แนวทางในการจัดการมิวคัสเมมเบรนเพมฟิกอยด์

ณัฐชาภรณ์ สงวนสิน* ไกรสร ทรัพยะโตษก*

บทคัดย่อ

โรคมิวคัสเมมเบรนเพมฟิกอยด์เป็นโรคกลุ่มภูมิต้านทานเนื้อเยื่อตนเองแบบเรื้อรัง ซึ่งมีลักษณะเป็นตุ่มน้ำใต้ชั้นเยื่อบุผิวที่แตกออกเป็นแผล มักพบที่บริเวณเยื่อเมือกต่าง ๆ ได้บ่อยกว่าบริเวณผิวหนัง แอนติเจนที่เป็นเป้าหมายหลักมีหลายชนิดและอยู่บริเวณชั้นเยื่อฐาน ความรุนแรงและการลุกลามของโรคมีความหลากหลาย ผู้ป่วยอาจมีรอยโรคเฉพาะในช่องปาก หรือผิวหนัง หรืออาจพบรอยโรคที่เยื่อเมือกอื่น ๆ ของร่างกาย สำหรับในช่องปากจะพบรอยโรคได้บ่อยที่สุดที่บริเวณเหงือก โดยมีลักษณะเป็นเหงือกอักเสบลอกหลุด การวินิจฉัยจะพิจารณาจากลักษณะทางคลินิก ลักษณะทางจุลพยาธิวิทยา และการตรวจอิมมูโนฟลูออเรสเซนต์ ปัจจุบันยังไม่มีการรักษาที่เป็นมาตรฐานสำหรับโรคมิวคัสเมมเบรนเพมฟิกอยด์ การรักษาจะพิจารณาเป็นรายบุคคล ขึ้นกับตำแหน่ง ความรุนแรง และการดำเนินของโรค ผู้ป่วยที่มีความรุนแรงของโรคไม่มากจะให้การรักษาด้วยยาทาเฉพาะที่ ได้แก่สเตียรอยด์เฉพาะที่ หรือยาต้านแคลซินิวริน สำหรับผู้ป่วยที่มีความเสี่ยงสูง ได้แก่ ผู้ป่วยที่พบรอยโรคที่เยื่อเมือกหลายตำแหน่งของร่างกาย หรือในรายที่มีการดำเนินของโรคเร็วจะให้การรักษาเพิ่มด้วยยาทางระบบ ได้แก่ สเตียรอยด์ทางระบบร่วมกับยากดภูมิคุ้มกัน ภาวะแทรกซ้อนที่สำคัญ คือ ทำให้เกิดแผลเป็นที่เยื่อเมือกบริเวณคอหอยหลังช่องปากและตา ซึ่งถ้าไม่ได้รับการรักษา อาจทำให้เกิดการตีบแคบของหลอดอาหารและตาบอดได้ตามลำดับ ดังนั้นการดูแลรักษาผู้ป่วยโรคมิวคัสเมมเบรนเพมฟิกอยด์ ทันตแพทย์จึงควรให้การรักษาร่วมกับแพทย์ผู้เชี่ยวชาญสาขาต่าง ๆ เพื่อประโยชน์ในการวินิจฉัยโรครวมถึงการดูแลรักษาผู้ป่วย บทความนี้ได้รวบรวมและเรียบเรียงเกี่ยวกับแนวทางการรักษาโรคมิวคัสเมมเบรนเพมฟิกอยด์ทั้งหมดในปัจจุบัน

คำสำคัญ: โรคภูมิคุ้มกันทำลายตนเอง มิวคัสเมมเบรนเพมฟิกอยด์ คอร์ติโคสเตียรอยด์ ยากดภูมิคุ้มกัน การจัดการ

**วิทยาลัยทันตแพทยศาสตร์ มหาวิทยาลัยรังสิต เลขที่ 52/347 เมืองเอก ถนนพหลโยธิน อำเภอเมือง จังหวัดปทุมธานี 12000*

Management of Mucous Membrane Pemphigoid

Nutchaporn Sanguansin* Kraisorn Sappayatosok**

Abstract

Mucous membrane pemphigoid (MMP) is a chronic autoimmune subepithelial vesiculobullous disorder predominantly affects the mucous membranes more frequently than the skin. Several target antigens in basement membrane zone have been identified in MMP. The disease severity and extension are highly variable. The patients may present with only mucosal or skin lesions or combined multiple sites. In the oral cavity, the most frequently affected site is the gingiva presented as desquamative gingivitis. The diagnosis of MMP is mainly based on clinical findings, histopathologic and immunofluorescence features. The treatment should be individualized based on the sites of involvement, clinical severity and disease progression because there is no gold standard therapy for MMP. Patients with mild disease can be treated effectively with topical therapy, such as topical corticosteroids or topical calcineurin inhibitors. In high-risk patients with multiple involving sites or rapid progression, systemic corticosteroids in combination with immunosuppressive drugs may be added to topical treatment. The significant complication is scarring of the oropharyngeal and ocular mucous membranes which can lead to strictures and blindness. Multidisciplinary approach is necessary for the diagnosis and management of MMP. This article mainly focuses on the management of MMP.

Keywords: Autoimmune, Mucous membrane pemphigoid, Corticosteroids, Immunosuppressants, Management

**College of Dental Medicine, Rangsit University, 52/347 Muang Ake, Phaholyothin Road, A. Muang, Pathum Thani 12000, Thailand.*

Introduction

Mucous membrane pemphigoid (MMP) is a chronic autoimmune subepithelial vesiculobullous disorder which frequently affects oral mucosa and conjunctiva, occasionally the skin. The nasopharynx, esophagus, larynx and anogenital mucosa may also be involved. It is caused by autoantibodies against components of basement membrane zone. Most MMP patients have bullous pemphigoid antigen 2 (BPAg2; a 180-kDa protein; BP180) as the target antigen (1). Clinically, the lesions present as blisters which finally rupture and develop irregularly shaped ulcerations surrounded by erythematous margin. In some patients, the disease is localized to the oral cavity with slowly progressive course without any complications. However, some MMP patients may present with combined multiple sites, such as skin, ocular, nasopharyngeal, esophageal, or laryngeal mucosa. Scar formation is commonly seen which can lead to esophageal and laryngeal stenosis, strictures or even blindness (2). Diagnosis of MMP is mainly based on clinical findings, histopathology and immunofluorescence studies. Early diagnosis and treatment decrease complications and morbidities associated with MMP. Treatment should be based on severity, extension of the disease and disease progression. Patients with mild disease can be managed with local therapies which topical corticosteroids are the mainstay of treatment. In high-risk patients with multiple involving sites or rapid progressive, systemic corticosteroids combined with immunosuppressive drugs may be added. Multidisciplinary approach is essential in management of MMP (3). Aim of this article was to review the update published data on MMP. We searched Pubmed/Medline using the term "mucous membrane pemphigoid". Only relevant published data were selected in this review.

MMP Management

Treatment of MMP is based on the involved sites, severity and disease progression. Additionally, it should be individualized depending on age, medical history and contraindications of systemic medications (4). In low-risk patients with lesions affecting only oral mucosa and/or skin, it can be treated effectively with topical therapy, such as topical corticosteroids or topical calcineurin inhibitors. For more severe or recalcitrant lesions or during exacerbation of disease in low-risk patients, systemic therapy must be combined. High-risk patients with rapid progression or multiple involving sites including ocular, genital, esophageal or nasopharyngeal mucosa require more aggressive systemic treatment, such as systemic corticosteroids combined with immunosuppressive drugs (4). A multidisciplinary approach including oral medicine experts, ophthalmologists, gastroenterologist, otolaryngologist, gynaecologist, and dermatologists is essential for the management of MMP and related to the treatment outcome (3).

Pharmacologic strategies

Topical agents

Topical corticosteroids

High potency topical corticosteroids are the first-line therapy for the localized lesions limiting only oral cavity or oral cavity and skin (5). Topical corticosteroids such as triamcinolone acetonide, betamethasone valerate, beclomethasone dipropionate, budesonide, fluocinonide, fluocinolone acetonide and clobetasol propionate have been used as the initial treatment of MMP (6).

Triamcinolone acetonide 0.1-0.5% in an aqueous rinse or ointment is generally not adequate for controlling the disease. Fluocinonide 0.05%, fluocinolone acetonide 0.1%, clobetasol propionate 0.05% or betamethasone dipropionate 0.05% are commonly effective and can be applied 2-3 times/day (7). Beclomethasone dipropionate or budesonide may be successful for patients MMP involving the palate, esophagus, pharynx or nasal mucosa. After application, the patients should be advised not to drink or eat for 30 minutes. When the lesions are improved, the frequency of application is tapered gradually. In patients presenting with gingival lesions in the form of desquamative gingivitis, topical corticosteroids are generally more effective when used in custom tray that covers the involved gingiva (5,8-9). The clinician must closely monitor the patient for side effects of systemic absorption, especially in patients with frequent and long-term use. The large desquamative lesions and the application with custom tray may enhance the absorption of topical steroid (4). The common adverse effect associated with topical steroid therapy is secondary candidal infection which can be treated with antifungal agents, such as nystatin oral suspension, miconazole gel or clotrimazole troche. For frequent recurrence of oral candidiasis, antifungal prophylaxis may be necessary (9).

Intralesional corticosteroid injection with triamcinolone acetonide 10 mg/ml 0.1 cc/cm^2, every 2-4 weeks can be used in the treatment of recalcitrant MMP or as an adjunctive therapy for topical steroid. Multiple site injection should be performed to distribute the drug throughout the lesion (4).

Topical calcineurin inhibitors

Topical calcineurin inhibitors including tacrolimus, pimecrolimus and cyclosporine are effective in patients not response to topical corticosteroids. Topical tacrolimus has been effectively used in the treatment of recalcitrant MMP affecting oral mucosa, skin and conjunctiva by down-regulating effect on local T-cells (9-10). Daily use of topical tacrolimus 0.1% may be combined with prednisolone (40 mg/day) to control the lesions and allow tapering of the prednisolone dose. Additionally, application of topical tacrolimus alone resulted in complete healing of erosive lesions after 3 months and can prevent disease progression (9-12).

The minor side effects from the use of topical tacrolimus have been reported, such as burning sensation. However, there have been some case reports of using tacrolimus topically with respect to carcinogenesis in the region where tacrolimus had been applied (12). Additionally, the Food and Drug Administration (FDA) has reviewed the safety of topical calcineurin inhibitors, tacrolimus, showing the possible association with an increased risk of cancer especially squamous cell carcinoma (13). Therefore, the clinician must carefully monitor this consequence in case of selecting tacrolimus as a second-line treatment for MMP.

Systemic corticosteroids

Systemic corticosteroids show high efficacy in patients with severe and multiple oral lesions or rapid progression (4). They have a rapid action since the treatment is initiated (3,5). Prednisolone 0.75-1 mg/kg/day is usually an initial dose, and this dose can be continued until the therapeutic response has been achieved (no new lesions

developed and all lesions are healed). After that, the dose should be reduced gradually by 5-10 mg/week. If the disease exacerbates while steroid tapering, the dose used before the disease flaring is represcribed and should be maintained for about 4 weeks. Several corticosteroid-sparing agents such as azathioprine, cyclophosphamide or mycophenolate mofetil have been used as an adjuvant therapy to decrease the dose of systemic corticosteroids and minimize many adverse effects of long-term corticosteroid treatment (4).

Long-term systemic corticosteroid therapy can cause several adverse effects, including hypertension, weight gain, hyperglycemia, hyperlipidemia, water retention, peptic ulcers, secondary infection, cataract, osteoporosis, myopathy, adrenal suppression, difficulty sleeping, and nervousness, so it should be used at the lowest effective dose and for the shortest time, possible. During the treatment, carefully clinical monitoring for potential comorbidities is necessary in every patient (14). Calcium and vitamin D supplementation along with bisphosphonate should be considered for osteoporosis prophylaxis. Additionally, H_2-blocker or proton pump inhibitor is necessary if the patient has a history of gastric ulcers. Bone density, blood sugar and blood pressure should be monitored regularly (15).

Azathioprine

Azathioprine is an immunosuppressant drug. The drug is a purine analog, and the mechanism of action is at the level of DNA. It is converted into 6-mercaptopurine (6-MP) which blocks purine metabolism. By inhibiting purine synthesis, less DNA and RNA are produced for the synthesis of white blood cells, thus causing immunosuppression (16).

Azathioprine is effective for management of autoimmune blistering diseases, including MMP (17). It is typically use as an adjuvant medication to corticosteroids because of its long onset of action (up to 8 weeks). The dose ranges from 1 to 2 mg/kg per day. However, the dosage should be individualized depended on the patient's thiopurine methyltransferase level (5).

The serious adverse effect of azathioprine is leukopenia especially neutrophils resulting in infection, pancytopenia, hepatotoxicity and drug-induced hypersensitivity syndrome. Other common side effects include nausea, vomiting and diarrhea. Appropriate laboratory monitoring should include regular complete blood count and liver function tests (3).

Cyclophosphamide

Cyclophosphamide is an immunosuppressive agent by supressing B-cell function more than T-cell resulting in decreasing antibody production (4). Cyclophosphamide combined with systemic corticosteroid is the first-line therapy for high-risk patients to prevent severe complications including esophageal stenosis, asphyxiation and blindness (1,18). In addition, for patients with severe refractory MMP, cyclophosphamide with or without corticosteroids achieve efficacy in controlling disease rapidly (1). The dose ranges between 1-2 mg/kg/day or 50-200 mg/day. However, the dosage should be determined according to the progression of the disease and the adverse effects (1,19).

The potential adverse effects of cyclophosphamide include bone marrow suppression, hemorrhagic cystitis, infertility and carcinogenesis (1,19). Because of the significant adverse effects, cyclophosphamide should be

used as a short-term treatment and changed to other alternative immunosuppressive agents when MMP is controlled. Regular laboratory monitoring such as complete blood count and urinalysis should be performed (5).

Mycophenolate mofetil

Mycophenolate mofetil is an immunosuppressant which inhibits inosine monophosphate dehydrogenase, an important enzyme in the de novo purine synthesis. This results in inhibition the proliferation of T-lymphocytes and B-lymphocytes and the production of antibodies (3,20).

The dose usually ranges from 1,000 to 2,000 mg/day. The onset of action of mycophenolate mofetil is quite long like azathioprine, it takes 6 to 8 weeks to achieve clinical effect (3,21). Mycophenolate mofetil has been reported the successful treatment of MMP combined with corticosteroids. Additionally, mycophenolate mofetil has been found to be helpful in uncontrolled MMP patients, it can control of inflammation in most of patients with minimal side effects (22, 23).

Mycophenolate mofetil is generally well-tolerated. The most common side effects are the gastrointestinal disturbances, including nausea, anorexia and diarrhea. Periodic complete blood count should be monitored, because it can possibly induce leukopenia (3). Mycophenolate mofetil may be the therapeutic option in MMP patients (4).

Methotrexate

Methotrexate is an antimetabolite that inhibits to dihydrofolate reductase, an enzyme that catalyzes the conversion of dihydrofolate to the tetrahydrofolate. Tetrahydrofolate is a cofactor necessary for the synthesis of nucleotides required for DNA and RNA synthesis. Methotrexate can also inhibit proliferation of the lymphocytes and other cells responsible for inflammation (3).

Oral methotrexate is a steroid-sparing agent and is moderately effective for the anti-inflammatory activity. In addition, methotrexate monotherapy is recommended as first-line therapy in mild to moderate ocular cicatricial pemphigoid. The dose ranges from 12.5 to 22.5 mg weekly (24).

Methotrexate is well-tolerated by most patients. The common gastrointestinal side effects are nausea, anorexia, abdominal pain and diarrhea. The adverse effects include hepatotoxicity, anemia, leukopenia, pancytopenia, pulmonary toxicity, mucositis and malignancy. Additionally, methotrexate is a folate antagonist, so it can lead to folic acid deficiency. Patients on long-term treatment should be regularly checked for side effects. Regular laboratory monitoring includes complete blood count and liver function tests (24).

Dapsone

Dapsone is an antibacterial agent commonly used for leprosy treatment by inhibiting bacterial synthesis of dihydrofolic acid. As an anti-inflammatory agent, dapsone suppresses neutrophil migration and inhibits the synthesis of prostaglandin E2. Some studies have reported the effectiveness of dapsone in management of MMP (25-27). Additionally, dapsone can be used as first-line treatment in localized MMP or extensive MMP without rapid progression. It can be used alone or combined with systemic corticosteroid (26). The initial dosage ranges from 25 to 50 mg per day. It can be eventually

raised by 25 mg every 1 week. The dose can be increased until clinical remission is achieved or until the maximum tolerated dose is reached (generally 200 mg). The patient may need to take a certain dosage of dapsone for weeks before increasing dose to allow the bone marrow adaptation preventing hemolysis. If the patient has no response within 3 months, other immunosuppressive agents such as azathioprine, methotrexate or cyclophosphamide should be added (3-5).

The adverse effects include dose-dependent hemolytic anemia and methemoglobinemia. Patients treated with dapsone must be evaluated the level of glucose-6-phosphate dehydrogenase (G6PD) due to the risk of hemolysis. G6PD is a metabolic enzyme involved in red blood cell metabolism, so the drug should not be administered to individuals with G6PD deficiency due to the high risk for developing extensive hemolytic anemia. Complete blood count should be performed every week for the first 4-6 weeks, every 2 weeks until week 12 and every 3 months thereafter. If hemoglobin decreases more than 2 gm/dl or below 10 gm/dl, dapsone should be discontinued (4,5).

The other side effect is agraunulocytosis. It can occur in approximately 1 in 400 patients and usually presents after 8 to 12 weeks of dapsone therapy (28). Another potential adverse effect is dapsone hypersensitivity syndrome which is an idiosyncratic reaction characterized by fever, lymphadenopathy, hepatitis, generalized erythematous pustules and peripheral eosinophilia. This syndrome is usually occurred during the first 4-5 weeks of therapy, so periodic monitoring of liver function is required during the treatment (4,5).

Cyclosporine

The combination therapy of cyclosporine and corticosteroids was proved to be an effective MMP therapy (29). However, Foster et al. reported cyclosporine was ineffective in the treatment of MMP (30). More studies are needed to determine the ability of cyclosporine in treatment of MMP. Side effects with cyclosporine therapy include nephrotoxicity, headache, convulsion, hypertension, hepatitis, hyperkalemia and neurologic changes. Cyclosporine should not be the first choice of adjuvant therapy in MMP (5,29).

Tetracyclines

Tetracyclines are a group of antibiotics which has potent anti-inflammatory and immunomodulatory effects. The mechanisms of anti-inflammatory and immunomodulatory actions are related to the inhibition of neutrophil and eosinophil chemotaxis, decrease antibody production and prostaglandin synthesis. Tetracyclines have also reduced various tissue enzymes, including collagenase, lipase, and metalloproteinases 2 and 9, resulting in reducing extracellular matrix breakdown (31,32). According to the treatment effect, tetracycline and minocycline have also been reported with successful treatment in low-risk MMP patients. The dose of tetracycline and minocycline ranges from 1,500-2,000 mg/day and 50-100 mg/day, respectively (33). Success in treatment of localized MMP with a combination of tetracycline (1-2 g/day) and nicotinamide (2-3 g/day) have also been used (34,35).

The side effects of tetracycline include nausea, vomiting, diarrhea, dizziness, light hypersensitivity and hyperpigmentation. It is not recommended in patients with renal impairment

or children less than nine years of age. The most common side effects of minocycline are nausea, vertigo, mild dizziness, as well as hyperpigmentation. For the treatments continued for more than 6 months, it is recommended to monitor hepatotoxicity every 3 months. It has been advised that treatment should be discontinued if these complications develop (4,5,36).

Biologics

More recently, biologic agents have been found to be effective for management of mucocutaneous diseases including MMP (37,38). Serum and blister fluid of patients with autoimmune blistering disorders have shown increased level of tumour necrosis factor alpha (TNF-α), so anti-TNF-agents such as etanercept, infliximab and thalidomide are considered as an alternative treatment for these conditions (39).

Etanercept has been reported to be successful in controlling patients with severe MMP not responsive to conventional immunosuppressive agents (40).

Thalidomide is also an anti-TNF-α inhibitor. The use of thalidomide 100 mg daily as an alternative agent to control refractory MMP has been reported (41). But severe teratogenic effect of thalidomide should be carefully considered.

Rituximab, an anti-CD20 monoclonal antibody, has been successfully in treatment of severe and refractory MMP (42). The combination therapy of rituximab and intravenous immunoglobulin has been shown the stabilization of ocular lesion progression and prevention of blindness (43). Daclimumab, an anti-interleukin-2 monoclonal antibody, has been reported to be successful treatment of one patient with recalcitrant MMP (44). However, further studies are needed to determine the efficacy of the biologic agents in controlling MMP and long-term follow up after the therapy is also important.

Long-term clinical monitoring of disease activity after discontinuation of biologic therapy is necessary, because there have been a few reports of relapsing of disease after discontinuation of drugs (33).

Immunomodulatory procedures

Intravenous immunoglobulin (IVIg)

IVIg has been used as monotherapy or adjuvant therapy for MMP (43). It offers an alternative therapy in the treatment of rapidly progressive, extensive, recalcitrant disease or for patients non-responsive to systemic steroid and immunosuppressive agents and has been reported to be more effective and safer than conventional therapy (3,45). Additionally, it may be used in patients that have contraindications to high-dose and long-term corticosteroids or other immunosuppressive agents (45). It has been shown to be useful in patient with progressive ocular MMP by arresting the progression of disease and preventing blindness (5). However, Iaccheri et al. reported IVIg was ineffective in controlling MMP (46).

There are several proposed mechanisms of action of IVIg. These include blockage the Fc receptors, decreasing circulating autoantibodies, inhibition of B-lymphocytes, alteration of T-lymphocyte function, alteration of cytokine production and inhibition of complement-mediated damage (4,47).

IVIg dosage ranges from 2-3 g/kg/cycle. A cycle composes of total dose which is infused in equally divided doses for 3-5 consecutive days. Initially, the frequency of administration varies from every 3 to 4 weeks, but the interval may be shortened to 2 weeks in patients with aggressive ocular MMP. Once the disease activity is effectively controlled, the interval between cycles is then gradually increased. After two cycles given 16 weeks apart and patients still have clinical remission, this is the endpoint of therapy and IVIg should be discontinued (45,48).

Common side effect occurring during IVIg infusion is infusion reaction. The symptoms generally are fever, chills, flushing, headache, nausea, vomiting, myalgia, tachycardia, hypotension and wheezing. In patient with a previous infusion reaction, antihistamine and acetaminophen as premedication may be prescribed. Other rare serious side effects include anaphylaxis, disseminated intravascular coagulation, thrombosis, acute renal failure, hemolysis, neutropenia, congestive heart failure, cerebrovascular disease and aseptic meningitis. Laboratory monitoring includes complete blood count, renal and liver function tests. Human immunodeficiency virus and hepatitis testing should be considered before the treatment (3,5,49).

Plasmapheresis

Plasmapheresis is a new option for the treatment of MMP in difficult cases. It is not recommended as initial therapy but may be considered as a short-term therapy to decrease autoantibody levels. Hashimoto et al., 2000 reported the case of a 73-year-old Japanese woman with antiepiligrin MMP being successfully treated with plasmapheresis. After combining corticosteroids and immunosuppressive agents with plasmapheresis, the ocular lesions improved and showed almost no progression (5,50).

Table 1 shows summary of pharmacologic treatment of MMP from literatures included in this review. Figure 1 summarized pharmacological treatment algorithm for MMP.

Table 1. Summary of pharmacologic treatment of MMP.

Medication	Reference	Result			
		Subject	Treatment	Result	Follow-up (FU): Complication
Topical agents 1. Topical corticosteroids	Motta et al., 2006 (51)	A patient with MMP involving oral mucosa; 36-year-old woman	Clobetasol propionate 0.05% ointment with occlusal tray applied three times daily	After 2 weeks of treatment, all areas of ulceration were healing.	Monthly for 3 months and every 3 months, thereafter
2. Topical calcineurin inhibitors Tacrolimus	Assmann et al., 2004 (10)	2 patients with recalcitrant MMP; 66-year-old woman, and 67-year-old man	Topical tacrolimus 0.1% ointment applied on dental swabs for 15 minutes twice daily	Complete remission within 2 to 3 months	No data
3. Systemic medications					
3.1 Systemic corticosteroids Prednisolone	Kharfi et al., 2010 (52)	A patient with MMP involving conjunctiva, oral and nasal mucosa; 20-month-old boy	Systemic corticosteroids (2 mg/ kg/day) for 12 months	Complete healing of lesions for 12 months	Dapsone and topical ocular cyclosporine are maintained to avoid relapse.

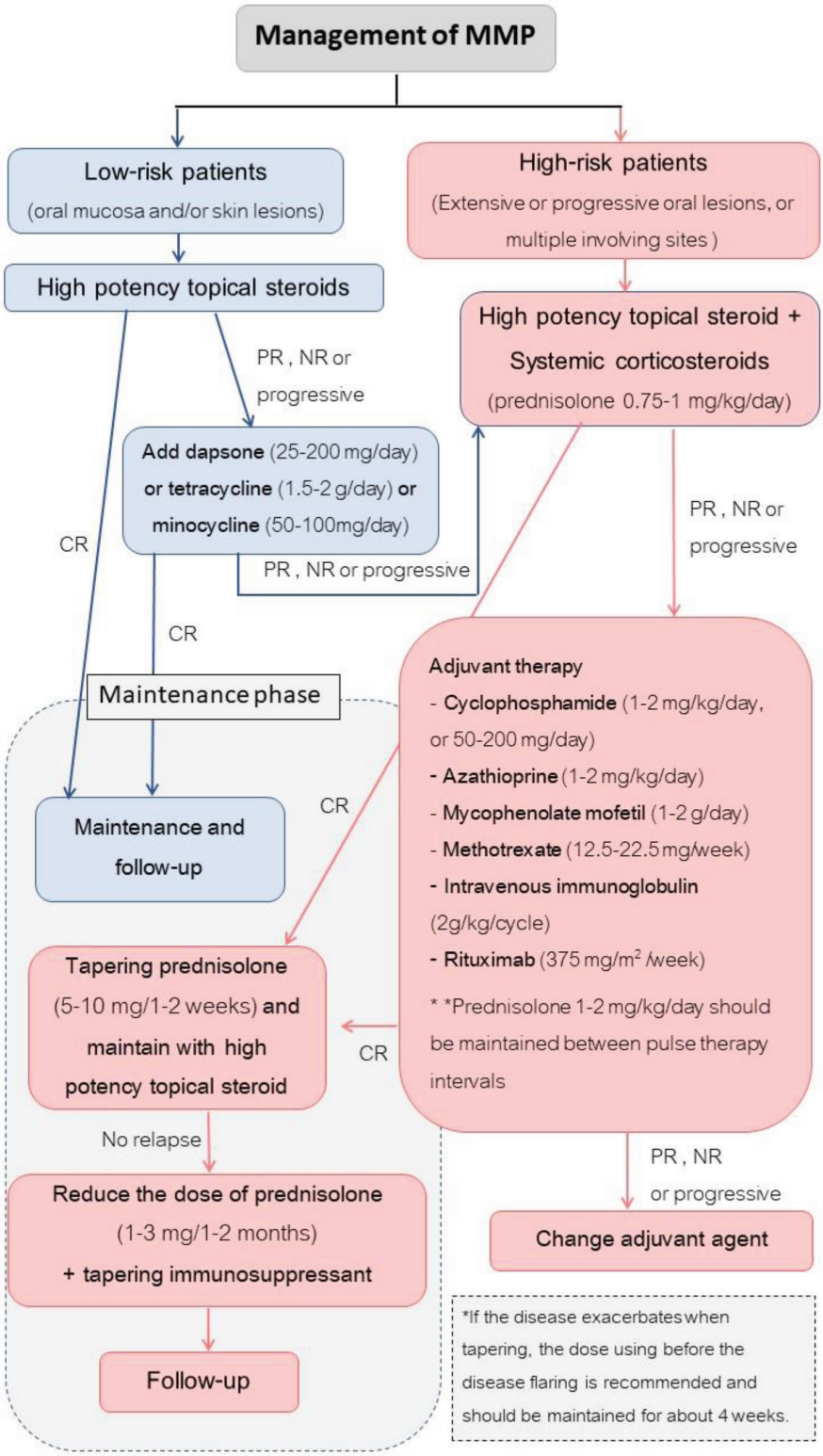
Medication	Reference	Result			
		Subject	Treatment	Result	Follow-up (FU): Complication
3.2. Immuno-suppressive drugs					
Cyclophosphamide	Thorne et al., 2008 (19)	94 patients with ocular MMP; range from 38 to 91 years	Prednisone and cyclophosphamide	91% of patients achieved a remission within 2 years after the initiation of therapy	74% of patients still remission with FU time 3 months to 17 years; Infections, hematuria, and anemia.
	Saw VP et al., 2008 (53)	115 patients with ocular MMP; range from 17 to 92 years	Cyclophosphamide mycophenolate mofetil, azathioprine, dapsone, and sulfapyridine	The most successful therapies were cyclophosphamide (69%), followed by mycophenolate (56%), azathioprine (49%), dapsone (48%), and sulphapyridine (38%).	At least 6 months of FU, the lesions still remission in 14% of patients; Lymphopenia, lethargy and malaise, nausea & vomiting, diarrhea, abdominal discomfort, anemia.
Mycophenolate fmofetil	Staines et al., 2012 (22)	6 patients with MMP involving oral mucosa; Range from 43 to 86 years	The combination of mycophenolate mofetil, dapsone, and prednisolone	Complete remission of all patients in 18 months of therapy	Monthly initially, and every 3 months after disease control

Medication	Reference	Result			
		Subject	Treatment	Result	Follow-up (FU): Complication
	Doycheva et al., 2011 (23)	Ten patients (19 eye lesions) with ocular MMP; range from 46 to 79 years	Mycophenolate mofetil 2 gram daily	Control of inflammation was achieved in 11 eye lesions (58%) of 6 patients	FU at least 4 years; Minor side effects were found in seven patients
Methotrexate	McCluskey et al., 2004 (24)	17 patients with ocular MMP and drug-induced ocular MMP; range from 63 to 81 years	Methotrexate monotherapy 5-25 mg weekly for 8-22 months	Control of inflammation was achieved in 89% of patients with MMP and 100% of drug-induced MMP.	FU 30.2 months; Gastrointestinal side effect
Cyclosporin	Kacmaz et al., 2010 (29)	6 patients with ocular MMP; range from 5.5 to 81.5 years	Cyclosporine	Completed control of inflammation was achieved in 20% of patients in six months after therapy	The median FU was 0.9 years; Hypertension, renal toxicity.
3.3 Antibiotics Dapsone	Arash A et al., 2008 (25)	15 patients with moderate to severe MMP; range from 27 to 65 years	Topical corticosteroid with dapsone 25 mg daily for 7 days, 25 mg twice daily for 7 days, 25 mg 3 times daily for 7 days, and 50 mg twice daily for 7 days	15 patients had significant effective effect.	FU 3 months; Hemoglobin decrease

Medication	Reference	Result			
		Subject	Treatment	Result	Follow-up (FU): Complication
Minocycline	Carrozzo et al., 2009 (54)	9 patients with oral MMP; range from 30 to 74 years	Minocycline (2 mg/day)	The major and minor response wear observed in 3, and 4 patients, respectively. 2 patients showed no improvement.	FU at least 2 years; Vertigo and gastrlgia
4. Biologics Rituximab	Lamberts et al., 2018 (55)	14 patients with pemphigoid diseases; mean age was 67.13 years	Patients were treated with Rituximab 500 mg at days 1 and 15 in 2010–2012. From 2012 the protocol was adjusted to 1,000 mg.	Disease control was achieved in 85.7% of patients, partial remission in 64.3% and complete remission in 28.6%.	FU (mean 72.5 weeks) 75% relapsed; Dizziness, infusion reactions, dyspnea with chest pain
	Lourari, 2011 (56)	7 patients with pemphigoid diseases; range from 33 to 85 years	Infusion of rituximab (4 infusions of rituximab at weekly intervals at a dose of 375 mg/m2) concomitant with immunosuppressive medications	The complete and partial remission were observed in 4, and 2 patients, respectively.	FU (Average) 8 months. 4 patients are still in maintained remission, but 1 patient relapsed after 4 months of complete remission. Follow-up time ranging from 1 month to 2 years 1 patient with a previous history of cardiac disease suddenly died 10 days after the first infusion of rituximab.

Medication	Reference	Result			
		Subject	Treatment	Result	Follow-up (FU): Complication
Etanercept	Canizares et al., 2006(40)	3 patients with MMP; 47-year-old, 49-year-old, and 60-year-old women	Subcutaneous injections of 25 mg of etanercept twice weekly	Oral mucosal disease improved in all patients. The patient with ocular involvement had stabilizered progression.	FU 1 month to 2 years; Myalgia
Infliximab	Hefferman, 2006 (57)	Patient with severe MMP; range from 46 to 79 years	Infliximab (a dose of 5 mg/kg by infusion at initial dose and received at 2 weeks and 6 weeks after initial dose and every 8 weeks thereafter)	The oral lesions and symptoms had rapid improvement.	FU more than 6 months
Bortezomib	Saeed et al., 2018 (58)	68-year-old male MMP patient with histoty of conjunctival inflammation, epistaxis, skin and oral erosions	4 cycles of bortezomib infusions over 10 months.	The skin lesions had rapid improvement and no new lesions were detected after the fourth cycle of treatment.	FU more than 14 months; Fever, malaise, myalgias, arthralgias, and rash
5. Intravenous immunoglobulin	Foster et al., 2010 (43)	12 patients with oculat cicatricial pemphigold: range from 39 to 78 years	6 patients received immunosuppressive therapies were compared to 6 patients treated with the combination of RIX and IVIg.	All patients received immunosuppression had progression of ocular lesions. All patients treated with RIX and IVIg had no further progression of ocular lesions.	Median follow-up from completion of the RIX and IVIg treatment protocol was 11 months.

Medication	Reference	Result			
		Subject	Treatment	Result	Follow-up (FU): Complication
	Letko, 2004 (59)	16 MMP patients with ocular involvement; range from 48 to 76 years	8 patients were treated with IVIg as monotherapy. The dose was 2 g/kg per cycle. 8 patients were continually treated with immunosuppressive therapy.	All patients had decreased conjunctival inflammation and initiated clinical remission.	No recurrence of ocular inflammation was found in patients treated with IVIg. 5 patients treated immunosuppressive agents had been found the ocular inflammation and progression; Headaches and nausea in IVIg, anemia in immunosuppression.
	Yeh et al., 2004 (60)	13 patients with severe involving multiple mucosae and the skin; range from 29 to 81 years	IVIg as monotherapy over a consecutive 18-month period.	The significant decline in the autoantibody titers to β-4 integrin was observed after 3.42 months of initiating the IVIg therapy. These titers were undetectable after 13 months of therapy.	Mean total duration of IVIg therapy thereafter was 20.6 months.



CR; complete response, PR; partial response, NR; no response

Fig 1. Treatment algorithm for MMP.

(Modified from Xu et al, 2013 (4), Pongsiriwet et al, 2018 (7), Bagan et al., 2005 (9), and Ujiie et al, 2019 (61))

Non-pharmacologic strategies

Surgical management

The goal of surgical management is not a curable treatment for MMP, but it could prevent the severe complications, such as ocular scarring progressing to blindness, upper airway stenosis, esophageal and anogenital strictures (62). Surgical treatment may be useful in alleviating symptoms, restoring functional impairment and improving quality of life. Ophthalmic surgical corrections include entropion surgery, tarsorrhaphy, surgical reconstruction of the fonices combination with mucous membrane grafting or amniotic membrane grafting, corneal transplantation and keratoplasty (1). The visual acuity was improved significantly after surgical management about 4 weeks, but this improvement disappeared thereafter (63). Esophageal strictures causing dysphagia can be treated with esophageal dilation (64). However, surgery should not be performed until the disease is remission, because it may aggravate the disease (3).

Laser

The efficacy of laser in the treatment of MMP has been reported. The application of low-level laser therapy (LLLT) using an 810 nm diode laser has been shown to be successful in a patient with MMP as an adjunct to local corticosteroids. The patient was followed up every month for a period of 12 months, and the lesions resolved uneventfully (65). Cafaro et al., 2012 reported 3 patients with MMP with oral mucosa involvement were received low-level laser therapy by two laser sessions per week with an average number of laser sessions of 9.66. After treatment, every patient had complete remission in clinical sign without complications or side effects (66). Moore et al. reported a patient with MMP with ocular involvement who was treated with transscleral diode laser cyclophotocoagulation. The patient had free of pain and decreasing of intraocular pressure without causing an exacerbation of the condition (67).

Oral care

Excellent oral hygiene care is important for patients with gingival lesions to decrease plaque-induced gingival inflammation and prevent oral infection (1). This consists of gently brushing teeth twice a day and flossing at least once a day. Professional teeth cleansing should be performed every 3-6 months (5). Arduino et al., 2012 reported that patients affected by MMP with specific gingival localization received oral hygiene instruction and periodontal therapy are associated with improvement of gingival status and decreasing in gingival-related pain (68). Furthermore, dental trauma and any irritations including poorly fitting denture, sharp edged teeth or restorations, hard or spicy food, toothpaste containing sodium lauryl sulfate, and mouthwash with alcohol should be avoided, because these irritate oral tissue and may exacerbate the disease. The patients with MMP should be evaluated to ensure that there are no any sharp-edged teeth and restorations and all dental prosthesis is fit properly. Topical anesthetic agent may be recommended additionally for relieving pain (1).

Recommendations for MMP Patients

1. MMP is a chronic autoimmune disease not the contagious disease and cannot be cured completely.

2. Excellent oral care including oral hygiene instruction, removing all irritations and periodontal treatment should be performed in all MMP patients with oral involvement.

3. Avoidance of trauma is necessary because it may induce the new blisters or erosions.

4. Patients should know about the medications such as application, dosage, frequency, consideration and side effects.

5. The treatment should be individualized based on disease severity, involving sites, progression of the disease, age and general conditions of the patient as well as contraindications to the systemic medication.

6. If the patients with ocular involvement do not receive adequate and proper treatment, the lesions may result in scarring and potentially progress to blindness.

7. Multidisciplinary approach is important for the diagnosis, management and treatment outcomes.

Conclusion

MMP is a chronic autoimmune disease characterized by subepithelial blisters that typically affects mucous membranes more often than skin. It is more common in female and mainly affects elderly people. Diagnosis is mainly based on clinical findings, histopathology and immunofluorescence studies. There is no gold standard therapy for MMP. The treatment depends on the sites of involvement, clinical severity and disease progression. Treatment for localized disease, topical therapy is the mainstay of treatment. For more severe, widespread disease or recalcitrant to previous therapies requires more aggressive therapy. Systemic corticosteroids in combination with immunosuppressive drugs are the treatment of choice. Scarring is commonly seen which can progress to esophageal and laryngeal stenosis, strictures and blindness. Early diagnosis and treatment may decrease disease-related morbidity and mortality. Multidisciplinary approach is necessary for the diagnosis and management of MMP.

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ติดต่อบทความ:
รศ.ทพ.ดร.ไกรสร ทรัพยะโตษก
วิทยาลัยทันตแพทยศาสตร์ มหาวิทยาลัยรังสิต
เลขที่ 52/347 เมืองเอก ถนนพหลโยธิน อำเภอเมือง จังหวัดปทุมธานี 12000,
โทรศัพท์: 02 997 2000
อีเมล์: kraisorn.s@rsu.ac.th

Corresponding author:
Assoc.Prof.Dr. Kraisorn Sappayatosok
College of Dental Medicine, Rangsit University,
52/347 Muang Ake, Phaholyothin Road, A. Muang, Pathum Thani 12000 Thailand.
Tel: (662) 997 2000
E-mail: kraisorn.s@rsu.ac.th

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