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REVIEW

Ocular Mucous Membrane Pemphigoid: Current State of Pathophysiology, Diagnostics and Treatment

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ABSTRACT

Mucous membrane pemphigoid (MMP) is a systemic cicatrizing autoimmune disease that primarily affects orificial mucous membranes, such as the conjunctiva, the nasal cavity, the oropharynx, and the genitalia. Ocular involvement occurs in about 70% of all MMP cases. Ocular MMP (OcMMP) also encompasses the conditions linear immunoglobulin A disease, mucosal dominated epidermolysis bullosa acquisita, and anti-laminin 332/anti-epiligrin/anti-laminin 5 pemphigoid. It is a complex clinical entity that may lead to ocular surface failure and result in inflammatory and infectious complications, as well as potentially devastating visual loss. Early diagnosis and appropriate treatment are of paramount importance and require a high level of expertise as this condition can be extremely challenging to diagnose and treat even for experienced clinicians. In this review we provide an up-to-date insight on the pathophysiology of OcMMP, with an emphasis on the current state of its diagnostics and therapeutics. Our the aim is to increase our understanding of OcMMP and highlight modern diagnostic and therapeutic options.

Keywords: Diagnostics; Mucous; Ocular pemphigoid; Pathophysiology; Treatment

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INTRODUCTION

Mucous membrane pemphigoid (MMP) is a systemic cicatrizing autoimmune disease that primarily affects orificial mucous membranes, such

as the conjunctiva, the nasal cavity, the oropharynx, and the genitalia. In some cases the esophagus, the trachea, and the skin may also be involved. The eyes are affected in about 70% of all MMP cases. The progressive inflammatory and scarring nature of MMP leads to severe visual impairment in 30% of affected eyes and bilateral blindness in 20% [1–4]. Systemic immunomodulatory therapy is often required to limit disease progression. The older term ocular cicatricial pemphigoid (OCP) has now largely been replaced by ocular MMP (OcMMP) after publication of the 2002 international consensus document [5]. OcMMP also encompasses the conditions linear immunoglobulin (Ig) A disease, mucosal dominated epidermolysis bullosa acquisita, and anti-laminin 332/anti-epiligrin/anti-laminin 5 pemphigoid [6]. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY

Ocular MMP is the leading cause of cicatrizing conjunctivitis in developed countries [4, 7, 8]. Its incidence in the UK is estimated as 0.8 per million, with MMP currently representing about 60% of cicatrizing conjunctivitis cases [8]. Similar incidences have been estimated France (1.13 per million) and Germany (0.87 per million) [4]. MMP may affect any race, but it seems to be more common in Caucasians than in Indians and Chinese. Expression of the HLA-DR4, HLA-DQw3, and HLA-DQβ*10301 alleles, which are involved in antigen presentation to T cells, is associated with development of OcMMP [9–13]. For most patients, however, no identifiable predisposing factor is found.

PATHOPHYSIOLOGY

The underlying pathophysiological mechanism of this mucocutaneous disease—which is rarely associated with the blistering cutaneous form—is a type 2 hypersensitivity reaction against the basal epithelial membrane of the conjunctiva [14]. Like most autoimmune diseases, environmental factors and genetic susceptibility are each believed to play a role to initiate a loss of tolerance to one or more components of the basal membrane zone.

The conjunctiva is composed of a superficial epithelium and an underlying connective tissue stroma (substantia propria). The conjunctival epithelium is a stratified, non-keratinized, secretory epithelium. This non-keratinized state of the conjunctival epithelium is crucial to its health, which is lost in keratinized ocular surface disorders, such as OcMMP. In OcMMP, the normal conjunctival epithelium undergoes squamous metaplasia and is transformed to a non-secretory, keratinized epithelium. Additional changes include loss of goblet cells, increased cellular stratification, enlargement of superficial cells, keratinization, and limbal stem cell deficiency [14].

The basement membrane zone (BMZ) of the conjunctival epithelium is between the epithelial cells and the superficial layer of the substantia propria. The basement membrane (BM) is composed of two layers: the lamina lucida, which is closer to the basal epithelial cells, and the lamina densa, which lies closer to the substantia propria. The BM is mainly composed of type IV collagen, laminin, and fibronectin. Desmosomes hold conjunctival epithelial cells tightly together, while hemidesmosomes, intracytoplasmatic cytokeratin filaments and anchorage fibers, and plaques facilitate the adherence of the conjunctival epithelium to the lamina lucida of the BM [14, 15]. A major component of the hemidesmosome protein complex is integrin α6β4. The ligands of this integrin (α6 integrin, β4 integrin, laminin 5 [laminin 332], collagen VII, BP180 [bullous pemphigoid 180-kDa antigen; also known as BP antigen 2], and BP230 [bullous pemphigoid 230-kDa antigen; also known as BP antigen 1]) are the main target antigens of OcMMP [15, 16].

BP230 is a cytoskeletal linker protein that connects hemidesmosomes with keratin intermediate filaments. It is not thought to be involved in the initiation of the inflammatory response due to its intracellular localization. BP180 is a transmembrane protein that spans the lamina lucida and projects to the lamina densa. The most important epitope of BP180 is

the non-collagenous 16A domain (NC16A), which is located at the membrane–proximal region. Circulating autoantibodies (IgG and IgE) prefer to recognize the phosphorylated BP180–NC16A ectodomain [17]. Another important target antigen is laminin 332 (laminin 5), which connects the transmembrane proteins of the epithelial cells to the anchoring filaments of the basement membrane. Antibodies against laminin 332 (laminin 5) are thought to induce subepidermal blisters [17].

Deep in the BMZ lies the fibrovascular connective tissue referred to as the stroma (substantia propria). The stroma contains blood and lymphatic vessels, fibroblasts, nerve fibers, melanocytes, accessory lacrimal glands, and numerous immune cells. In normal conjunctiva, dendritic antigen-presenting cells (Langerhans cells) and CD8 suppressor T cells are in the epithelium, and CD8 suppressor T cells, CD4 helper cells, and Langerhans cells are in the substantia propria. This diffuse layer of numerous subepithelial lymphocytes forms the conjunctival associated lymphoid tissue (CALT), which in turn is part of the mucosa-associated lymphoid tissues (MALT) [14].

The immunopathological progression of OcMMP has three distinct phases: the injury phase, the acute inflammation and proliferation phase, and the fibrosis phase. The trigger for the onset of the OcMMP is unknown.

In the *injury phase*, autoantibodies are directed against conjunctival BM antigens, such as BP180, laminin 332 (laminin 5), collagen VII, and α6β4 integrin [17]. The activated T cells generate specific B-cell clones, and these clones produce circulating autoantibodies (IgG and IgA) that bind to the specific BMZ component, initiate a type 2 hypersensitivity reaction, and activate the complement cascade (C3) [15].

In the *acute inflammation and proliferation phase*, damage to the complement-mediated epithelial, BMZ, and connective tissue leads to vasodilatation and consecutive inflammatory cell infiltration. Neutrophils, macrophages, antigen-presenting cells, mast cells, platelets, and T cells accumulate in the substantia propria and initiate a destructive inflammatory cascade. Activated neutrophils play a major role in collateral tissue damage by releasing proinflammatory cytokines, proteinases, and reactive oxygen species. The acute inflammatory cytokines, such as interleukin-1 (IL-1), IL-17, and tumor necrosis factor-alpha (TNFα), that are released stimulate conjunctival fibroblasts and promote further inflammatory cell infiltration [15]. In cases of mild conjunctival inflammation, the ratio of CD4:CD8 T cells is < 0.5, while in severe forms it increases to 1.0 [18]. Type 1 helper T cells produce interferon gamma and IL-2, and type 2 helper T cells release IL-4, IL-5, and IL-13. IL-13. The aforementioned cytokines have a strong proinflammatory and profibrotic effect on conjunctival fibroblasts. Macrophages secrete profibrotic cytokines, transforming growth factor-beta (TGFβ), and platelet-derived growth factor, which leads to the fibrosis phase [15].

In the *fibrosis phase*, conjunctival fibroblasts are activated, proliferate, and produce extracellular matrix (ECM), connective tissue growth factor, TGFβ, and other (detected but unexamined) cytokines. Consecutively, vascular endothelial cells proliferate to form fibrovascular granulation tissue and subconjunctival scarring. Proteolytic enzymes, such as matrix-metalloproteases (MMP-2, 9, 13) and their inhibitors (tissue inhibitors of metalloproteinases; TIMPs), vascular endothelial growth factor and fibrovascular growth factor, and IL-1β, -2, -4, -5, -6, -8, -10, -15, and -16 play a role in the tissue remodeling that occurs, although their exact role remains to be elucidated [17]. A neurotrophic growth factor-driven mechanism of fibroblast proliferation has recently been proposed, which may also be a target in the treatment of OcMMP [19]. Phenotypic changes in fibroblasts isolated from OcMMP patients include increased motility, contractile function, ECM synthesis, and myofibroblast transformation, and it has been speculated that conjunctival fibroblasts may be activated independently of cytokines in OcMMP [20]. Recently, it has been shown that the aldehyde dehydrogenase 1 subfamily (ALDH 1) plays a role in immune-mediated ocular mucosal scarring and that ALDH inhibition has an antifibrotic action [21].

In summary, circulating autoantibodies have a key role in the pathogenesis of OcMMP as they bind to antigens within the epithelial BMZ

of the conjunctiva and activate the complement cascade, with C3 complement fragments depositing within the lamina lucida [16]. Immune cells are recruited secondarily and lead to fibroblast activation and ECM remodeling via cytokine release.

DIFFERENTIAL DIAGNOSIS

A wide range of ocular surface diseases associated or not with systemic conditions may result secondarily in cicatricial conjunctivitis [22]. Cicatricial conjunctivitis can be broadly catagorized as (1) static/slow, when the underlying disease is controlled or when withdrawing the drug inducing the disease the halts its progression, and (2) progressive with sight-threatening potential [23]. Recognizing causes and associated clinical signs is of paramount importance for the management of disease progression.

The differential diagnosis of OcMMP includes other causes of cicatrizing conjunctivitis, such as drug-induced progressive conjunctival cicatrization [24], Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) [25, 26], mucosal-predominant epidermolysis bullosa acquisita, linear IgA disease, dermatitis herpetiformis, anti-laminin 332 pemphigoid [4, 6], ocular surface squamous neoplasia (OSSN) [27], sebaceous cell carcinoma (SCC) [28], atopic keratoconjunctivitis [7, 29, 30], ocular rosacea [7, 31], adenoviral conjunctivitis [32, 33], trachoma [34], conjunctival trauma (chemical, thermal, surgical, or radiation-induced) [4, 35], paraneoplastic pemphigus [36, 37], pemphigus vulgaris [38, 46], graft-versus-host disease [39], and the congenital disease ectodermal dysplasia [40], as depicted in Table 1.

Although several of the aforementioned etiologies of cicatrizing conjunctivitis have a similar clinical appearance, careful examination of the patient and careful clinical history taking can aid in making the correct diagnosis. The following five clinical pearls can be used to distinguish MMP from the above-mentioned conditions.

Table 1 Differential diagnosis of ocular mucous membrane pemphigoid

Causes of cicatrizing conjunctivitis
Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)
Paraneoplastic pemphigus
Graft-versus-host disease
Mucosal-predominant epidermolysis bullosa acquisita
Linear immunoglobulin A disease
Dermatitis herpetiformis
Pemphigus vulgaris
Ocular surface squamous neoplasia (OSSN)
Sebaceous cell carcinoma (SCC)
Trachoma
Adenoviral conjunctivitis
Conjunctival trauma (chemical, thermal, surgical, or radiation-induced)
Atopic keratoconjunctivitis
Ocular rosacea
Ectodermal dysplasia

Is the Disease Unilateral or Bilateral? Although OcMMP can be asymmetric, with one eye significantly more affected than the other, it is rarely unilateral [4, 41]. In a series of 115 cases of OcMMP only 6% were unilateral [1]. Unilateral cases of conjunctival scarring should alert the clinician that a tumor, either OSSN or SCC, may be masquerading as OcMMP [42]. Moreover, if topical drugs with preservatives have been used unilaterally, then toxic conjunctivitis rather than OcMMP may be the correct diagnosis.

Is There Involvement of Other Mucous Membranes or the Skin? Distinguishing the ocular features of OcMMP from the chronic conjunctivitis observed in the aforementioned mucocutaneous and immunobullous disorders can be challenging given that the clinical phenotype is often identical [22]. A useful pointer is that ocular involvement is preceded by cutaneous or

oral involvement in mucocutaneous and immunobullous disorders and the severity of the ocular signs is generally milder in these conditions [22], except for a small number of patients affected by SJS and TEN who can also suffer from progressive cicatricial conjunctivitis [22].

A medical history of a skin "rash" or "blisters" may indicate MMP skin involvement while a history of "difficulty swallowing" may suggest esophageal involvement. The oral mucosa should be examined for signs of gingival or palatal inflammation and scarring in all patients with progressive conjunctival cicatrization. This can be easily done during a routine appointment using a penlight. Skin and other mucosal involvement may precede any ocular signs and symptoms. Alternatively, the eyes may be the first—or the only—tissue to be affected; in 32–48% of MMP cases the eyes are the only tissue affected [2, 8]. These intricacies of MMP make diagnosis even more challenging for the ophthalmologist, and it is therefore not surprising that the mean diagnostic delay for patients with OcMMP is about 2.5 years, with a range of up to 10 years [8].

Is There an Associated Systemic Disease? Other than MMP, systemic diseases associated with conjunctival scarring include SJS/TEN, graft-versus-host disease, paraneoplastic pemphigus, pemphigus vulgaris, graft-versus-host disease, and ectodermal dysplasia. Of these, MMP, paraneoplastic pemphigus, pemphigus vulgaris, and sarcoid can manifest in the eyes before there is any other systemic manifestation [2, 8, 36, 38, 43]. This presents an additional diagnostic challenge for the ophthalmologist who should have a high index of suspicion in cases of progressive cicatrization that do not fit into any other disease category.

Is There Meibomitis, Eyelid Margin Telangiectasias, and/or Facial Rosacea? Chronic meibomitis, often accompanied by eyelid margin keratinization, is a typical chronic manifestation of patients with history of SJS/TEN or graft-versus-host disease. In such cases, the etiology of the progressive conjunctival cicatrization is evident by the patient's clinical history. Meibomian gland inflammation, inspissation, or dropout associated with eyelid margin telangiectasias is seen in ocular rosacea, which can also cause some bilateral conjunctival scarring [4].

Is There Chronic Use of Topical Medications? Chronic use of topical glaucoma drops, and rarely of other topical medications, can lead to progressive conjunctival inflammation and scarring. Although preservatives play a role, even non-preserved glaucoma medications have been associated with drug-induced conjunctival cicatrization [44]. Upon withdrawal of the culprit medication, in most cases the inflammation quiets down and progression of scarring halts within 2–6 weeks [24]. In rare cases, however, a small subset of patients develops progressive scarring that is indistinguishable from OcMMP, even after withdrawal of the offending medication [24].

Other clues from the patient's history include history of being born or raised in a region where trachoma is endemic, history of acute severe viral conjunctivitis, history of conjunctival trauma, and history of atopy (eczema, allergic rhinitis, asthma).

CLINICAL PRESENTATION

Ocular MMP can affect both young and adult patients (reported age ranges of patients in studies 20–91 years), but the median age in two of the largest studies conducted to date is over 65 years [2, 8]. When young patients are affected, the disease is typically more severe and more rapidly progressive despite treatment. Gender preponderance of OcMMP is unclear [45]. Involvement of the medial canthus with loss of the caruncle and plica semilunaris may be the initial clinical sign of OcMMP and occurs more frequently in this disease than in other cicatrizing disorders [22]. Chronic and low-grade subconjunctival inflammation in OcMMP induces feltwork-like reticular fibrosis and infiltration of the tarsal and bulbar conjunctiva, which leads to forniceal foreshortening, symblepharon formation (i.e., fibrotic adhesions between the bulbar and the palpebral conjunctiva), secondary cicatricial entropion, and

ankylopblepharon (i.e., fibrotic adhesions between the lids) [22, 46].

Tear film instability occurs in the more advanced stages of OcMMP due to impairment of all three layers of the tear film. Inflammation and fibrosis of the main and accessory lacrimal glands are responsible for aqueous tear deficiency. Conjunctival goblet cell loss leads to impairment of the mucin layer, whereas scarring at the orifices of the meibomian glands accounts for the lipid deficiency [47]. Ultimately, conjunctival keratinization secondary to severe dry eye confers a skin-like appearance to the ocular surface [4].

Corneal involvement includes punctate epithelial keratitis (secondary to chronic conjunctivitis, toxicity induced by topical medications, and blepharitis), filamentary keratitis (due to the combination of aqueous tear film deficiency and blepharitis), corneal irritation (promoted by cicatricial entropion and trichiasis), exposure keratitis (subsequent to poor lid closure from eyelid cicatrization), persistent epithelial defects, corneal ulceration, and perforation (due to the resultant limbal stem cell deficiency) [4].

Clinical presentation can vary markedly. Patients can present either with slowly progressive chronic conjunctivitis that failed to respond to topical treatments (often with symblepharon due to misdiagnosis and inappropriate treatment) or with acute conjunctivitis and limbitis that can rapidly progress towards conjunctival cicatrization and ocular surface failure if not promptly and adequately treated [22]. Recurrent entropion and trichiasis after surgical correction should also alert physicians, especially if associated with conjunctival fibrosis [22].

In 1986, Foster proposed a staging system in which subconjunctival scarring and fibrosis represented stage 1; foreshortening of the fornix, stage 2; symblepharon, stage 3; and ankyloblepharon, stage 4 [46]. Mondino and Brown proposed four stages for the loss of inferior fornix depth, in which 0–25% loss was defined as stage 1; 25–50% loss, stage 2; 50–75% loss, stage 3; and 75–100% loss, stage 4 [48]. Other staging systems were subsequently proposed by Tauber et al. [49], Rowsey et al. [50], and Reeves et al. [51], respectively.

DIAGNOSTIC STUDIES

Indirect immunofluorescence (IIF) microscopy testing of salt-split skin can be used to identify serum autoantibodies in OcMMP (α6β4 integrin, BP180, BP230, laminin 332, laminin γ1, and type VII collagen), but this method has poor sensitivity and specificity [4]. Bulbar perilesional conjunctival biopsy allows for histopathological investigation and confirmation of the MMP diagnosis through direct immunofluorescence (DIF) testing [4, 52]; the former is crucial to rule out OSSN, atopic keratoconjunctivitis, and sarcoid, whereas the latter helps to confirm OcMMP [4]. However, it should be remembered that other disorders, such as some cases of SJS, TEN, and drug-induced scarring, pemphigus vulgaris, lichen planus, ectodermal dysplasia, and lupus, also test positive for DIF and that the result may be indistinguishable from that for bullous pemphigoid. DIF testing is not mandatory for diagnosing OcMMP when the biopsy result from other mucosal/skin tissues is positive and the ocular phenotype is characteristic of OcMMP [4].

Although the first international consensus on OcMMP strongly recommended that OcMMP diagnosis requires clinical findings and positive immunopathology, DIF is neither a sensitive nor specific marker of OcMMP [4, 5]; moreover, DIF is often negative or can become negative with remission of the disease. Therefore, it has been proposed that OcMMP can be diagnosed even if DIF is negative when IIF is positive or—in cases of negative IIF—when other causes of cicatricial conjunctivitis have been ruled out [4, 53, 54]. The diagnostic criteria of OcMMP are summarized in Table 2.

TREATMENT

Management of OcMMP is aimed at controlling the immune-mediated inflammatory disease,

Table 2 Diagnostic criteria of ocular mucous membrane pemphigoid

Diagnostic criteria of ocular mucous membrane pemphigoid
Chronic conjunctivitis
Conjunctival fibrosis
Conjunctival keratinization
Loss of plica semilunaris and/or caruncle
Fornix shortening
Symblephara
Cicactricial entropion
Punctate keratitis
Filamentary keratitis
Exposure keratopathy
Persistent epithelial defects
Corneal ulceration
Limbal stem cell deficiency
(+) or (−) direct immunofluorescence
Extraocular involvement

preventing fibrosis, and managing the ocular surface disease.

Management of the Inflammatory Disease

Occular MMP requires systemic immunosuppression to control the inflammatory process, halt the fibrotic process, and prevent progression to more advanced stages. Secondary ocular surface inflammation needs to be identified and managed as well, as it contributes to progressive damage. The patients requiring systemic treatment need to be properly identified. A quarter of patients with OcMMP do not require systemic treatment if the disease is very mild and non-progressive [55]. Moreover, end-stage disease patients with total surface failure will not benefit from systemic immunosuppression. For this group of patients, efforts should be directed towards managing the symptoms and sequalae. Topical treatment is not effective in controlling the immune-mediated disease and preventing progression, but it is employed for symptomatic relief. When topical steroids are used, patients should be monitored for the development of cataract and glaucoma.

A stepladder approach is used to select immunosuppressive agents and to escalate treatment, depending on disease severity (mild, moderate, severe; see Table 3). The medications used are dapsone, sulphapyridine, sulphasalazine, azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), cyclophosphamide, and short courses of oral steroids. CD20 monoclonal antibodies, TNFα inhibitors, and intravenous immunoglobulin (IVIg) are used to treat disease non-responsive to conventional immunosuppressants. Dapsone, sulfapyridine, and sulfasalazine are sulfa drugs used to treat mild to moderate disease,

Table 3 Step-by-step treatment used to select immunosuppressive agents and escalate treatment according to disease severity

Step-by-step treatment
Mild disease
Dapsone
Sulfapyridine/sulfasalazine
Moderate disease
Mycophenolate mofetil
Methotrexate
Azathioprine
Severe disease
Cyclophosphamide
Oral or IV steroids are used only for acute control of very severe disease; no role for long-term control
IVIg, Anti-TNFα, rituximab, or a combination thereof—in cases of resistance to conventional treatment, poorly controlled disease, or adverse reactions to conventional treatment
A combination of the above-mentioned agents can be used; refer to the text and references for details

IV Intravenous, *IVIg* intravenous immunoglobulin, *TNFα* tumor necrosis factor-alpha

but they are contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency and those allergic to sulpha drugs. Their most common side effect is hemolytic anemia; other side effects include skin rash and gastrointestinal problems. The treatment dose for dapsone is 1 mg/kg/day (with a maximum dose of 200 mg/day). If there is intolerance to dapsone, it can be substituted by sulphasalazine or sulphapyridine. The doses for sulfasalazine and sulfapiridine are 1–4 g/day and 500 mg once or twice/day, respectively [4, 55].

MMF, AZA and MTX can be used to treat moderate disease. Of these agents, MMF has the best safety profile and is very well tolerated, having the lowest drop-out rate among the agents used. The recommended dose is 1 g twice daily, and this treatment achieves control of the disease in 59% of patients [1, 56]. In cases of intolerance to MMF, AZA or MTX can be used as alternative agents. AZA achieves control in 47% of patients as monotherapy [1]. MTX can also be considered in the treatment of moderate OcMMP (10–15 mg once/week). McCluskey and colleagues reported a success rate in 83% of patients receiving MTX [57]. The most common side effects seen with MTX use are gastrointestinal problems, fatigue, and alopecia, although long-term use of MTX is associated with pulmonary and hepatic fibrosis.

In cases of severe or poorly controlled inflammatory disease, the use of cyclophosphamide is indicated (1–2 mg/kg/day) [1, 58–60]. Cyclophosphamide has serious side effects with prolonged use, such as bladder carcinoma, so it should be used for a maximum duration of 12–18 months. If cyclophosphamide needs to be substituted, one of the less toxic drugs is then used. Oral steroids may need to be used in the acute phase of the disease to achieve control until the immunomodulatory agents begin to have effect, at which point they are then tapered [4, 57]. For acute control of very severe disease, oral or intravenous corticosteroids may need to be used. There is no role for long-term oral corticosteroids.

There are different approaches to the choice of immunomodulatory agent and the mode of escalation of the stepladder approach proposed in the literature. The choice of agents used to control the disease depends on physician experience, hospital setting, and availability of the medication. Our review is not meant to serve as a guide for treatment but rather as an overview of the existing treatment strategies. The two stepladder approaches presented here are from Sobolewzca et al. [56] and Saw et al. [1], respectively.

Saw et al. [1] and Dart et al. [4] reported the use of a step–up and step–down treatment strategy for the choice of drugs depending on disease severity and patient response to treatment, using monotherapy or combination of medications. In cases of partial success in controlling the disease, a combination of the above-mentioned agents should be used. Sulfa drugs (dapsone, sulfasalazine, sulphapyridine) can be combined with myelosuppressive agents (MMF, AZA, MTX, cyclophosphamide). In the case of failure of conventional immunosuppressive treatment, anti-TNFα [61–63], the anti-CD20 monoclonal antibody rituximab [64–66], IVIg treatment [67, 68], or a combination of the above has been described [69]. Once the disease has been controlled, immunosuppression should continue for 1 year and can then be tapered and discontinued if the disease is of mild or moderate severity. Lifelong monitoring is needed, however, as one-third of patients will relapse [70].

It is crucial for the clinical monitoring to be standardized in order to properly assess progression of the disease process. Forniceal foreshortening has been described as a quantifiable means of objectively measuring the extent of the fibrosis [71]. The normal depth of the conjunctival fornix has been documented for healthy South Asian [72] and Caucasian [73] populations. Fornix depth measurers have been used and validated for the measurement of fornix depth, providing reproducible results and facilitating the monitoring of conjunctival scarring [74].

Management of the Ocular Surface Disease

Conjunctival fibrosis causes a number of problems, including dry eyes, punctate epitheliopathy, blepharitis, lid disease, trichiasis, entropion, and lagophthalmos. All of these

conditions contribute to secondary ocular surface inflammation, ocular surface failure, epithelial breakdown, and persistent epithelial defects (PED) and predispose to corneal ulceration, infective keratitis, corneal melt, and perforation.

The severity of dry eyes in OcMMP varies and ranges from mild to very severe. In case of mild to moderate dry eyes, artificial tears should be used. The preparations should be preservative free to avoid ocular surface toxicity. In cases of severe tear deficiency, NaCl 0.9% can also be used as it does not cause blurring of vision [1]. In cases of keratinization, paraffin-based eye ointments can provide great symptomatic relief [1]. Autologous serum can also be used in cases of severe ocular surface dryness. The lacrimal puncta may be occluded by conjunctival fibrosis; if not, then permanent punctal occlusion should be considered once the ocular surface inflammation is controlled.

Blepharitis is common in OcMMP and can be managed with lid hygiene and use of oral tetracyclines. Secondary dry eye-induced ocular inflammation may require the short-term use of topical preservative-free steroid drops. Topical ciclosporin, although not beneficial for the suppression and control of the systemic immune-mediated disease, can be of help in managing the secondary ocular surface inflammation. Mucous filamentary keratitis due to poor-quality tear film can be managed with the use of topical mucolytics, such as acetylcysteine 5% used 3–4 times/day.

The cicatrizing disease causes conjunctival fibrosis, resulting in shortening of the fornices. Although occasionally this requires no intervention, if this condition is associated with a compromised Bell's phenomenon, cicatricial entropion, and lagophthalmos resulting in exposure keratopathy, then fornix reconstruction with oral mucosa grafts is indicated [75, 76]. Fornix reconstruction may also be required in patients who need to use contact lenses.

Trichiasis can be managed with epilation of aberrant lashes, which is a short-term management option as the lashes grow back within 4–6 weeks. A more permanent solution is electrolysis or trephination of the lash follicle and cauterization. Gray line split and anterior lamellar repositioning may be needed for upper lid cicatricial entropion [77], and gray line split with inferior retractor plication may be needed for lower lid entropion [78].

Keratinization occurs most frequently on the lid margin and tarsal conjunctiva. It can be removed manually, although it tends to recur very soon, causing irritation. The use of topical vitamin A preparations is reported to be of benefit; however it may be difficult to source [1]. In these cases, scleral contact lenses can help alleviate the symptoms.

Dry eyes, punctate epitheliopathy, poor blink, lagophthalmos, and ocular surface disease predispose eyes with OcMMP to epithelial breakdown, risk of persistent epithelial defects (PEDs), risk of perforation, and risk of infectious keratitis. Any epithelial defect may harbor a corneal infection, bacterial or viral (such as herpetic keratitis). However, it must be noted that due to systemic and topical immunosuppression, the clinical presentation may be atypical. If infection is suspected or confirmed, it is treated with fortified or broad-spectrum topical antibiotics (for bacterial keratitis) or oral antiviral agents (for herpetic keratitis).

Tarsoraphy may be needed for the management of PEDs. An amniotic membrane graft as an inlay in the area of the PED supplemented by an onlay amniotic membrane graft to cover the whole cornea is effective in reducing ocular surface inflammation and in promoting epithelial healing. Use of autologous serum is also useful in cases of PED.

Corneal perforation should be managed with corneal gluing. A lamellar or patch graft may be required although corneal grafting in OcMMP has a very poor prognosis due to poor epithelial healing, melt, and infection and may need to be combined with a conjunctival or amniotic membrane graft.

Summarizing the treatment strategy for OcMMP, a stepladder approach is used to choose medications and escalate treatment according to disease severity and activity. A step–up and step–down approach and combination of immunosuppressive agents is effective in achieving and maintaining control of the immune-mediated disease. Secondary ocular surface disease, lid disease, trichiasis, and other

factors that predispose to corneal exposure, ulceration and risk of keratitis, and corneal melt must be managed promptly and aggressively.

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