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REVIEW

Ocular mucous membrane pemphigoid: a review

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Abstract

Ocular mucous membrane pemphigoid (MMP) is a rare, immuno-mediated chronic progressive condition of the conjunctiva characterized by blisters developing from sub-epithelial tissue through disruption of the adhesions between the conjunctival epithelium and the sub-epithelium. Patients with ocular MMP, in many cases, develop profound conjunctival scarring and visual impairment. Furthermore, ocular MMP may lead to a progressive secondary corneal vascularization and to corneal opacification. Ocular MMP is difficult to diagnose during the initial stages because of false negatives during biopsy and variability in the clinical presentation. Most of the current pharmacological treatments aim to control the inflammatory response to reduce the progressive tissue remodeling which leads to the formation of a fibrotic scar. The course and prognosis of ocular MMP depend on the severity and progression of the disease after systemic immunomodulatory therapy. The aim of this review is to provide a comprehensive analysis of the current literature on established and emerging concepts in ocular MMP, with special attention to its clinical presentation, diagnosis, treatment, and pathogenic mechanisms, including the role of some cytokines and growth factors in the development of the disease.

Keywords Ocular pemphigoid · Mucous membrane pemphigoid · Autoimmune disease · Fibrosis · Cytokines · Growth factors

Introduction

Mucous membrane pemphigoid (MMP) is a systemic cicatrizing autoimmune disease that primarily affects mucous membranes, such as the conjunctiva, nasal cavity, oropharynx, esophagus, trachea, skin, and genitalia. Ocular involvement in MMP is frequent (ocular MMP) and occurs in nearly 70% of cases [1]. Ocular MMP is a chronic progressive condition of the ocular conjunctiva characterized by blisters developing from sub-epithelial tissue through disruption of the adhesions between the conjunctival epithelium and the sub-epithelium [1].

The anterior barrier of the eye surface is made up of the conjunctiva together with the cornea. The conjunctiva performs different functions, constitutes the mechanical barrier against the attack of pathogens, produces the mucin component of the tear fluid, and concurs to the immune defense. Therefore, a correct function of the conjunctiva is fundamental to maintain the integrity of the ocular surface [1, 2]. Ocular surface disorders such as recurrent pterygium, cicatricial pemphigoid, and Steven–Johnson syndrome may severely involve conjunctival tissue, leading to scar formation with progressive ocular surface inflammation, pain, and vision impairment [2–4]. Chronic conjunctival inflammation in ocular MMP can lead to progressive sub-epithelial fibrosis, tissue remodeling, and neovascularization [1, 4–6] resulting in vision loss in up to 50% of cases caused by limbal epithelial stem cell failure [1].

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The annual incidence of ocular pemphigoid is estimated to be between 1.3 and 2 per million population with a mean age at onset between 60 and 65 years [2] and a greater incidence in females (2:1) over males [3]. Ocular MMP may affect any race, but it seems to be more common in Caucasians [2, 3].

It has been hypothesized that cytokines play an essential role in the pathogenesis of MMP. In the process of remodeling of the extracellular matrix, different cytokines and growth factors are involved. In particular, transforming growth factor-β1 (TGF-β1) and interleukin (IL)-4 can affect the survival of activated fibroblasts and their consequent collagen lamellae deposition [5–8]. Furthermore, Lambiase et al. reported involvement of a nerve growth factor (NGF) pathway in MMP [8]. In fact, it was shown an increased immunoreactivity of the neurotrophic tyrosine kinase receptor A (Trk-A) observed in ocular MMP conjunctival stroma and a consistent NGF release in tears of affected subjects [8]. The aim of this review is to provide a comprehensive analysis of the current literature on established and emerging concepts in ocular MMP, with special attention to its clinical presentation, diagnosis, treatment, and pathogenic mechanisms, including the role of some cytokines and growth factors in the development of this disease. For this purpose, a literature review has been performed on articles retrieved from PubMed and Scopus from the last 30 years on the following topics: ocular mucous membrane pemphigoid, ocular cicatricial pemphigoid, ocular mucous membrane pemphigoid and cytokines, ocular mucous membrane pemphigoid and pathogenic mechanisms, ocular mucous membrane pemphigoid and inflammation, ocular mucous membrane pemphigoid and growth factors, ocular mucous membrane pemphigoid clinical aspects, ocular mucous membrane pemphigoid diagnosis, ocular mucous membrane pemphigoid treatment, autoimmune chronic conjunctival inflammation.

Clinical presentation and diagnostic approach

Ocular MMP is a systemic autoimmune disease developed by a type II immune reaction that leads to bilateral, chronic cicatrizing conjunctivitis and symblepharon formation, compromising the ocular surface and the cornea [3]. Ocular MMP has remissions and exacerbations [3]. The main symptoms of ocular MMP are conjunctival hyperemia, ocular irritation, and secretion of mucus. In the initial stage, the disease usually manifests as a chronic, recurrent cicatricial conjunctivitis.

Ocular MMP is characterized by linear deposition of IgG and IgA autoantibodies directed against epithelial BMZ proteins, with formation of sub-epithelial bullae and scars that represent the initial clinical signs of this condition [2]. Moreover, disorders of the conjunctival layers lead to goblet cell destruction and symptoms of dry eye with burning, itching, foreign-body sensation, and tearing are often found in the early stages. During the development and progression of the disease, inflammatory infiltrates and activated fibroblasts (FBs) actively contribute to the remodeling process of the extracellular matrix (ECM), leading to structural and functional changes [6, 7]. Cicatricial lesions can also affect the eyelids determining lagophthalmos and entropion, damaging the lid margins and producing keratinization and trichiasis. These changes induce corneal scarring and, occasionally, secondary infectious keratitis (Fig. 1).

Ocular MMP is often diagnosed at an advanced stage due to non-specific early clinical manifestations and lack of clinically visible inflammation of the ocular surface, poor sensitivity of immunopathological diagnosis, and difficult differential diagnosis. By performing conjunctival biopsies, it is possible to demonstrate with direct immunofluorescence the presence of blisters and immune-deposits in the basement membrane zone (BMZ) [3, 4]. However, recent studies have demonstrated that only about 50% of patients with ocular MMP have positive direct immunofluorescence on biopsies and 26% require multiple biopsies for a positive result [9–11].

Late diagnosis leads to nearly 40% of patients with ocular MMP suffering from progressive conjunctival fibrosis caused by delayed treatment [11–13]. Furthermore, differential diagnosis can be difficult because many conditions with ocular surface involvement, such as dry eye, Stevens–Johnson syndrome, mucous membrane pemphigoid, chemical/thermal burns, pterygium, and vitamin A deficiency often show the same symptoms as MMP in association with chronic inflammation [14–19].

Pathogenic mechanisms

During the course of ocular MMP, destruction of the corneal epithelial stem cells located at the corneal limbal layers occurs, leading to conjunctival invasion with consequent corneal neovascularization, chronic inflammation, and stromal scarring. These lesions determine vision impairment in affected subjects [19, 20].

In the past years, several studies aimed at elucidating the association between chronic ocular surface diseases and intraocular inflammation [21–23]. Binding of MMP autoantibodies to the dermal-epidermal junction initiates effector cell recruitment by still unidentified mechanisms. Thus, during the acute phases, sub-epidermal cellular infiltration constituted by neutrophils, T cells, and eosinophils occurs. The main expression of these effector cells produces proteases and radical oxygen species that are responsible for the disruption of dermal-epidermal adhesion resulting in mucosal blistering [21–23].

The etiopathogenesis of ocular MMP has a definite immunological basis, although the exact immune mechanisms underlying the disease onset and progression are still unknown.

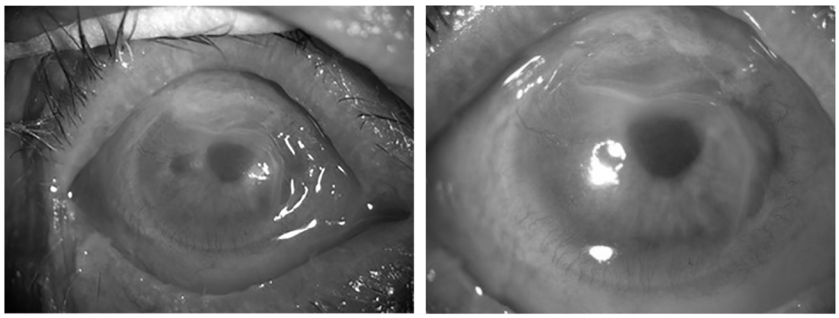

Fig. 1 **a** Clinical signs of ocular mucous membrane pemphigoid, such as bilateral cicatrizing conjunctivitis with symblepharon formation and shortening of the fornices. **b** In some cases, the disease presents eyelid margin thickening, conjunctival erosion, pseudomembranous conjunctivitis, and corneal epithelial erosions

Some studies reported loss of adhesion between keratinocytes, induced by autoantibody production, which is associated with both T helper (Th)-1 and Th-2 [24, 25]. The corneal scarring in ocular MMP follows chronic inflammation involving T cells, macrophages, dendritic cells [26], high levels of pro-inflammatory cytokines tumor necrosis factor (TNF) [27], interferon (IFN)-γ [28], IL-5, and IL-13 [29]. Moreover, it has been reported that IL-17 [27] and the profibrotic cytokines TGF-β [30] and IL-4 [31–39] are more present in affected tissues compared to healthy ones. Activation of inflammatory response leads to a remodeling of the ECM by fibroblasts with scar formation in the ocular anterior compartment [32–34]. Consequently, a corneal scarring induces neovascularization, conjunctivalization, and opacification resulting in the marked loss of vision typical of this condition.

Mechanisms of inflammation

Ocular MMP is characterized by a type II immune reaction depending on specific autoantibodies directed towards basement membrane antigens. This type II reaction leads to activation of the complement cascade provoking an intense inflammation [8, 35].

The inflammatory process that occurs in ocular MMP manifests with conjunctival inflammation and consists of redness, edema, limbitis, and pain [36–38]. Unfortunately, conjunctival and corneal scarring often advance even when the eye is apparently uninflamed [36, 39]. At this level, fibroblasts play a crucial role in the maintenance of inflammation by producing cytokines and chemokines, recruiting and maintaining the survival of T cells and other inflammatory cells via soluble factors, and by cross talking with lymphocytes via the CD40/CD154 pathway [29, 30].

IL-13 is expressed in the conjunctiva in MMP and has direct effects in stimulating normal human conjunctival fibroblast collagen contraction and migration, and modifying matrix metalloproteinase secretion in vitro, which could lead to connective tissue remodeling [40]. It has been demonstrated that IFN-γ can upregulate CD40 expression in human lung fibroblasts, and that IL-13 can increase CD154 levels in such cells [40]. Levels of inflammatory cytokines in the aqueous humor (AqH) have been shown to be elevated during various pathologic processes, such as uveitis, post-cataract surgery, and glaucoma [34–36]. Determination of levels of IL-6, IL-10, IL-17, IFN-γ, E-selectin, and ICAM-1 in the aqueous humor showed a statistically significant elevation in ocular surface diseases [41]. IL-6 is an important inflammatory mediator during various serious systemic conditions [42]. E-selectin and P-selectin have been proposed as are important molecules for the recruitment of immune cells into the AqH in a murine model of endotoxin-induced uveitis [43]. Therefore, the elevated levels of cytokines may predispose patients to the development of certain ocular diseases including MMP.

Repeated phases of inflammation and fibrosis cause progressive cicatrization, symblepharon formation, and ankyloblepharon. Inflammation and scarring are mediated by different groups of inflammatory cells (neutrophils, dendritic cells, mast cells, eosinophils, macrophages, and T cells) with concurrent high expression of cytokines as IL-2, IL-4, IL-5, IL-13, IFN-γ, and growth factors as TNF-α, platelet-derived growth factor (PDGF), TGF-β, and heat shock protein 47 (HSP47) [2]. While the role of autoantibody-mediated inflammation and the formation of typical blistering in MMP has been comprehensively explained, the pathogenesis of the scar process is still debated [30]. Inflammatory and fibrotic processes are induced by different cells: neutrophils, dendritic cells, mast cells, eosinophils, macrophages, and T cells. During the inflammatory process related to MMP, these effects are mediated by inflammatory cytokines (IL-2, IL-4, IL-5, IL-13, IFN-γ) and by the growth factors TNF-α, PDGF, and TGF-β [44]. TGF-β has gained importance in the pathogenesis of autoimmune disorders [44]. In fact, it has been demonstrated that TGF-β is a pivotal differentiation factor involved in the control of tissue homeostasis as well as in the development of T regulatory cells, which furtherly

counteracts inflammation and autoimmunity by regulating the effects of other T helper cells [44, 45].

Despite the fact that different cytokine studies have described Th1/Th2 cytokine levels in ocular disease [25, 46, 47], the studies that found significant IL-17 and TGF-β levels in MMP are still limited. Histological analysis in patients with ocular MMP showed that fibrosis of sub-epithelial tissues appears as striae surrounding the superficial vessels. When these striae contract, they induce the development of bands of abnormal connective tissue which subsequently contribute to producing a conjunctival "shrinkage." The fibrogenic nature of autoimmune ocular diseases, including ocular MMP, has been attributed to the action of TGF-β and of other pro-inflammatory cytokines which are involved in the activation of fibroblasts [27, 48, 49]. Some researchers have identified different factors that may be involved in the profibrotic process, including Serpinh1 (HSP47), connective tissue growth factors, TGF-β, IL-4, IL-5, and IL-13 [5, 27]. Growth factor TGF-β has been shown to induce both fibroblast activation and ECM remodeling by collagen deposition together with other inflammatory cytokines and growth factors that influence fibroblast activity during inflammation [50]. The inflammatory response induces fibrosis through the activation of profibrotic mediators released by macrophages, T cells, mast cells, and eosinophils acting on fibroblasts, including growth factors such as PDGF and TGF-β.

Acutely inflamed conjunctiva in ocular MMP is associated with high stromal levels of TGF-β1 [51, 52]. This suggests that TGF-β may play a role in the pathogenesis of the fibrosis. This process may be mediated by similar mechanisms to those described in the studies on liver fibrosis [53, 54]. In fact, during hepatic injury, the activation of TGF-β leads to the development of the fibrotic process [39, 55]. Active TGF-β induces fibroblast activation and ECM production together with other cytokines and growth factors that affect fibroblast activity [56]. TGF-β1 transform the fibroblast in myofibroblast; these cells express α-smooth muscle cell actin (α-SMA), produce increased amounts of ECM proteins, such as collagen type I, and fibronectin, proliferate and have contractile properties. Their usual activators are IL-6 and TGF-β1, although they can also be activated by a variety of other cytokines, chemokines, and growth factors. Overexpression of myo-fibroblasts during fibrosis determines the remodeling of extracellular matrix prone to tissue regeneration, thus leading to fibrotic scar formation. However, the precise mechanisms that link the recruitment of profibrotic molecules in the lesion site have not been identified [32, 33, 57].

Treatment options

The aim of drug therapy in ocular MMP is to inhibit the processes of ocular inflammation and conjunctival scarring by restoring the normal relationship between the eyelid and the ocular surface [58]. Therapy is based on immunosuppressants [9, 59] although they may have significant side effects and their dose reduction can cause a rapid exacerbation of the disease [36, 39, 60–63] (Fig. 2). Surgical treatment, such as eyelid surgery, amniotic membrane transplantation, and corneal transplantation may be proposed for ocular surface reconstruction and visual rehabilitation in patients with advanced ocular MMP (Fig. 3) [61, 62]. However, the success rate of surgical treatment in ocular MMP is low, and mechanical damage with consequent worsening of the disease can occur. Furthermore, if the eye inflammation is not well controlled

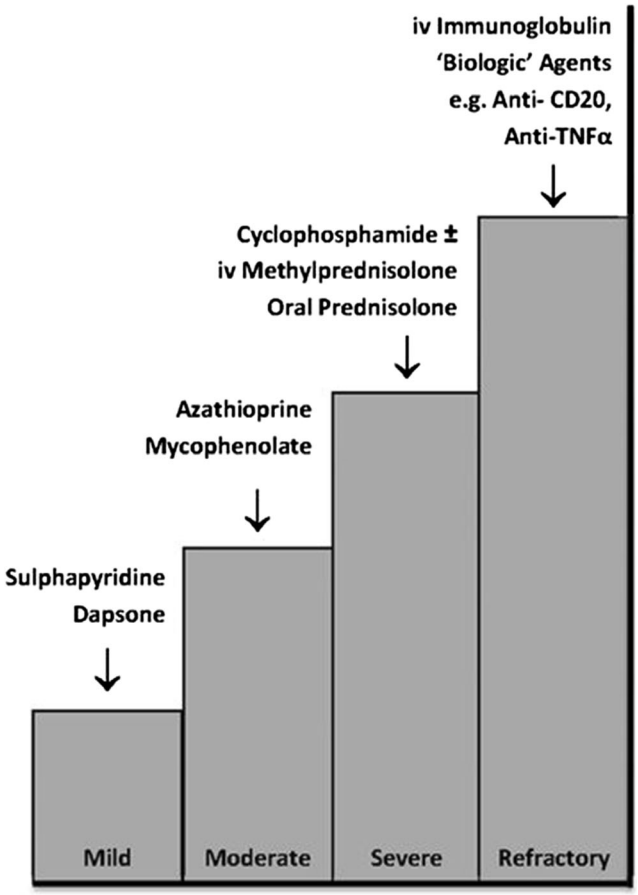

Fig. 2 Immunosuppression strategies (based on Rauz et al). A step-ladder approach to treatment with agents having the fewest side effects to those that have the greatest side effects is adopted according to disease activity (mild, moderate, or severe), which is used to guide therapy. Dapsone (25–50 mg twice a day) or sulphapyridine (500 mg twice a day) can be used for mild inflammation; azathioprine (1–2.5 mg/kg/day) or mycophenolate mofetil (500–1000 mg twice a day if intolerant to azathioprine) may be added or substituted for persistent disease. Severe inflammatory disease is treated with cyclophosphamide (1–2 mg/kg/day) and adjuvant prednisolone (1 mg/kg/day with or without supplementary loading doses of 1 g intravenous methylprednisolone preceding oral therapy) for up to 3 months until the optimal effects of cyclophosphamide have taken effect. Patients with refractory disease are managed through intravenous immunoglobulin or 'biological' agents such as anti-CD 20 (rituximab) or anti-TNF-α therapy. From Williams et al. [39]

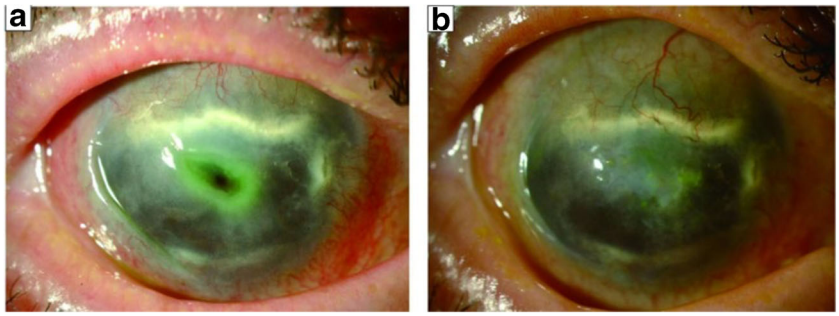

Fig. 3 Representative slit-lamp biomicroscopic photograph of a noninfectious corneal perforation treated by amniotic membrane transplantation. **a** Corneal perforation associated with severe dry eye of ocular mucous membrane pemphigoid. A paracentral small perforation can be noted in the corneal ulcer with a positive Seidel test. Inflamed conjunctiva, corneal pannus, and symblepharon are present. **b** One year after treatment with cryopreserved human amniotic membrane with punctal occlusion. The ocular surface is re-epithelialized and the best corrected visual acuity was equal to the preoperative level. From Yokogawa et al. [62]

during the peri- and postoperative phases, it may lead to ulcerative keratitis after surgery [64, 65]. Hervas Ontiveros et al. [66] suggested that methotrexate alone can be used as a first-line treatment for rapid medium or progressive MMP treatment. However, only a few clinical studies have reported a satisfactory efficacy and safety of methotrexate in the treatment of advanced ocular MMP [63, 67].

Several topical and systemic therapies have been proposed to treat patients with ocular MMP; however, topical agents have proven to be ineffective in controlling disease activity, while systemic immunomodulatory treatment showed some degree of success in suppressing the immune system to sufficiently limit the autoimmune process [1, 36, 68] (Fig. 4).

Cases of MMP with low ocular involvement may be managed effectively using Mycophenolate Mofetil, azathioprine, dapsone, or methotrexate [36, 44, 63, 69–73].

Dapsone and methotrexate were the first drugs to be used for MMP treatment, but they have a considerable number of adverse effects that leads to a low compliance rate. Alternatively, sulfapyridine and sulfasalazine have a lower percentage of adverse effects. McCluskey et al. reported a good control of conjunctival inflammation in 83% (10/12) of cases treated with Mycophenolate Mofetil and methotrexate over a 15-month period [63].

In resistant cases, excellent results were obtained by combining intravenous immunoglobulin (IVIg) and rituximab [74–77]. This combination has been proposed for

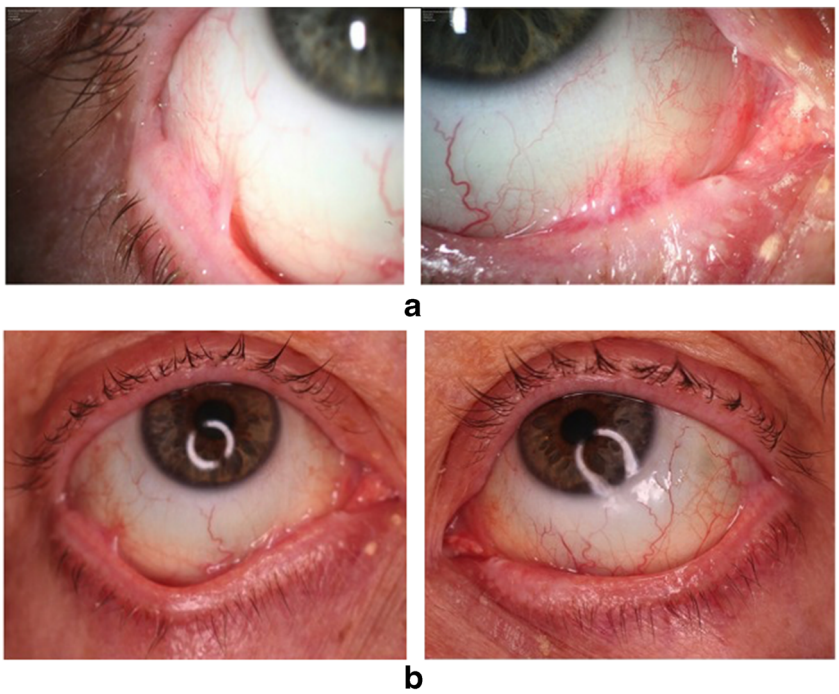

Fig. 4 **a** Active bilateral stage 4 symblepharon according to Tauber und Foster classification in a patient with ocular mucous membrane pemphigoid treated with Intravenous methylprednisolone, oral azathioprine and prednisolone and topical Hylogel. **b** Post-treatment picture 8 weeks later showing a stable ocular involvement. Modified from Wittenberg and Worm [68]

the treatment of ocular MMP and has proven to be effective in counteracting the expression of TNF-α. In fact, some studies have demonstrated an overexpression of growth factor TNF-α in MMP [78, 79]. TNF-α is released by epidermal keratinocytes at the site of intra-epidermal detachment [78, 79] and its expression may be related to MMP activity [78, 79].

In cases of secondary ocular inflammation, the treatment of choice is usually based on cyclophosphamide, a non-specific alkylating agent that is also useful to prevent vision impairment [58, 80, 81].

Intravenous cyclophosphamide (IVC) is also one of the more effective treatment agents in patients with serious ocular inflammatory reactions which has not responded to other safer immunosuppressive agents [82]. Previous trials with IVC have shown that low-dose pulsed IVC treatment is probably suitable for a preferential use in ocular MMP, particularly in aged patients who generally present other concomitant diseases.

IVIg therapy alone is currently considered only for patients not responding to conventional treatment options [83].

Topical and subconjunctival corticosteroids may offer short-term positive effects but are not efficacious in blocking disease progression [58]. Topical and subconjunctival applications of mitomycin C, a drug that blocks cell proliferation, are also used in the treatment of ocular MMP with some degree of success. As reported by Secchi and Tognon, the treatment with topical mitomycin C, on surgical lysis of conjunctival scarring, was characterized by no recurrences after 12–19 months at follow-up [84]. Donnenfeld et al. also reported the use of subconjunctival mitomycin C in subjects with ocular MMP: in their study, after a follow-up ranging from 12 to 40 months, the untreated control eyes presented greater conjunctival inflammation compared to the treated ones [85]. On the contrary, Celis Sánchez et al. reported no positive effects after treatment with mitomycin C in cases of recurrent MMP [86].

Discussion

Patients with ocular MMP often develop vision loss as a consequence of the scarring process, but in 42% of cases, the disease progresses in the absence of clinical signs that confirm the presence of an inflammatory process [35, 38, 77] leading to late diagnosis and irreversible ocular damage. In the light of these data, the future availability of biomarkers to monitor progression of the disease is of paramount importance. As previously described, some studies have demonstrated altered serum levels of cytokines, IL-1, and TNF-α in patients with ocular MMP [87], while other authors described a deregulation of TGF-β levels in the inflamed conjunctiva [71]. All these findings could play a role as potential indicators of disease progression and might be promising for the identification of specific biomarkers allowing the development of targeted biological therapies for ocular MMP [77].

A better understanding of the pathogenic mechanisms of MMP is necessary to ameliorate the identification of the pathology, the definition of its progression and the achievement of a careful therapeutic target. Precise knowledge of the cytokines involved in the development of ocular MMP could be helpful to better understand its pathogenesis. Previous studies reported that the clusters of differentiation of CD4+ T cells as well as Th1 or Th2 cells are generally involved in the remission or progression of the disease. Th1 cells produce a great quantity of IL-2 and IFN-γ; these molecules are fundamental for macrophage activation, which plays an essential role in increasing microbial killing and functionality of cell-mediated immunity. Th2 cells produce IL-4, IL-6, and IL-10; these molecules participate in the stimulation of the immune humoral response, through the activation of B cells, which are involved in the production of antibodies and in the loss of adhesion between keratinocytes [88–90].

Inflammatory cytokines play an important role in the immunopathogenesis of MMP [69] and have become the targets of different therapeutic strategies [91, 92]. A better knowledge of their expression in ocular tissues in affected patients may provide information concerning the immunopathogenic mechanisms of this condition [93]. Based on these observations, a potential clinical application of anti-cytokines therapies in MMP could be proposed, which could become the main perspective of future experimental studies.

Hidden conjunctival inflammation in ocular MMP undoubtedly provides a major clinical challenge. Future studies could use gene expression in order to identify potential therapeutic biomarkers and to delineate potential antifibrotic therapeutic targets. During the development of liver fibrosis, retinoic acid exasperates hepatic stellate cell function by increasing plasminogen activator levels and by producing proteolytic activation of latent TGF-β1, with consequent increase of collagen production [94] supporting liver fibrosis [95]. Similar mechanisms have been shown for MMP [96]. In fact, different histological analysis of ocular MMP samples have demonstrated that, even when the conjunctiva appears clinically "white" and uninflamed, an important cellular infiltrate is present (white inflammation) [28, 96]. Profibrotic processes could be driven by white inflammation, which is supported by ongoing release of cytokines; large doses of anti-inflammatory drugs could control the white inflammation process although evidence is lacking [77].

Recent data suggests that TGF-β1 may contribute to conjunctival fibrosis in ocular MMP and promote the capacity for cross-talk between conjunctival fibroblasts and other inflammatory cells, facilitating fibroblast-generated chronic inflammation and promoting the fibrotic process [97, 99]. The role of NGF in tissue remodeling and fibroblast activity during MMP

is actually unclear, because NGF could exert pro/anti-inflammatory effects or pro-fibrogenic activity. Moreover, NGF could act as a "modulator" during local immune/inflammatory response depending on the receptor. Micera et al. described that during the inflammatory process occurring in ocular MMP, both cytokines and growth factors actively participate to sub-epithelial fibrosis and conjunctival scarring [97–99]. Therefore, a cross-talk between NGF and other pro-fibrogenic factors during ocular MMP could be hypothesized. Elevated expression of some inflammatory cytokines such as TGF-β and IL-4 during the fibrotic process has been extensively investigated, and it has been described that these cytokines actively participate in tissue remodeling during the fibrosis through the activation of myo-fibroblasts [4, 31, 99–101]. Therefore, it is possible that NGF may contribute to the induction of TGF-β release.

Conclusion

The main goal of recent research in MMP is to identify pharmacologic treatments useful to prevent the development of the fibrotic process induced by activation of profibrotic fibroblasts. To date, the exact mechanisms that induce the development of ocular fibrosis in ocular MMP are still unclear. As previously described, the overexpression of fibroblast and myo-fibroblast occur during conjunctival inflammation. These cells play an important role in the development of fibrosis and tissue remodeling; furthermore, the same fibrotic process that occur during ocular MMP take place also in other diseases of ocular surface such as pterygium and vernal keratoconjunctivitis.

Histone deacetylase inhibitors may modulate the activity of corneal stromal cells through the prevention of differentiation of fibroblasts in myo-fibroblasts, preventing also cells proliferation and migration and inducing cell senescence [99].

Epigenetic mechanisms might be involved in the pathophysiology of MMP, which shows an upregulation of conjunctival NGF and Trk-A and an involvement of NGF in cultured MMP-derived fibroblasts [99, 102]. The blockage of the drug that metabolize the enzyme aldehyde dehydrogenase during ocular fibrosis has been reported [103]. This evidence supports the hypothesis of a possible involvement of epigenetic factors in conjunctival fibroblasts and also at the dendritic level through dendritic cells retinoid metabolism [103]. However, further studies are necessary to better understand the mechanisms involved in ocular MMP and to develop an effective long-term treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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