

Treatment of Mucous Membrane Pemphigoid With Mycophenolate Mofetil

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Purpose: To evaluate the clinical outcomes of mycophenolate mofetil (MMF) treatment of mucous membrane pemphigoid (MMP).

Methods: This is a retrospective analysis of consecutive patients with clinical MMP seen in the Ocular Surface Disease Clinic at the Wills Eye Institute, between January 1, 2004, and December 31, 2010, treated with MMF. The main outcomes measured were control of inflammation and discontinuation of MMF.

Results: A total of 23 MMP patients taking MMF were identified. The median age of the MMF-treated patients was 77.0 years. Eleven of the 23 patients (47.8%) had biopsy-proven MMP. All patients were at least Foster grading system stage 2, with most stage 3 or 4. Eight patients (34.8%) failed previous treatments with dapsone, methotrexate, prednisone, azathioprine, cyclophosphamide, or 6-mercaptopurine. The average duration of MMF treatment was 23.32 ± 33.17 months (range 1–124.83 months, median 7.4 months). Of the 23 patients with MMP, control of inflammation was achieved with MMF within 3 months for 56.5% [95% confidence interval (CI) 54.5–59.6], within 6 months for 69.6% (95% CI 65.2–76.6), and within 12 months for 82.6% (95% CI 75.3–92.4) of the patients. Nineteen patients (82.4%) achieved control of inflammation, with 16 of the 19 (84.2%) achieving control of inflammation with MMF as monotherapy. Fifteen patients were treated with MMF as initial therapy. Twenty-one percent of patients (5 of 23) were taken off MMF for failure of inflammatory control (4) or an allergic reaction (1).

Conclusions: Treatment of MMP with MMF in this uncontrolled case series resulted in control of inflammation in the majority of patients with minimal side effects. Our data support consideration of MMF as an initial treatment option for active ocular MMP.

Key Words: mucous membrane pemphigoid, ocular cicatricial pemphigoid, mycophenolate mofetil, immunosuppression

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Mucous membrane pemphigoid (MMP), also known as ocular cicatricial pemphigoid, is a systemic cicatrizing autoimmune disease in which autoantibodies deposit along the epithelial basement membrane of skin and mucosa. The rate of ocular involvement varies in ophthalmic and oral literature and ranges from 30% to 70% depending on the source.^{1,2} Chronic, progressive, cicatrizing conjunctivitis with foreshortening of the fornices, symblepharon formation, severe ocular surface disease, corneal ulceration, and subsequent corneal scarring resulting in visual loss can occur without treatment. Immunosuppressive therapy is used in an attempt to halt the progression of this disease.

Various immunosuppressive agents have been used to suppress the inflammatory response in MMP. Current literature suggests that inflammation can be controlled with dapsone,³ sulfasalazine,⁴ or methotrexate⁵ in mild to moderate disease; azathioprine⁶ in moderate disease; cyclophosphamide^{7,8} with prednisone at induction for moderate or severe active disease; intravenous immunoglobulin⁹ for treatment failures; and tumor necrosis factor inhibitors^{10–12} for treatment failures.

Recent reports have indicated that mycophenolate mofetil (MMF; CellCept; Roche, Nutley, NJ) may offer comparable immunosuppression when compared with the various aforementioned treatments.^{13–18} MMF was first introduced in the 1990s and has been gaining popularity as a corticosteroid-sparing therapy for solid organ transplant rejection and multiple autoimmune diseases.^{19–23} The mode of action is reversible inhibition of inosine monophosphate dehydrogenase in purine biosynthesis. As an immunosuppressant, MMF selectively inhibits the replication of T and B lymphocytes. Because it does not affect the salvage pathway of purine nucleoside synthesis, MMF may have fewer side effects than other antimetabolites, such as azathioprine.¹³ MMF has also been found to be effective in the treatment of ocular inflammation.^{13–15} Cyclophosphamide offers superior immunosuppression but is potentially more toxic than MMF.⁸ In current literature, there are only a limited number of MMP patients treated with MMF. The largest case series of MMP patients treated with MMF included 34 patients, but MMF was used only as an adjunctive agent.¹⁶ All studies report favorable disease suppression with limited side effects.^{13–19}

For nearly a decade, MMF has been used with increasing frequency in the Wills Eye Institute Ocular Surface Disease Clinic as the preferred monotherapy and first-line systemic immunosuppressive agent for MMP. The purpose of this study was to evaluate the outcomes of treatment and side effect profile using MMF for MMP.

MATERIALS AND METHODS

Study Population

This study was performed with the approval from the Wills Institutional Review Board. A retrospective analysis of all MMP patients, seen in the Ocular Surface Disease Clinic from January 1, 2004, to December 31, 2010, who were treated with MMF, was conducted. All information, regarding study patients, was HIPAA [Health Insurance Portability and Accountability Act] compliant.

Information on all patients with MMP was entered into a custom database. The available information for every eye of every patient at every visit was entered. Demographics and clinical characteristics, including duration and severity of disease, medical and surgical treatment history, level of inflammation, side effects, biopsy results, and reason for discontinuation of therapy, were obtained.

Main Outcome Measures

The main outcome measured was the control of inflammation, which was defined as control of conjunctival inflammation/hyperemia. At each visit, the ocular inflammation was assessed and determined to be either active (conjunctival hyperemia and/or progression of conjunctival cicatrization), slightly active (mild conjunctival hyperemia), inactive (no active conjunctival hyperemia), remission (no ocular disease activity for 3 months after cessation of immunosuppressive drugs), or relapse (flare of ocular disease in either eye after remission based on the classifications in the SITE [Systemic Immunosuppressive Therapy for Eye Diseases Cohort] study).⁵ The initial dosing of MMF was 500 mg twice a day and adjusted based on clinical response to the lowest dose possible for disease suppression. We documented the time required for disease suppression. Treatment failure was defined as not having control of conjunctival inflammation/injection. Discontinuing treatment indicated treatment failure or adverse events. Adding an additional agent was considered to be MMF treatment failure as well. Outcomes were not accepted until they had been observed over ≥ 2 visits spanning ≥ 28 days to avoid counting transient improvements and brief interruptions of therapy as successes or failures. Once MMF was initiated, it was continued indefinitely in most cases. Some patients were also placed on oral prednisone initially and slowly tapered. The presence of secondary malignancy or infection while on MMF was derived from the medical history and review of systems.

Ophthalmologic Exam

Ophthalmologic examination included measurements of best-corrected visual acuity from Snellen acuity charts with conversion to logarithm of the minimum angle of resolution (logMAR) scale, conjunctival inflammation, and staging/progression of cicatrization according to the Foster staging system (stage 1, subepithelial fibrosis; stage 2, fornical foreshortening; stage 3, symblepharon; and stage IV, ankyloblepharon formation).²⁴ External photographs were taken upon presentation and at varying intervals to facilitate documentation of disease progression.

A diagnosis of MMP was based upon biopsy results and clinical evaluation. Biopsies were taken from ocular or oral mucous membranes in perilesional areas, preferentially from oral samples if patients had active oral ulcerations. If there was not an active lesion, the biopsy was performed of the inferior conjunctiva. All specimens were sent for pathological evaluation and for direct immunofluorescence testing at experienced diagnostic centers (Beutner Laboratories, Buffalo, NY; or Johns Hopkins Dermatoimmunology Laboratory, Baltimore, MD). All reasonable attempts were made to obtain a positive immunopathologic tissue diagnosis, but a negative or inconclusive biopsy did not exclude the diagnosis of MMP in this study if patients demonstrated characteristic clinical features of the disease. A clinical diagnosis of MMP was made in the setting of conjunctival cicatrization, after excluding other causes of scarring such as Sjögren syndrome, atopic keratoconjunctivitis, rosacea, chemical/thermal injury, adenoviral conjunctivitis, Stevens–Johnson syndrome, lichen planus, pemphigus vulgaris, paraneoplastic pemphigus, chronic conjunctivitis of lupus, and long-term use of topical antiglaucoma medications.

Laboratory test results, including complete blood count and differential, blood urea nitrogen, creatinine, and liver enzymes, were obtained before starting MMF, then every 2 weeks for a month, and then every 1 to 3 months depending on the stability of the test results. Immunosuppression was comanaged with a dermatologist or rheumatologist.

RESULTS

Study Population

A total of 201 patients were seen in the Ocular Surface Disease Clinic at the Wills Eye Institute from January 1, 2004, to December 31, 2010, and all medical records were reviewed for a diagnosis of MMP. One hundred seven patients were excluded because of a diagnosis other than MMP. Of the 94 patients with MMP, a total of 23 (24.5%) were treated with MMF during this time period. Table 1 summarizes the demographic characteristics of the study population. Ten of the 23 patients (43.5%) had concomitant oral ulcers. One patient (4.3%) had another systemic autoimmune disease (ankylosing spondylitis). At the initiation of MMF, 13 of the 46 eyes (28.3%) had other ocular comorbidities.

In the study group of 23 MMP patients treated with MMF, 11 (47.8%) had biopsy-proven MMP, 5 from buccal mucosa, 4 from conjunctiva, and 2 from an unknown site (Table 1). The yield for positive biopsies was 45.5% from buccal mucosa (5 of 11), and the yield from conjunctival specimens was 33.3% (4 of 12). The median duration from diagnosis to the start of MMF therapy was 1.2 (0.33–7.1) months.

Before starting MMF, 8 patients (34.8%; 3 with biopsy-positive disease and 5 with biopsy-negative disease) failed or developed side effects from previous treatments: dapsone (4), methotrexate (2), prednisone (3), azathioprine (2), cyclophosphamide (1), or 6-mercaptopurine (1; Table 2). Of these 8 patients, 3 (37.5%) were on >1 immunosuppressive agent before beginning treatment with MMF. Dapsone, the only

TABLE 1. Characteristics of the Study Population (N = 23)

	n (%) [*]
Age (yr), median (range)	77.0 (66.2–81.5)
Sex	
Female	12 (52.2)
Male	11 (47.8)
Race	
White	22 (95.7)
Black	1 (4.3)
Bilateral disease	23
Biopsy positive	11 (47.8)
Buccal mucosa	5 (45.5)
Conjunctiva	4 (36.3)
Unknown location	2 (18.2)
Foster stage (eye)	
2	10
3	35
4	1
Duration (mo) of disease at the start of MMF therapy, median (range)	1.2 (0.33–7.1)
Visual acuity (logMAR) at the start of MMF therapy, median (range)	0.40 (0.13–0.63)
Ocular comorbidities at presentation	
Cataracts	3
Age-related macular degeneration	2
Retinal detachment	1
Ocular HTN or glaucoma	1
Corneal scar s/p PK	1
Ptosis	1
Floppy eyelid syndrome	1
SLK	1
Uveitis	1

^{*}Unless otherwise noted.

HTN, hypertension; s/p PK, status postpenetrating keratoplasty; SLK, superior limbic keratoconjunctivitis.

medication stopped secondary to ineffectiveness, was discontinued in 3 patients (2 biopsy-positive patients and 1 biopsy-negative patient). One of these patients also developed hemolytic anemia. One biopsy-positive patient developed hemorrhagic cystitis, thrombocytopenia, and leukopenia from cyclophosphamide before it was terminated. Two patients developed elevated liver enzymes, one secondary to methotrexate and one secondary to azathioprine. Significant fatigue occurred in 1 patient on methotrexate and 1 patient on 6-mercaptopurine. One patient could not tolerate the nausea from azathioprine. Prednisone was used for an extended period of time in 3 patients before they were referred to this clinic. The treatment for all 3 patients was changed to MMF to avoid the adverse effects of long-term steroid therapy.

Treatment Outcomes

All patients were started on MMF at a dose of 500 mg twice daily and the dose was titrated to achieve disease control. The median (25%–75% quartile) maximum dose of MMF used was 2000 mg/d (1000–2000 mg/d). The dose required

TABLE 2. Prior Immunosuppressive Drug Therapy in Patients Treated With MMF

Previous immunosuppressive therapy, n (%)	
Any previous immunosuppressive drug use	8 (34.8)
>1 immunosuppressive drug before MMF	3 (13.0)
Patient No. 1 (+) dapsone (F), cyclophosphamide (SE), prednisone (O), MMF (TS)	
Patient No. 2 (+) dapsone (F), MMF (TS)	
Patient No. 3 (+) azathioprine (SE), 6-mercaptopurine (SE), prednisone (O), MMF (TS)	
Patient No. 4 (–) dapsone (F), MMF (SE [*])	
Patient No. 5 (–) dapsone (SE), azathioprine (SE), MMF (TS)	
Patient No. 6 (–) methotrexate (SE), MMF (F, changed to cyclophosphamide)	
Patient No. 7 (–) methotrexate (SE), MMF (F, changed to IVIg)	
Patient No. 8 (–) prednisone (O), MMF (TS, A methotrexate)	

^{*}SE resolved with a lower dose of MMF and the patient had treatment success with MMF.

–, biopsy negative; +, biopsy positive; A, additional agent; F, failure of medication; IVIg, intravenous immunoglobulin; O, other (stopped to avoid side effects of long-term steroid use); SE, side effect of medication; TS, treatment success.

for disease suppression was higher in the biopsy-negative group (2000 mg/d, 1375–2125 mg/d, vs. 1000 mg/d, 1000–2000 mg/d; $P = 0.2257$, Mann–Whitney test). The median duration of the MMF treatment was 7.4 (3.4–29.1) months. Once initiated, MMF was not discontinued if disease suppression was achieved unless there were adverse side effects, except for 1 patient. One biopsy-negative patient stopped MMF after 3 years of successful treatment. This patient had disease remission for 7 years with subsequent relapse of ocular inflammation. The patient was restarted on MMF with successful suppression of inflammation.

Control of inflammation was achieved with MMF within 3 months for 56.5% [95% confidence interval (CI) 54.5–59.6], within 6 months for 69.6% (95% CI 65.2–76.6), and within 12 months for 82.6% (95% CI 75.3–92.4) of the patients. Fifteen of the 23 patients (65.2%) were treated with MMF as initial therapy. Sixteen of 19 patients (84.2%) achieved inflammation control on MMF as monotherapy. Three patients required concomitant treatment with either prednisone (1 biopsy positive and 1 biopsy negative) or methotrexate (1 biopsy negative). The prednisone dose was initiated at the same time as MMF for both patients. The dose was started at 60 mg/d and tapered to 10 mg/d over a few months. The methotrexate dose was 15 mg/wk and was started first and then MMF was added with the intent to stop methotrexate once disease suppression was achieved. Neither medication was stopped because the patient tolerated both medications well with control of inflammation.

The median length of time to disease control was 3.27 (2.15–5.55) months for all patients who had suppression of inflammation (19 of 23; Fig. 1). Patients who failed previous treatment with other immunosuppressive agents before MMF and achieved disease suppression required 4.10 (2.8–5.34) months (6 of 19) versus 3.85 (2.1–4.2) months in the naive

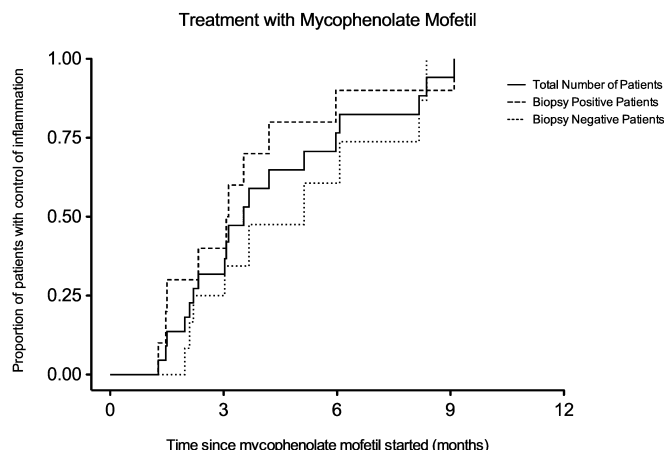


FIGURE 1. Kaplan-Meier curve showing time of treatment success with MMF.

immunosuppressive group (13 of 19; $P = 0.7049$, log rank). The biopsy-positive group (9 of 19) took 3.10 (2.20–6.07) months to achieve disease control versus 3.67 (1.17–4.03) months in the biopsy-negative group (10 of 19; $P = 0.4218$, log rank). Of the patients who did not achieve disease suppression, 2 of 4 (50%) were on previous immunosuppression before initiation with the MMF treatment. Twenty-five percent (2 of 8) of patients who failed previous immunosuppression also failed MMF, whereas 13.3% (2 of 15) who were naive to immunosuppression before starting MMF failed MMF ($P = 0.4348$, Fisher exact test, 2-tailed). The 2 patients who failed previous immunosuppression and failed MMF were both biopsy-negative patients. For the naive group, one was biopsy positive and the other biopsy negative.

The median best-corrected logMAR vision pretreatment was 0.40 (0.13–0.63) and posttreatment was 0.365 (0.10–0.67; $P = 0.6989$, Mann-Whitney test). For the biopsy-positive patients, the median best-corrected logMAR vision pretreatment was 0.45 (0.24–0.67) and posttreatment was 0.4 (0.1–0.67; $P = 0.5772$, Mann-Whitney test). For the biopsy-negative patients, the median best-corrected logMAR vision pretreatment was 0.37 (0.13–0.5) and posttreatment was 0.33 (0.1–0.63; $P = 0.6385$, Mann-Whitney test).

Side Effects

Five patients (21.7%) had to stop treatment with MMF, 1 for side effects (biopsy positive) and 4 for failure to control inflammation (3 biopsy negative and 1 biopsy positive). Of the 4 patients (17.4%) who failed MMF treatment, 2 patients were changed to cyclophosphamide, and 1 each to azathioprine and intravenous immunoglobulin with resultant control of inflammation. The total number of patients that developed side effects from MMF was 3 (13% within the first year), and all were biopsy positive, but only 1 patient required cessation of MMF for a rash. Of the other 2 patients, one had mild thrombocytopenia, which resolved with lowering the dose of MMF, and the other had hypokalemia, myalgia, insomnia, and anorexia, which resolved with lowering the dose and changing to mycophenolate sodium (MPS; Myfortic; Novartis, Basel,

Switzerland). There were no reports of infection or malignancy while taking MMF. No patients required hospitalization because of the adverse effects.

DISCUSSION

MMF has been reported to be effective in disease suppression of MMP. Previous studies have reported success as monotherapy,^{13,14,17} in combination with other agents (including prednisone and dapsone),^{25,26} and as second-line therapy.¹⁶ Our study provides additional data to support the use of MMF as initial therapy and monotherapy in treating active ocular MMP, controlling inflammation in 82.6% of patients at 1 year. Only 3 patients used concomitant treatments with either prednisone (2) or methotrexate (1). The majority of our patients were treated with MMF as the initial immunosuppressive agent (65.2%). Prior use of alternative immunosuppressive agents had a lower likelihood of treatment success in our patients but was not statistically significant.

Our data suggest that MMF provides control of inflammation in the majority of patient with active ocular MMP. Almost three fourths of the patients had inflammation control at 6 months and 82.5% had control at 12 months. Our 6-month data report higher success rates than the SITE study,¹⁴ which reported a success rate of 41% at 6 months and of 71% at 12 months for 18 MMP patients treated with MMF. Our study reinforces the conclusions from the SITE study that MMF is reasonably effective for MMP, and may be a reasonable initial choice for management of cases that are not immediately vision-threatening, based on its relatively favorable side effect profile.

For MMF dosing, we started at 500 mg once daily and increased according to the effect. In our patients who achieved disease suppression, the MMF dose was tapered to the lowest dose possible for disease suppression. If the disease activity increased during the MMF tapering process, the dose was returned to the disease-controlling level. Because we started at a lower initial dose, this may have decreased the number of patients with adverse events on MMF. Perhaps inflammation control may have been achieved in a higher percentage of patients at 3 months if we had started at a higher dose of 1000 mg once daily that was recommended by Larkin and Lightman for ocular inflammation.²⁰

MMF has a favorable safety profile in that it does not produce any major organ toxicity and has not been associated with incremental nephrotoxicity, hepatotoxicity, neurotoxicity, glucose intolerance, or hypertension to the degree of other immunosuppressive agents.²⁰ The most common side effects are diarrhea, vomiting, and fatigue.^{15,20} Only thirteen percent of our patients developed side effects, and only 4.3% of patients required cessation of MMF within 1 year of MMF use. This is comparable with the findings for MMF from the SITE study, which found that 12% of patients discontinued MMF for side effects.¹⁴ Current literature has debated whether MMF or MPS offers a better side effect profile.^{27,28} All patients in this study were initially placed on MMF. One patient was switched to MPS secondary to hypokalemia, myalgia, insomnia, and

anorexia. On MPS, the side effects resolved. Because MMP affects an older population of patients who have significant systemic comorbidities, the tolerability of MMF is appealing as a treatment option.

In our study, MMF was maintained as chronic treatment except for 1 patient who achieved 7 years of disease remission. Our use of MMF has demonstrated that remission is not the goal of treatment as it is with cyclophosphamide. Cyclophosphamide can be a very effective treatment modality for MMP, with a reported remission rate of 91% within 2 years after initiation of immunosuppressive drug therapy.⁸ However, adverse events are common with this drug including life-threatening pancytopenia and hepatotoxicity.¹⁶ A recent article by Thorne et al⁸ reported infections in 48.6%, hematuria in 45.5%, and malignancy in 11.6% of their patients on cyclophosphamide. Cyclophosphamide is a very effective therapeutic agent for MMP, but we reserve its use for patients who have failed less toxic medications or who manifest particularly aggressive disease that we feel is unlikely to respond to other agents. MMF suppresses the ocular surface inflammation in MMP but spares the cytotoxic side effects of cyclophosphamide.

When comparing the results of disease suppression with those of other agents as evaluated by the SITE studies, our study with MMF showed a favorable percentage of disease control when compared with cyclophosphamide (43% at 6 months, 68.7% at 12 months, $n = 98$),⁷ methotrexate (39.5% at 6 months, 65% at 12 months, $n = 58$),⁵ azathioprine (39% at 6 months, $n = 33$),⁶ and cyclosporine (20% at 6 months, 20% at 12 months, $n = 6$).²⁹ The rates at which immunosuppressive medication was stopped because of side effects in the SITE study are as follows: MMF, 12%¹⁴; cyclophosphamide, 33.5%⁷; methotrexate, 16%⁵; azathioprine, 24%⁶; and cyclosporine, 10.7%.²⁹ MMF had the least side effects among the immunosuppressive drugs that are listed above except for cyclosporine. Our study only required cessation of MMF for its side effects 4.3% of the time. Compared with the other antimetabolites for the treatment of various inflammatory eye diseases, MMF has a faster onset of action than methotrexate.¹⁷ The length of time for onset of disease suppression with MMF was 3.27 months in our study.

In our study, 47.8% of the patients were biopsy positive, which is slightly less compared with the other reports on this subject. Saw et al¹⁶ reported a 69% biopsy-positive rate in their study. When comparing biopsy-positive to biopsy-negative patients in this study, the results were similar for treatment success. The number of patients who failed treatment with MMF was slightly higher in the biopsy-negative group (3 biopsy negative vs. 1 biopsy positive). There were 2 patients from the biopsy-negative group who failed both previous treatments and MMF, but this was not statistically significant. In regards to time to treatment success, there was a slightly faster response time in the biopsy-positive group, but this was not found to be statistically significant. The required dose to sustain disease control was higher in patients who were biopsy negative (2000 mg/d, 1375–2125 mg/d, vs. 1000 mg/d, 1000–2000 mg/d), but this was not statistically significant. Side effects from MMF were only seen in the biopsy-positive group (3).

Our study is limited by its retrospective observational design and the limited number of patients. There may also be a selection bias because we are a tertiary referral center. The patients referred to our center are probably ones with more severe disease, which further enhances the apparent effectiveness of this treatment. Previous studies report a biopsy-positive rate of 69% to 97%,^{16,30} whereas our study only had 47.8% of patients with a positive biopsy. Our biopsies were sent to reputable laboratories for diagnosing MMP. The lower number of patients with positive biopsies can be a limitation of the study.

Because trichiasis secondary to cicatricial entropion is a major cause of ocular morbidity and can aggravate the inflammatory process, patients with MMP require careful monitoring and treatment for mechanical ocular surface irritation caused by lash–globe contact. It can be very difficult to determine if an MMP patient has active inflammation from disease activity or from mechanical irritation from lashes. In our population, the mechanical component of MMP was addressed aggressively with multiple modalities. If the cause of conjunctival injection were unclear, the dose of MMF would be increased in addition to treating the mechanical component. Treating patients' lashes aggressively promotes greater disease control and less corneal scarring.

In conclusion, treatment of MMP with MMF resulted in control of inflammation in the majority of our patients with minimal side effects. Our data significantly add to the small body of literature evaluating MMF for MMP and support consideration of MMF as an initial and/or monotherapy treatment option for active ocular MMP.

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