressive therapy of ocular pemphigoid. *Klin Monbl Augenheilkd* **218**: 222–228.