REVIEW ARTICLE

Drugs 2005; 65 (13): 1767-1779
0012-6667/05/0013-1767/$39.95/0

Autoimmune Bullous Diseases

Ocular Manifestations and Management

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Abstract

The ocular manifestations of autoimmune bullous diseases are common and potentially sight-threatening. Major ophthalmic involvement is most commonly seen in mucous membrane pemphigoid (cicatricial pemphigoid), epidermolysis bullosa acquisita, linear IgA bullous disease, pemphigus vulgaris and paraneoplastic pemphigus. The main pathological process is related to autoimmune-induced conjunctival inflammation with consequent lid and corneal pathology, which may eventually result in permanent visual loss. Ocular involvement can be asymptomatic. Early detection is aided by careful attention to symptoms and signs of early ophthalmic disease. Ocular disease can be difficult to treat and management usually involves systemic therapy with immunomodulators to control inflammation and prevent progression to irreversible blindness, as well as surgical intervention in advanced disease. Recent advances in treatment, including metho-

trexate, mycophenolate mofetil, monoclonal antibodies and topical tacrolimus therapies, have led to promising results.

Autoimmune blistering diseases frequently involve the ocular mucous membranes, often with potentially sight-threatening consequences. Major ophthalmic involvement is seen in subepidermal diseases: mucous membrane pemphigoid (MMP; cicatricial pemphigoid), epidermolysis bullosa acquisita (EBA) and linear IgA bullous disease (LABD); intraepidermal bullous disease; pemphigus vulgaris; and paraneoplastic pemphigus.[1-7] There is one published study[4] reporting ocular involvement in bullous pemphigoid (subepidermal disease), but this is rare. Mucous membrane involvement in pemphigus foliaceus (intraepidermal) is also extremely rare and these two conditions are not covered in this review.[5] Commonly used terms throughout this review are defined in table I.

Autoimmune bullous diseases result from the inappropriate response of a dysregulated immune system. In this setting, autoantibodies directed against specific immunoreactants initiate an inflammatory response in the skin and/or mucous membranes.[8-10] The diagnosis is determined on the basis of clinical features and characteristic histological and immunopathological findings (table II).[4,6-8] Ophthalmic manifestations of autoimmune bullous diseases can broadly be divided according to the anatomic sites involved: the conjunctiva, cornea and eyelids. The initial stage of ocular involvement is characterised by conjunctival inflammation,[2,9,10] which is the result of deposition of autoantibodies (immunoglobulins) and complement at the basement membrane zone or intracellular substance in the conjunctival epithelium.[2,9,10] Conjunctival inflammation leads to subepithelial fibrosis. Cytokines released by activated conjunctival cells or inflammatory cells may play a role in the development of fibrosis by inducing remodeling of the extracellular matrix.[11]

Table I. Commonly used ophthalmological terms and their definition

Term	Description
Ankyloblepharon	Formation of adhesions between superior and inferior conjunctivae
Cicatrisation	Process of progressive scarring
Ectropion	Outward turning of the eyelid margin
Entropion	Inward turning of the eyelid margin
Lagophthalmos	Inability to close eye completely
Metaplastic lashes	Aberrant lashes arising from damaged meibomian glands
Neovascularisation	Formation of abnormal new blood vessels
Penetrating keratoplasty	Corneal grafting operation
Symblepharon	Formation of adhesions between the palpebral and bulbar conjunctivae
Trichiasis	Posteriorly misdirected lashes arising from their original sites

Progressive fibrosis can destroy important structures contributing to tear production and delivery. This leads to deficiency and destabilisation of the tear film, which normally provides an important protective covering for the ocular surface.[1,6] The tear film is made up of three layers: oil, aqueous and mucin. The oil layer is secreted by the meibomian glands and prevents evaporation of the tear film. The aqueous layer, secreted by the main and accessory lacrimal glands, creates a smooth optical surface as well as providing nutrition to the cornea. The inner mucin layer is secreted by goblet cells and creates a hydrophilic coating, allowing the cornea to be wetted by the aqueous layer.[12] Progressive subepithelial fibrosis leads to a reduction in goblet cells and occlusion of the ducts of the lacrimal glands, reducing tear production and causing tear film destabilisation.[1,6,9] Clinically, this manifests as dry eyes and leaves the ocular surface vulnerable to external damage.[1,6]

Ongoing fibrosis results in cicatrisation with conjunctival shrinkage and shortening of the conjunctival fornices. The combination of conjunctival shrinkage and adhesion formation can lead to alterations in lid architecture, resulting in distorted lid positioning and lagophthalmos.[2,3,6,13-15] Lid malposition combined with tear film disruption obstruct the protective mechanisms of the eye, leaving the

Table II. Antigens and immunofluorescence findings in autoimmune bullous diseases with ocular involvement[4-10]

Condition	Antigen	Direct immunofluorescence	Indirect immunofluorescence
Mucous membrane pemphigoid	Bullous pemphigoid antigen 180, laminin 5	Linear deposition of IgG and C3 and IgA on lamina lucida BMZ	IgG or IgA anti-BMZ (10–30%)
Epidermolysis bullosa acquisita	Type VII collagen	Linear deposition of IgG and/or C3 on lower lamina densa at the BMZ	IgG anti-BMZ (50%)
Linear IgA bullous disease	Varying antigens	Linear deposition of IgA on lamina lucida or lamina densa at BMZ	IgA anti-BMZ (20%)
Pemphigus vulgaris	Desmoglein 3	Intercellular staining with IgG (100%) and C3 (50%)	IgG anti-ICS (90%)
Paraneoplastic pemphigus	Desmoplakin I, bullous pemphigoid antigen I, periplakin, envoplakin/desmoplakin II doublet, 170 kDa molecule	Intercellular or BMZ deposition of IgG and C3	IgG anti-ICS (100%)

BMZ = basement membrane zone; **ICS** = intercellular cement substance.

corneal surface exposed and vulnerable to damage (figure 1). The exposed corneal surface is highly susceptible to secondary bacterial infection, which is a further insult to the already damaged eye.[1,2,6]

1. Ophthalmic Presentation

Ocular involvement in bullous disease most commonly presents with the nonspecific symptoms of irritation, burning, tearing and itching.[1,2,12,14] In some cases these may be the first symptoms of generalised bullous disease.[16] In known cases, patients should be directly questioned about the history of these symptoms (table III). Conjunctivitis produces swollen, inflamed conjunctivae and sometimes a mucoid discharge.[1,2] If untreated, chronic inflammation and fibrosis ensues and patients may present with complications from the associated lid and corneal pathology.[1,2] For example, patients can present with corneal abrasion secondary to exposure or trauma from misdirected lashes on distorted lids. In some cases, patients do not experience ocular symptoms, even with advanced signs of conjunctival shortening; therefore, signs of ocular involvement should be specifically looked for (table III).[1,14,16] It should be noted that bullous diseases can be associated with other autoimmune diseases, and so may present in this context.[13,17]

2. Specific Disorders

2.1 Mucous Membrane Pemphigoid (MMP)

MMP is a chronic, progressive, idiopathic autoimmune bullous disease, characterised by subepithelial blisters.[1,6,7,15] The term MMP replaces 'cicatricial pemphigoid' following the International Consensus on Mucous Membrane Pemphigoid in 2002.[18] MMP affects the oral mucous membranes in up to 85% of cases.[19] MMP is most commonly idiopathic but in rare cases can be induced by medications.[10,16,20]

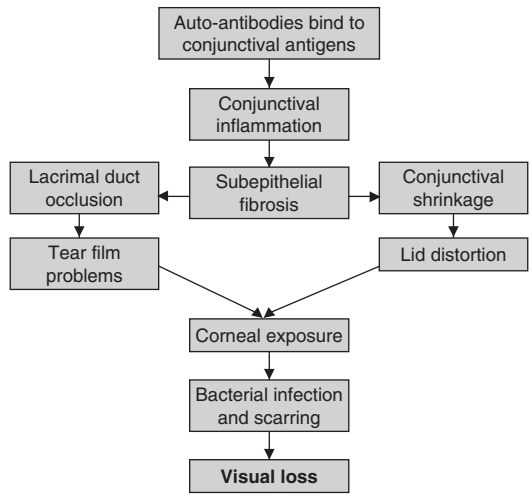

Fig. 1. Schematic diagram of the flow of events leading to visual loss in patients with autoimmune bullous disease.

Table III. Clinical features of ocular involvement in autoimmune bullous diseases

Ophthalmic symptoms	Irritation, burning, foreign body sensation, pain, discharge, decreased vision
Ophthalmic signs	Redness, conjunctival injection, discharge, conjunctival scarring or shortening, entropion, misdirected lashes, corneal abrasion

2.1.1 Ocular Features

Ocular involvement is present in 64–89% of patients with MMP.[4,13,16,19,21-24] The risk of ocular disease developing in patients seen without ocular involvement is estimated to be 5% per annum for the first 5 years of follow up (22% cumulative risk at 5 years).[25] Although the disease may initially be unilateral, it generally progresses to bilateral inflammation. Nevertheless, with bilateral disease the severity and rate of progression is often asymmetrical.[13,14] There are two well recognised staging systems for ocular involvement in MMP, as shown in table IV.[6,26-29]

Ocular involvement is characterised by chronic conjunctivitis, which heals by fibrosis and scarring[1,13,14] (figure 2). Studies indicate that the likelihood of progression of ocular involvement in MMP increases with each stage.[6,15] The first stage is marked by conjunctival inflammation with subepithelial fibrosis. This can be seen clinically as white lines on the inferior palpebral conjunctiva while the patient is looking upwards.[6,30] The conjunctival fornices become shortened as a result of progressive fibrosis and formation of adhesions follows[6,14,30] (figure 3). Symblephara are adhesions that form between the palpebral and bulbar conjunctiva, typically involving the inferior fornix first.[1,6,13-15] Ankyloblephara describes the formation of adhesions between superior and inferior conjunctivae, typically at the lateral canthus.[2,14,31,32] Leonard and colleagues[20] found signs of cicatrising conjunctivitis on examination of nine MMP patients without any ocular symptoms, demonstrating that significant ocular involvement can be asymptomatic in MMP. Further progression leads to distortion of lid architecture that can result in lagophthalmos (figure 4) or entropion (figure 5), which may redirect the lashes. In addition, subepithelial fibrosis can alter lash follicles producing trichiasis.[1,9,14] These complications alter the relationship between lash and globe, with the potential for damage to the ocular surface from posteriorly misdirected lashes.[1,14] In these cases patients may present with corneal abrasion.

The intensity of conjunctival inflammation is evaluated independent of stage and is graded from inactive (0) to severe (4+). Recurrent attacks of intense conjunctival inflammation often interrupt the course of disease, occasionally precipitating new bulla formation.[6,10,15,27] These intermittent episodes of inflammation can lead to fibrous occlusion of the lacrimal gland ductules and destruction of goblet cells, which reduces the volume of mucin production. The resultant tear film instability and deficiency contributes to erosion and ulceration of the unprotected corneal surface with consequent scarring of corneal tissue.[2,6,14] Total keratinisation of the ocular surface may result from this.[14] Corneal disease may be complicated by microbial keratitis.[6,12] End-stage disease is characterised by obliteration of the conjunctival fornices, neovascularisation and opacification of the ocular surface, and, finally, visual loss.[2,6,13-15]

2.2 Epidermolysis Bullosa Acquisita (EBA)

EBA is a chronic acquired autoimmune bullous disease, characterised by subepidermal blisters forming on trauma-prone body surfaces. Blisters rupture to produce erosions that heal with scarring. Mucous membrane involvement can be seen in the conjunctiva, mouth, oesophagus and larynx.[33-36]

Table IV. The two staging systems for mucous membrane pemphigoid

Stage	Mondino and Brown[26,29]	Foster et al.[28]
0	No conjunctival shrinkage	-
1	≤25% shrinkage of conjunctival fornices	Chronic conjunctivitis with subconjunctival fibrosis
2	25–50% conjunctival shrinkage	Inferior fornix foreshortening
3	Approximately 75% conjunctival shrinkage	Symblepharon formation
4	End stage	End stage

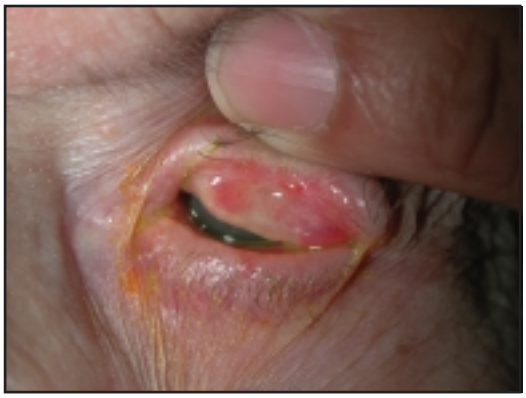

Fig. 2. Drug-induced mucous membrane pemphigoid leading to marked fibrosis of the upper lid conjunctiva and tarsal plate.

2.2.1 Ocular Features

There are a number of reports documenting ocular involvement in EBA;[1,37-40] however, it is uncommon and the incidence is not recorded in the literature. Presentation is usually with bilateral conjunctivitis and subsequent bullae formation on the eyelids and conjunctiva. In line with the process of cicatrisation, this may progress to scarring and complications including pseudomembranes and symblepharon.[1,2,34] Corneal damage is usually secondary to lid distortion and inadequate tearing. However, in one study ulcerative keratitis was demonstrated in the absence of entropion and trichiasis, suggesting that corneal inflammation can also be a direct manifestation of the autoimmune disease process.[1] Persistent insult to the cornea may lead to corneal opacification and perforation.[1] Luke and colleagues[37] described four patients with EBA; two had ocular symptoms and all four had signs of ocular involvement (symblepharon and lacrimal duct occlusion). There are a number of reports of such ocular manifestations resulting in blindness in patients with EBA.[38-40]

2.3 Linear IgA Bullous Disease (LABD)

LABD is a rare autoimmune disease, characterised by subepidermal blisters. Tense cutaneous blisters form on normal or urticarial skin.[1,2,25,41] Mucosal involvement is common in the mouth and conjunctiva.[25]

2.3.1 Ocular Features

Ocular disease is estimated to be present in 50–60% of cases of LABD.[16,42,43] Ocular involvement presents in a similar fashion to MMP. Conjunctivitis may be persistent or may manifest as recurrent acute episodes and blisters may develop on the margins of the lids or tarsal conjunctiva. Complications of conjunctival scarring such as symblephara may occur; however, progression of cicatrisation to the end-stage disease of corneal opacification and visual loss is rare.[44] Leonard and colleagues[20] report ocular involvement in 4 of 7 patients with LABD. Three patients (75%) had no ocular symptoms. In another study,[43] 6 of 12 patients with LABD selected for ophthalmological examination were found to have cicatrising conjunctivitis identical to that seen in MMP. A similarly high proportion of patients (5 of 6) were asymptomatic, emphasising the importance of a thorough ophthalmological examination in all patients with LABD. One case of LABD limited to the eye has been reported.[45]

2.4 Pemphigus Vulgaris

Pemphigus vulgaris describes an autoimmune, mucocutaneous blistering disorder, characterised by intraepidermal blisters and acantholysis upon histologic examination. Mortality rates have decreased from 90% to 10% since the advent of systemic corticosteroids.[1,33,46]

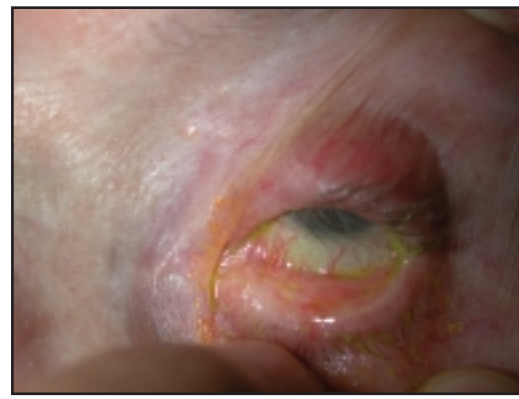

Fig. 3. Medial symblepharon in a patient with mucous membrane pemphigoid.

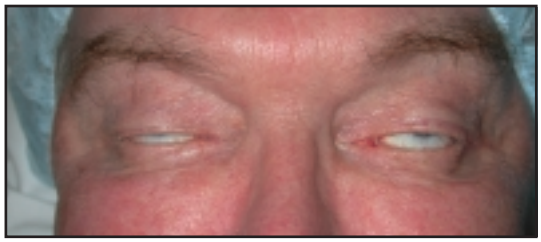

Fig. 4. Bilateral lagophthalmos in a patient with mucous membrane pemphigoid.

2.4.1 Ocular Features

While oral lesions are commonly the initial presentation of pemphigus vulgaris, ocular symptoms may herald the onset of disease.[16,30,33,47] In one study of 11 patients with pemphigus vulgaris and ocular involvement, 8 (72.7%) had symptoms of ocular irritation, tearing and foreign body sensation prior to the development of oral or cutaneous lesions.[16] Typical findings in pemphigus vulgaris are bilateral conjunctivitis and blepharitis.[3,9,47-50] In milder cases the inflammation may only manifest as conjunctival hyperaemia. There may be conjunctival blisters and erosions and eyelid margin erosions may develop on rare occasions[1,3,16,48-50] (figure 6).

Ocular involvement is usually transient and responds readily to systemic immunosuppression.[2,3,46] In contrast with MMP, conjunctival inflammation does not typically progress to scarring, and symblephara and trichiasis are uncommon. Visual loss from corneal opacification is rare.[1,2] A case of corneal perforation has been reported.[47]

2.5 Paraneoplastic Pemphigus

Paraneoplastic pemphigus describes a severe, autoimmune, blistering mucocutaneous disease most commonly associated with B-cell lymphoproliferative disorders. It can be fatal despite treatment.[51-53] Paraneoplastic pemphigus is distinct from pemphigus and other blistering diseases, and is diagnosed on the basis of histological and immunopathogenic studies in the correct clinical context (table II).[53,54] It is characterised by polymorphic cutaneous bullous lesions with associated mucous membrane disease.[51,52] The eyes are involved in 66–72% of cases.[54-56] It usually leads to conjunctivitis but, unlike pemphigus, it typically progresses to cicatrising disease, with the involvement of the associated scarring complications.[1,33,54] A case of bilateral corneal melting has been reported in a patient with paraneoplastic pemphigus and a peripheral neuronal shaft tumour.[57]

3. Treatment

Treatment of ocular manifestations of autoimmune bulous diseases can be divided into general measures and specific measures, which are further divided into medical and surgical interventions (figure 7).

3.1 General Measures

Dry eye should be treated with aggressive lubrication in the form of preservative-free artificial tears.[7,15,30] Schirmer's tear test should be performed regularly to assess deterioration in the tear film.[14] Severe dry eye may necessitate either temporary (punctal plugs) or permanent (surgical) punctal occlusion to increase tear volume, if this has not already occurred as a consequence of scarring.[14,15]

For conjunctivitis, lid hygiene involving regular eye toilet and sterile irrigation, along with lid scrubs and compresses should be employed. Regular cultures should be obtained from the conjunctiva and lids, with appropriate topical antibacterials prescribed according to sensitivities.[6,7,15] Cultures

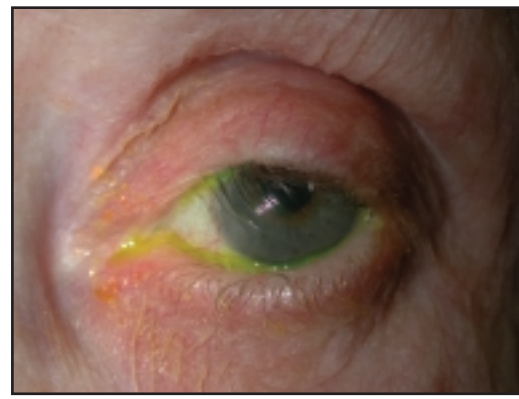

Fig. 5. Upper lid entropion in a patient with mucous membrane pemphigoid.

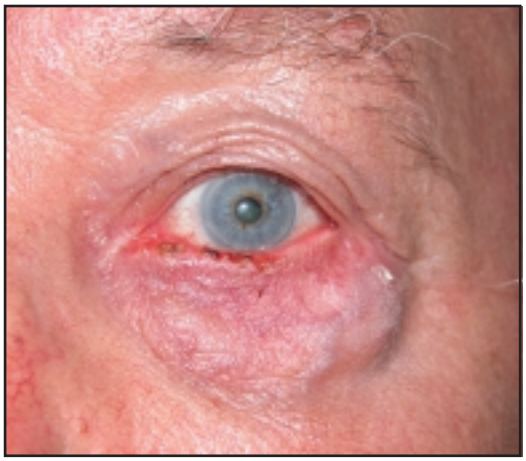

Fig. 6. Lower lid margin erosions in a patient with pemphigus vulgaris.

have been shown to be positive in >80% of cases in MMP.[27]

Bandage contact lenses provide protection from exposure and trichiasis for the cornea and are typically utilised as a temporary measure while awaiting surgical management of scarring complications.[2,6,7,15,46]

3.2 Specific Measures

3.2.1 Medical Management

Medical management of bullous disease requires close collaboration between treating dermatologist and ophthalmologist. Ocular disease may be more resistant to treatment than skin disease, and needs special attention when considering management for the patient as a whole.

Topical treatments include corticosteroids, retinoids and antibacterials. Topical corticosteroids may be used in conjunction with systemic treatment, but on their own are insufficient to control ocular disease and they do not prevent progression of scarring.[7,15] Their benefit is seen when used in patients with acutely inflamed eyes, and should not be prescribed as long-term maintenance therapy.[15] Topical retinoid treatment can be of benefit in treating keratinisation of the ocular surface, but is generally discontinued if there is no response after a 1- to 2-month trial.[15,27] Topical antibacterials are used to treat infections and blepharoconjunctivitis.[1,15]

Systemic corticosteroids and immunomodulating therapies are the mainstay of systemic treatment for bullous disease with ocular involvement. These have significant adverse effects, the risk of which must be balanced with the benefit of treatment (table V).[5,7,8,15,46,58] The role of corticosteroids should be limited to use in severe inflammation or rapidly progressing disease. Patients are often elderly and require frequent monitoring during therapy.[5,7,8,15,46,58] The medical management for each disorder is discussed separately.

MMP

The management of MMP with ocular involvement depends on the stage of disease and the degree of inflammation. Dapsone is the first-line treatment (50–200 mg/day) for mild-to-moderate inflammation.[7,15,18,27,59,60] In rapidly progressing disease or severe inflammation, systemic therapy should consist of prednisolone and intravenous cyclophosphamide pulses.[28,60,61] This combination has been

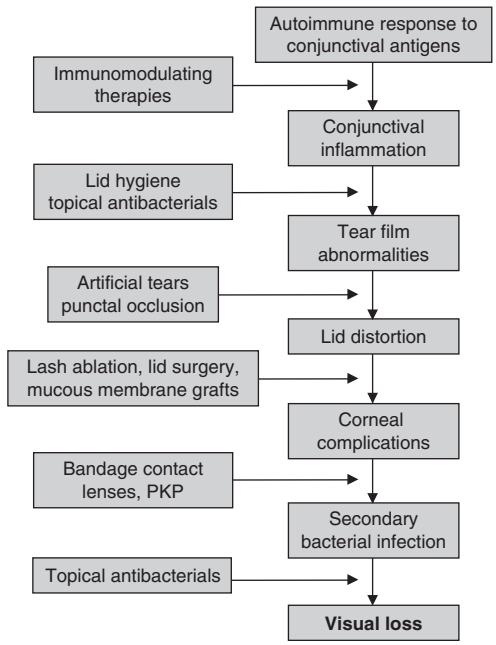

Fig. 7. Schematic diagram of the possible medical and surgical treatment modalities in patients with ocular autoimmune bullous disease. **PKP** = penetrating keratoplasty.

Table V. Adverse effects and monitoring requirements for commonly used therapies[5,7,8,15,46,58]

Treatment	Adverse effects	Monitoring
Prednisolone	Depression, psychosis, myopathy, oedema, hypertension, hypokalaemia, osteoporosis, delayed wound healing, Cushingoid appearance, hyperglycaemia	Baseline: blood pressure, weight, blood glucose level, electrolytes Repeat: weekly for the first month then as clinically indicated
Azathioprine	Hepatitis, increased risk of infection, dose-dependent bone marrow suppression, teratogenicity, increased risk of internal and cutaneous malignancy	Baseline: CBC, electrolytes, renal and liver function tests Repeat: CBC weekly for 8 weeks (as long as the dose is increasing) then monthly with renal and liver tests
Cyclophosphamide	Nausea, vomiting, bone marrow suppression, haemorrhagic cystitis, azoospermia, alopecia, teratogenicity, increased risk internal malignancy	As for azathioprine PLUS weekly urinalysis for 12 weeks then urinalysis every 2 weeks PLUS cardiac monitoring during pulse therapy
Methotrexate	Gastrointestinal disturbance, nausea, stomatitis, fatigue, alopecia, liver toxicity	Baseline: CBC, electrolytes, renal and liver function, urinalysis Repeat: CBC weekly for 8 weeks (as long as the dose is increasing) then monthly with renal and liver tests
Ciclosporin (cyclosporin)	Hypertension, renal dysfunction, electrolyte disturbance, anaemia, gastrointestinal upset, raised lipids, hepatotoxicity, neurotoxicity, increased risk of infection, increased risk malignancy	Baseline: blood pressure, CBC, electrolytes, renal and liver function, magnesium, fasting lipids, 24-hour urinary protein, urinalysis Repeat: weekly for 3 months then monthly
Dapsone	Dose-dependent haemolysis and methemaglobinaemia, peripheral neuropathy, blood dyscrasias, exfoliative dermatitis, anorexia, nausea, vomiting, sulphone syndrome and other mental changes	Baseline: CBC, reticulocyte count, electrolytes, renal function, lactate dehydrogenase, glucose-6-phosphate deficiency must be excluded Repeat: weekly
Plasmapheresis	Bleeding tendency (from addition of anticoagulants and clotting factor depletion), electrolyte disturbance, allergic reactions to foreign proteins, pulmonary oedema, cardiac arrhythmias, septicaemia, fever, hypotension	Baseline: CBC, electrolytes, renal and liver function, hepatitis serology, coagulation studies, serum protein electrophoresis Repeat: weekly During procedure: vital signs and cardiac monitoring

CBC = complete blood count.

shown to be superior to prednisolone alone in MMP with ocular involvement.[13,61] A systematic literature review by Kirtschig and colleagues[60] found evidence that severe MMP responds best to cyclophosphamide. Azathioprine, ciclosporin (cyclosporin) and methotrexate have been used successfully in some cases, and are implemented as second-line therapy or in addition to other agents in order to gain control of the disease.[7,62-64] In a promising trial conducted by McCluskey and colleagues,[63] 12 patients with ocular involvement of MMP were commenced on a once-weekly oral dose of methotrexate 5–15mg as first-line systemic monotherapy. The result was complete control of conjunctival inflammation in 89% of affected eyes in MMP and 100% of affected eyes in drug-induced MMP, with a mean follow-up period of 30 months. Progression of cicatrisation was halted in 72% of eyes in MMP and 90% of eyes in drug-induced MMP. Methotrexate was well tolerated with 92% of patients remaining on treatment without significant adverse effects. Mycophenolate mofetil has been proven effective as an immunosuppressive therapy in a variety of clinical settings.[8,65-69] It was successful in combination with dapsone in obtaining and maintaining control of inflammation in 10 of 14 MMP patients, with good tolerability in >90% of patients.[67] In general, adverse effects are minimal and include gastrointestinal disturbance, anaemia, leukopenia and an increased risk of infection.[5,66]

Intravenous immunoglobulin (IVIg) has been used effectively in patients with ocular involvement of MMP that were unresponsive to other immunomodulating therapies.[62,70] A recent review[70] reported favourable responses in 100% of patients (43 patients with MMP in six studies) treated with IVIg.

Foster and Ahmed[62] successfully treated ten patients with MMP using IVIg, without any significant treatment-induced adverse effects.

Miserocchi and associates[71] reported on a series of 61 patients with MMP and ocular involvement who were receiving a variety of regimens. Control of inflammation was achieved with systemic treatment in 90% of patients; however, cicatrisation progressed in the remaining 10%, despite active treatment.

New experimental therapies include mitomycin C, which acts by inhibiting DNA synthesis. Promising results from two studies[72,73] demonstrate its potential to decrease inflammation in MMP, without significant adverse effects. Subconjunctival injection of mitomycin C was shown to stop progression of scarring and conjunctival erythema in eight of nine eyes treated. This was in comparison with progression of disease in five of nine untreated eyes.[72] Intraoperative mitomycin C has also been used to successfully improve outcomes following surgical management.[73] In contrast, Celis and colleagues[74] found persistent disease progression in three of four MMP patients treated with mitomycin C.

Hall and colleagues[75] reported successful results with topical tacrolimus 0.03% therapy in a 74-year-old patient with ocular MMP resulting in conjunctivitis, blepharitis and symblepharon. After 3 months of therapy, ocular symptoms had resolved and there were no signs of ocular inflammation. A controlled, larger scale study is required to confirm these results.

Daclizumab is a humanised monoclonal antibody directed against the receptor of interleukin-2, a surface protein expressed on activated lymphocytes. It has been shown to be an effective immunosuppressant in a number of clinical situations.[8,76] Recently, Papaliodis and colleagues[76] reported successful treatment of ocular inflammatory disease with daclizumab; amongst those treated was a patient with MMP. This is a promising path to pursue in future research.

EBA

EBA usually responds poorly to treatment. A recent systematic review found no randomised controlled trials for the treatment of EBA.[60] Corticosteroids and immunosuppressant therapy have not been proven effective. The exception is ciclosporin, which may be of benefit in severe disease, but which has significant adverse effects limiting the duration of therapy.[1,5] Dapsone has been shown to be beneficial in patients with IgA-mediated EBA,[77] and extracorporeal photochemotherapy and plasmapheresis have shown some success in cases of resistant EBA.[5,78] A case report documents successful treatment of a 60-year-old woman using mycophenolate mofetil, without recurrence of disease during the 6-month follow-up period.[79] This may be a promising future direction for therapy. There may be a role for IVIg in the treatment of EBA with ocular involvement, with two EBA patients refractory to other measures showing transient improvement following IVIg monotherapy.[80]

LABD

Skin lesions show significant improvement with oral dapsone or sulfapyridine, whereas mucous membrane disease is often more resistant.[5,33,44] Oral corticosteroids should be added in those patients who fail to gain resolution of disease with the first-line therapies. Corticosteroids can also be used in conjunction with the combination of tetracycline and nicotinamide.[44] Ocular involvement usually requires aggressive combination therapy of corticosteroids and cyclophosphamide to prevent complications due to cicatrisation.[5] Recently, successful results were reported with IVIg therapy in recalcitrant cases.[45,70,81]

Pemphigus Vulgaris

Corticosteroids are the main treatment modality in ocular manifestations of pemphigus vulgaris.[2,5] Dapsone and sulphonamides may be used as first-line therapy in mild disease; however, oral or intravenous corticosteroids with adjuvant medications are usually necessary for disease control. Many corticosteroid-sparing agents have been tried with some success, including azathioprine, cyclophosphamide, dapsone, ciclosporin, hydroxychloroquine, gold and

mycophenalate.[42,46,82] Azathioprine is the most frequently used adjuvant agent, and has been shown to prolong remission and to allow a reduction in the dosage of corticosteroid therapy.[46,83] Mycophenolate mofetil has been used alone and in combination with prednisolone to treat pemphigus vulgaris effectively, and may have less severe adverse effects than azathioprine.[67,84-86] Enk and Knop[84] reported successful treatment in 11 of 12 patients treated with mycophenolate mofetil, with no recurrence over the 9- to 12-month period of follow-up. Pasricha and colleagues[87] demonstrated that pulsed intravenous dexamethasone-cyclophosphamide therapy was successful in inducing remission in 60 of 67 patients with pemphigus vulgaris and ocular involvement. Disease unresponsive to any of these agents may be treated with plasmapheresis, IVIg or extracorporeal photophoresis.[5,70] In one trial of 42 patients with pemphigus vulgaris treated with high-dose IVIg,[70] improvement was reported in 38 patients (90.5%), allowing reductions in concomitant therapies.

The use of topical tacrolimus for the treatment of ocular involvement in pemphigus vulgaris has been reported in one patient. A 49-year-old man with conjunctival inflammation had resolution of inflammation after 2 months of treatment.[75]

Paraneoplastic Pemphigus

Patients with paraneoplastic pemphigus have a very poor prognosis.[53] The course of the disease is related to progression of the underlying neoplasm, treatment of which is the most important consideration in paraneoplastic pemphigus.[54] Disease usually arrests when the associated benign tumour is removed. However, in many cases the associated neoplasm is a progressive malignancy and pemphigus manifestations are difficult to control. Typically, mucous membrane lesions are more resistant to treatment than cutaneous lesions.[52,53,88] Corticosteroids, azathioprine and ciclosporin have been used with limited success.[7,46] A case report[88] describes the use of mycophenolate mofetil in a 40-year-old patient with chronic lymphocytic leukaemia, with resolution of skin and mucous membrane lesions and sustained remission at 10 months. Prednisolone and azathioprine were subsequently ceased with success. Adverse effects were thrombocytopaenia, herpes simplex infection and community-acquired pneumonia.

Alemtuzumab is a humanised monoclonal antibody, directed against a cell surface protein (CD52) on lymphocytes. A recent report describes ongoing alemtuzumab-induced remission of paraneoplastic pemphigus in a 68-year-old man with B-cell chronic lymphocytic leukaemia.[53] This may be a promising way forward in treating this previously refractory disease.

3.2.2 Surgical Management

It is important to determine whether cicatrisation is chronic and progressive or non-progressive, as this will influence surgical management and the prognosis. Surgery is rarely indicated in early disease,[27] and in more advanced disease, exacerbation of inflammation and disease progression is well documented when surgery is performed on inflamed eyes.[6,89,90] Surgical failure is often the result of such complications and, therefore, all surgical management should be delayed until inflammation is inactive and disease progression has stabilised.[15,89,90] Immunosuppressant therapy can be given for 6 months perioperatively to reduce risk of reactivation of inflammation.[27] Patients with end-stage scarring generally respond poorly to all forms of therapy.

Corrective surgery is primarily aimed at eyelid problems. Concern is focused around the potential injury resulting from direct contact between the eyelashes and the ocular surface, and the associated complications that threaten sight. Therefore, the aim of surgical therapy is to prevent lash-globe contact.[89,90] Elder and Collin[90] broadly divide interventions into lash ablation procedures and surgical repositioning of the eyelid. Lash ablation is used in the treatment of trichiasis and metaplastic lashes, aiming to destroy all cells with the ability to regenerate to form hair follicles. This is achieved using one of the following modalities: cryotherapy, laser thermoablation or electrolysis.[37,89-92]

Surgical correction of lid position in cicatrising disease may be complicated by reactivation of inflammation.[6,80,93] Surgical techniques for entropion

repair can essentially be divided into three categories: tarsal rotation procedures (incision through the tarsal plate and rotation of the margin); grey line split procedures (split eyelid margin with recession of the anterior lamellae); and spacer grafts (hard palate, mucous membrane or amniotic membrane grafts).[89] Mucous membrane grafting has been shown to reverse abnormalities of the lid and conjunctiva with sustained benefits in some cases of MMP, but it can cause significant postoperative corneal complications. Surgery should not be attempted in active or advanced disease.[94] Amniotic membrane grafting has been used successfully in conjunctival surface reconstruction in MMP[95-97] and may represent a promising direction for future surgical management.

The prognosis for corneal disease is typically poor, although bandage contact lenses can be used as a temporary protective measure.[2,6,7,15,46] Advanced corneal scarring and corneal perforation can be treated with penetrating keratoplasty (PKP); however, surgery is often unsuccessful, and the potential for sight restoration is limited.[14,98] One study reports 32 PKP performed on 16 eyes in 13 patients: 50% resulted in clear grafts, and only 18.7% resulted in 20/200 visual acuity or better. Main contributors to graft failure were the formation or persistence of an epithelial defect, perforation, stromal ulceration and graft rejection.[98]

Each patient must be assessed individually to determine the most suitable surgical intervention. Complete control of inflammation and avoidance of surgery to the conjunctiva are essential to ensure the best chance of surgical success.

4. Conclusion

Autoimmune bullous disorders involving the eyes have the potential for sight-threatening complications. The features of ocular involvement are due to a combination of conjunctival inflammation with consequent scarring and tear film dysfunction. The end result may be corneal epithelial damage and, ultimately, visual loss. Ocular disease can be difficult to treat, but recent studies show promising results for methotrexate therapy, mycophenolate mofetil, monoclonal antibodies, subconjunctival mitomycin C and topical tacrolimus. However, further research is needed in these areas. Successful treatment requires close collaboration between the dermatologist and the ophthalmologist. A history and examination should be sought to determine ocular involvement in autoimmune bullous diseases and patients with positive findings should be referred for ophthalmological assessment, as early recognition of ocular involvement can prevent progression to irreversible blindness.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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