Current Medical Treatment of Ocular Mucous Membrane Pemphigoid

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ABSTRACT Ocular mucous membrane pemphigoid (MMP), as a potentially blinding disease, is an indication for systemic immunosuppressive treatment. Immunosuppressive agents are chosen with a "stepladder" approach, beginning with drugs having the fewest side effects. Dapsone, sulfapyridine/sulfasalazine and azathioprine are less successful in controlling inflammation than mycophenolate mofetil (MMF) and methotrexate (MTX). Moreover, compared to other immunosuppressive agents, MMF, followed by MTX, has the lowest rate of discontinuation due to side effects. Cyclophosphamide is the most potent immunosuppressive agent used for ocular MMP, but it should be used with caution because of life-threatening adverse effects. Intravenous immunoglobulin therapy (IVIg) should be considered for patients who are resistant to conventional immunosuppressive therapy, have significant adverse effects or contraindications to conventional therapy, or have uncontrolled rapidly progressive disease. If IVIg monotherapy is not successful after a period of $\geq$1 year, therapy with biological agents, such as rituximab or anti-TNF-α drugs, is suggested.

KEY WORDS anti-TNF-α agents, azathioprine, biologic agents, cyclophosphamide, dapsone, intravenous immunoglobulin, immunosuppressive agents, methotrexate, mycophenolate mofetil, ocular cicatricial pemphigoid, ocular mucous membrane pemphigoid, rituximab, sulfapyridine, sulfasalazine

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I. INTRODUCTION

Ocular mucous membrane pemphigoid (**MMP**), known also as ocular cicatricial pemphigoid (**OCP**), is a sight-threatening, subepithelial, blistering disease characterized by bilateral, asymmetrical, chronic progressive or relapsing conjunctivitis with conjunctival cicatrization, secondary corneal vascularization, and opacification.[1] The conjunctiva is the second most common site of ocular MMP. Usually, MMP starts with desquamative gingivitis, which is found in up to 65% of MMP patients. Extension of the disease to the larynx or esophagus can lead to strictures and aspiration, which are seen in up to 26% of patients. Some patients have recurring genital lesions, which are highly suggestive of the disease.[2,3] The extraocular manifestation is present in approximately half of patients with ocular MMP.[4,5]

MMP is relatively rare, reported to affect between 1/8000 persons and 1/60 000 ophthalmic patients.[4,6,7] The recent findings of the British Ophthalmological Surveillance Unit study estimated an incidence of 0.7 per 1,000,000 population with a regional variance between 1.1 per million in Greater London to 1.8 per million in the West Midlands.[4] However, the true incidence seems to be underestimated, because the reported cases are usually in their later stages. Ocular MMP occurred two to three times more frequently in women than in men and at an average age of 65 years.[8]

Ocular MMP is a complex autoimmune disorder with a genetic predisposition, but environmental factors may trigger its onset. The presence of the HLA-DQ7 (HLA-DQβ1*0301) gene is linked to increased susceptibility to disease development.[9]

MMP is characterized by a linear deposition of immunoreactants (IgG, IgA, IgM, and/or complement C3) along the epithelial membrane zone, seen with direct immunofluorescence staining. Additionally, autoantibodies against β4 integrin can be detected in a subgroup of MMP patients.[10]

The diagnosis of ocular MMP is based on both clinical findings and immunohistopathology of biopsied conjunctiva. Since the initial complaints are not specific (conjunctival redness, tearing, burning, foreign body sensation) and conjunctival changes of subepithelial fibrosis are subtle, ocular MMP can be easily misdiagnosed at the early stage.

OUTLINE

Conjunctival scarring progresses to foreshortening of the fornix and development of symblepharon, and chronic conjunctival inflammation leads to squamous metaplasia with keratinization of the ocular surface epithelium. In the end stage of ocular MMP, ankyloblepharon develops.

Ocular symptoms are graded according to the staging systems that are used for detecting progression and monitoring therapy of ocular MMP. The four most common systems of staging ocular MMP were established by Foster,[3] Mondino and Brown,[11] Tauber et al,[12] and Rowsey et al[13](Table 1). In 2012, a new grading system for both oral and ocular involvement in MMP was proposed by Reeves et al, who suggest that changes greater than 1.5 mm vertical and 3 mm horizontal are significant.[14] This staging may simplify detection of progression of fibrosis, but it does not grade active inflammation, as the other grading systems do (Table 1).[3,11,12]

For definitive evidence of ocular MMP, a positive conjunctival biopsy is needed. In the study of Thorne et al, the diagnosis could be established in 80% of patients with ocular MMP using direct immunofluorescence (**DIF**) of the initial conjunctival biopsy.[15] Jonkman et al also reported that the DIF is the most reliable diagnostic method.[16] If the DIF is negative, circulating autoantibodies against basement membrane zone (**BMZ**) antigens may be of diagnostic value.[15,16] However, negative immunopathology tests do not exclude ocular MMP in the presence of characteristic clinical features, and repeat biopsy may be indicated.

II. GOALS OF TREATMENT

According to the first international consensus on MMP, ocular involvement is defined as "high risk" and is an indication for systemic immunosuppressive treatment.[17] Hence, therapy should be started when active grade 2 disease is diagnosed. Immunosuppressive agents are selected with a "stepladder" approach, starting with agents having the fewest side effects, then progressing to more potent drugs with more important side effects, depending on disease activity (mild, moderate, or severe).[18] Before an immunosuppressive therapy is chosen, the patient should consult a dermatologist. The choice of agents depends on the spectrum of systemic involvement and clinical severity.

Table 1. Grading systems of ocular mucous membrane pemphigoid (MMP)

Systems	Characteristics
Foster stages[3]	
I	Subconjunctival scarring and fibrosis
II	Fornix foreshortening of any degree
III	Presence of symblepharon, and degree
IV	Ankyloblepharon, frozen globe
Mondino and Brown stages[11]	
I	0-25% loss of inferior fornix depth
II	25-50% loss of inferior fornix depth
III	50-75% loss of inferior fornix depth
IV	75-100% loss of inferior fornix depth
Tauber stages based on Foster stages with subdivisions within stages II and III (a-d corresponding to Mondino and Brown stages)[12]	
II	% loss of inferior fornix depth
III (n)	% loss of horizontal involvement by symblephara (number of symblephara)
Rowsey stages mm/45 (%/100%): total of three measurements of the distance from the inferior limbus to the posterior edge of the retracted lower eyelid (at 5, 6 and 7 o'clock).[13]	
35-45 mm	<25% od conjunctival loss
24-34 mm	25-50% od conjunctival loss
12-23 mm	50-75% od conjunctival loss
0-11 mm	>75% od conjunctival loss
Reeves stages[14]	
Vertical grade: mm/10 (%/100%); the distance from inferior limbus to start of fibrosis at 6 o'clock (10mm is a standard fornix depth)	
a	<25% of conjunctival loss
b	25-50% of conjunctival loss
c	50-75% of conjunctival loss
d	>75% of conjunctival loss
Horizontal grade: % of involvement of bulbar conjunctiva width 2 mm above level of fibrosis, between the inner aspect of the nasal and lateral edges of the inferior posterior lid margin	
a	<25% of conjunctival loss
b	25-50% of conjunctival loss
c	50-75% of conjunctival loss
d	>75% of conjunctival loss

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